Exploring Outcomes of Antidepressant Treatment and Polypharmacy in People with Comorbid Depression and Type 2 Diabetes

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Declaration: I, Annie Jeffery, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Aim: In adults with comorbid depression and type 2 diabetes (T2DM), to determine:

Objective 1: The association between polypharmacy and antidepressant treatment trajectories;

Objective 2: The association between antidepressants and long-term physical health outcomes.

Methods and findings: In adults with comorbid depression and T2DM:

I conducted two systematic reviews examining:

i) Prevalence of antidepressant treatment and associated polypharmacy. The prevalence of antidepressant treatment varied from 18-87%. There was no evidence of an association between diabetes medication and antidepressant prescribing. I identified no studies investigating other polypharmacy.

ii) Long-term outcomes of antidepressant treatment (no studies identified).

I carried out four observational studies using electronic health record data from the UK Clinical Practice Research Datalink, to understand:

Objective 1:

i) Association between polypharmacy and stopping antidepressants before the recommended treatment duration: The median number of 7 concurrent medications was associated with a 65% decrease in the rate of stopping antidepressants (HR 0.45, 95% CI 0.37-0.55) compared to no concurrent medications.

ii) Association between polypharmacy and restarting antidepressants: The median number of 9 concurrent medications was associated with a 64% increase in the rate of restarting antidepressant treatment (HR 1.64, 95% CI 1.44-1.86) compared to no concurrent medications.

Objective 2:

iii) The association between antidepressant prescribing and starting insulin: Antidepressants were associated with a 278% increase in the rate of starting insulin (IRR 3.78, 95% CIs 3.53-4.04).

iv) The association between antidepressant prescribing and mortality: Antidepressants were associated with a 176% increase in the rate of all-cause mortality (RR 2.76, 95% CIs 2.53-3.01).

Conclusions: Polypharmacy is associated with continuing and restarting antidepressants. Antidepressant prescribing is associated with worse long-term physical health outcomes. However, rather than a causal relationship, these are likely to be markers of worse depression severity which is in turn associated with worse long-term physical health outcomes.

Impact Statement

My thesis has improved understanding of antidepressant treatment trajectories, polypharmacy (the use of multiple medications) and long-term outcomes in people with comorbid depression and type 2 diabetes (T2DM). Before my thesis, we knew that people with depression were more likely to develop T2DM and vice versa. We also knew that each condition may worsen the other. However, the trajectories of antidepressant prescribing alongside polypharmacy in this common comorbid patient group were unknown. Short-term improvements in depression symptoms and diabetic control following antidepressant treatment had been reported in randomised-controlled trials. However, there had been no research investigating the long-term health outcomes associated with antidepressant treatment in this patient group. My thesis addressed these gaps using UK-based electronic health record data.

My thesis has shown that people with comorbid depression and T2DM have high rates of non-adherence to antidepressant medication. This has highlighted a need for adherence support in these individuals, so that treatment for depression is not jeopardised. My thesis has also shown that people in this patient group commonly restart antidepressants after stopping, which indicates clinically identified depression relapse. This was particularly the case for people who were taking more concurrent medications, who may have worse overall health and therefore be more severely depressed. This finding is important, as it highlights the need for enhanced mental health support for these individuals.

My thesis has identified antidepressant prescribing as a marker of considerably worse physical health outcomes in people with comorbid depression and T2DM. This included the long-term decline of diabetic control and mortality from a range of causes (diabetic, cardiovascular, respiratory, cancer, and unnatural). Individuals who are prescribed antidepressants are likely to have a clustering of risk factors for worse physical and mental health outcomes. The identification of antidepressant prescribing as a marker for this enables these individuals to be targeted for enhanced holistic care.

My results were unexpected, in that polypharmacy was associated with improved medication adherence and that treated depression was associated with worse physical health outcomes. I performed a large number of secondary and sensitivity analyses that suggested my findings were not caused by the use of multiple medications or by

antidepressant medications themselves. Rather, my analyses suggested that these were markers for worse depression severity and overall health. This has highlighted confounding by indication as key limitation in the use of electronic health record data. This can guide future pharmacoepidemiological research. It has also identified a need for the exploration of novel methods of causal inference for this type of research.

Of the six analytical studies in my thesis: one is published, one has been pre-printed, two are at the second stage of peer review, one has been submitted to a journal and one is currently being drafted for journal submission. I presented three of the studies at the International Conference of Pharmacoepidemiology 2022. The thesis in full has been presented to a group of individuals with lived experience of physical-mental health multimorbidity. I am currently working with the NIHR on wider dissemination.

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Table of contents

Abbreviations

ACE – angiotensin-converting enzyme

ARB – angiotensin II receptor blocker

ATC – Anatomical Therapeutic Chemical

BME – black and minority ethnicities

BMI – body mass index

BNF – British National Formulary

CI – confidence interval

CKD – chronic kidney disease

CPRD – Clinical Practice Research Datalink

CVD – cardiovascular disease

DKA – diabetic ketoacidosis

DPP-4 – dipeptidyl peptidase 4

EHR – electronic health record

EMIS – Egton Medical Information System

GLP-1 – glucagon-like peptide-1

GP – general practitioner

HbA1c – haemoglobin A1C

HPA – hypothalamic-pituitary adrenal

HR – hazard ratio

HHS – hyperosmolar hyperglycaemic state

ICD – International Classification of Diseases

ID – identification

IQR – interquartile range

IRR – incident rate ratio

MAOI – monoamine oxidase inhibitor

MeSH – medical subject headings

NASSA – noradrenaline and specific serotoninergic antidepressant

NHS – National Health Service

NICE – National Institute for Health and Care Excellence

NNT – number needed to treat

ONS – Office for National Statistics

OR – odds ratio

PHQ – Patient Health Questionnaire

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analysis

QOF – quality outcomes framework

RCT – randomised controlled trial

RR – rate ratio

SGLT-2 – sodium-glucose cotransporter-2

SMD – standardized mean difference

SNRI – serotonin and norepinephrine reuptake inhibitor

SSRI – selective serotonin reuptake inhibitor

T1DM – type 1 diabetes mellitus

T2DM – type 2 diabetes mellitus

TCA – tricyclic and related antidepressants

THIN – The Health Improvement Network

WHO – World Health Organisation

UK – United Kingdom

USA – United States of America

UTI – urinary tract infections

Chapter 1: Introduction

1.1 Summary

In this chapter, I describe the context for my thesis. I provide an overview of the characteristics of, and bidirectional relationship between, depression and type 2 diabetes (T2DM). I also provide an overview of the recommended pharmacological therapies in both depression and T2DM, and introduce the concepts of appropriate and inappropriate polypharmacy. I outline the key research priorities that are addressed by this thesis, introduce the aims and objectives for each study and discuss the existing literature relating to each objective. Finally, I examine the limitations of randomised controlled trials (RCTs) in understanding the outcomes associated with antidepressant treatment and associated polypharmacy in this context, and the opportunities provided by real-world data.

1.2 Introduction to depression

1.2.1 Description and burden of depression

Depression is the leading cause of disability worldwide and a major contributor to the global burden of disease (1). It is a significant contributor to premature mortality (2). Depression was estimated by the Global Burden of Disease Study in 2017 to affect more than 264 million people worldwide, a figure which is predicted to rise (3).

Depression can be a seriously distressing and disabling condition, with symptoms including persistent low mood, loss of interest in pleasure and fatigue, change in appetite/weight, sleep disturbance, psychomotor agitation/retardation, low self-esteem, loss of concentration, and suicidal thoughts (4,5).

In addition to the symptoms of depression itself, depression can have a negative influence on an individual's physical health. People with depression are more likely to be sedentary (6), eat unhealthy diets (7,8) and engage in risky health-behaviours such as smoking (9,10) and/or alcohol and substance abuse (11). Depression is also associated with somatic symptoms, such as unexplained aches, pains, or gastrointestinal disturbances (12).

Ultimately, depression can lead to suicide. Depression is also associated with non-suicide premature mortality through increased risk of unhealthy lifestyle and physical health conditions (13).

It is estimated that depression costs England up to £23.8 billion each year, through health service costs, lost earnings, lower productivity and human costs (14). This figure did not include the cost of informal care and public service costs. In comparison, cancer costs England £18.3 billion each year.

1.2.2 Depression aetiology

There is no single model that adequately explains all aspects of depression aetiology. I will describe, briefly, in the following **Sections 1.2.2.1-2** how there are a number of different potential biological and psychosocial factors which might cause depression episodes in different people or even different episodes in the same person.

1.2.2.1 Biological causes of depression

The monoamine hypothesis: Monoamines are neurotransmitters that are essential for signalling in the central and peripheral nervous systems. They include serotonin, dopamine and norepinephrine. In the 1950's, there were two simultaneous discoveries that led to the theory that depleted monoamines could cause depression. Firstly, it was discovered that the sedative-antihypertensive medication, reserpine, reduced monoamines and could trigger episodes of depression (15). Secondly, it was discovered that a new anti-tuberculosis medication, iproniazid, which enhanced monoamine neurotransmission could relieve symptoms of depression (15). This theory has endured, partly because of the clinical effectiveness of monoaminergic antidepressant medication (see **Section 1.2.5**) (16). However, it does not fully explain why different antidepressants work in some people and not others. Nor does it explain why antidepressants take weeks to work.

The neurogenic hypothesis: The hypothalamic-pituitary-adrenal (HPA) axis is a major neuroendocrine mechanism which mediates reactions to stress and regulates a number of the body's processes, including metabolism, immune responses and the autonomic nervous system. The stress-response pathway of the HPA-axis results in the production of cortisol. Increased levels of cortisol have consistently been shown to be associated with severe depression (17). It is also hypothesised that stress and excess cortisol may impair hippocampal development and adult hippocampal neurogenesis – both of which are associated with depression (18–20). However, it is not known whether these factors lead to depression or vice versa.

The inflammation hypothesis: Cytokines are a category of cell-signalling proteins that play an important role in the body's inflammatory immune response. Elevated cytokines have been observed in people with depression (21) and people with autoimmune diseases and severe infections are more likely to have depression (22). In addition, pro-inflammatory treatments have been shown to trigger depression (21), which suggests inflammation may play a role in causing depression.

Hormonal causes of depression: Women have an increased risk of developing depression which begins during puberty, peaks during perimenopause and declines after menopause (23). This may be, in part, caused by the fluctuation of reproductive hormones, which has been shown to be associated with an increased risk of depression in females (24), and may be responsible for perinatal depression (25). In addition, people with thyroid disorders are more likely to develop depression

symptoms, however, the mechanisms underlying this mechanism are not fully understood (26).

Genetics: People with depression are more likely to have a first degree relative with depression compared to people without depression (27). Twin studies can be used to distinguish between environmental and genetic causes of disease by comparing monozygotic (sharing 100% of DNA) to dizygotic (sharing 50% of DNA) twins. Such studies have shown that depression is more likely to occur between monozygotic twins compared to dizygotic twins, and that up to 40% of depression risk may be attributed to genetic factors (27). Although genome-wide association studies (GWAS) have struggled to identify significant genetic variants associated with clinician-diagnosed depression (27), there have been two large GWAS that successfully identified 45 genome-wide significant variants associated with self-reported depression (28,29). However, when combined in a polygenic risk score, GWAS identified variants have only been able to predict 1.9% of the variance in depression in adults (28).

1.2.2.2 Psychosocial causes of depression

Individual level factors: Maltreatment in childhood (30) and stressful life-events as an adult (such as physical ill-health (31), bereavement (32,33), separation (34), loss of employment (35), financial difficulties (36), relocation (37), natural disasters (38) and violence (38–40)) are well established as precipitating factors associated with depression. However, personal traits, such as resilience, self-identity, aspirations, attachment style and autonomy, may influence a person's ability to cope with such stressful life-events and whether or not they lead to the development of depressive symptoms (41). In addition, a person's day-to-day lifestyle may include risk factors known to cause depression, such as, lack of sleep (42), lack of physical activity (43), poor diet (44,45), excessive alcohol consumption (46) and substance abuse (11). On the other hand, a number of activities may be protective against depression, such as, volunteering or donating to charity (47), engaging in multiple leisure activities (48), hobbies (49) and pet ownership (50).

Family level factors: The structure and dynamics of a person's family can be a risk factor or protective factor against developing depression. For example, depression is more likely to develop in children and young people who are from single parent or step-parent families (51). Being married (52) and family cohesion both decrease the

risk of depression (53). On the other hand, family conflict can increase the risk of depression (54,55). While living with a parent may be protective against risk factors for depression, such as excessive alcohol consumption, it may also increase some risk factors, such as sedentary behaviour (56). In addition, the pressure of having caring responsibilities for family and friends can be a risk factor for psychological distress (57).

Neighbourhood level factors: High social cohesion (58) and having large social networks with high quality social support (59,60) are protective factors against depression. The environment in which people live can also affect their mental health. For example, access to nature (61), employment and education opportunities (62) may be protective against depression, while factors such as high crime rates (63) and high socio-economic deprivation (64) may increase a person's risk of depression.

Societal factors: Social norms and values can be protective against depression if they encourage, for example, family connectedness (65); or they may increase the risk of depression if, for example, they encourage discrimination (66), discourage help seeking (67) or stigmatise mental health problems (68). Other societal factors that may influence an individual's risk of depression include the political climate and provision of public services (41).

1.2.3 Diagnosing and treating depression in UK primary care

1.2.3.1 Depression assessment instruments

There are a number of validated scales that can be used to screen for depression. The most widely used of these are short self-report questionnaires that assess the frequency of depression symptoms (such as low mood, loss of interest in pleasure) in a set time frame, such as two weeks. These include the Beck Depression Inventory (69), the Patient Health Questionnaire Mood Scale (PHQ-9) (70), and the Geriatric Depression Scale (71). A cut off is used to classify questionnaire scores as screening positive or negative for depression, as well as to classify the severity from mild to severe. The PHQ-9 is the scale most commonly used in UK primary care (72).

1.2.3.2 Diagnosing depression in UK primary care

Primary care is intended as the first point of call for all health conditions, including mental health, in the UK. While depression is not routinely screened for, national

guidelines (73) advise primary care clinicians to be alert to possible depression, and if suspected, to screen individuals with the following two questions:

- During the last month, have they often been bothered by feeling down, depressed or hopeless?
- During the last month, have they often been bothered by having little interest or pleasure in doing things?

If the patient answers ‘yes’ to either question, the clinician is advised to perform a comprehensive assessment, including the person's mental state and associated difficulties, experience of trauma, living conditions, social support, lifestyle, history of depression, available support and any past experience with treatments for depression (73).

1.2.3.3 Treating depression in UK primary care

Most depression in the UK is treated in primary care (74). A stepped care model is advised by UK National Institute for Health and Care Excellence (NICE) to decide when to start treating depression, and which treatment may be the most suitable (73). Choice of treatment should be made collaboratively with the patient, and involve a discussion including their preferences, clinical needs, barriers to any treatments, comorbidities and previous experience of treatment. Possible treatment options include: guided self-help, group/individual cognitive behavioural therapy, group/individual behavioural activation therapy, group exercise, interpersonal psychotherapy, counselling, short-term psychodynamic therapy or antidepressant medication. For less severe depression, it is recommended that the least intrusive and least resource intensive treatments are trialled first. While psychological therapies are available for free via the NHS Talking Therapies programme, waiting times can be up to 18 weeks (75). As such, antidepressants are usually the only treatment immediately available. Approximately 2.1 billion doses of antidepressant medication are prescribed to 52 million people in England and Wales each year, covering 11% of the population (76).

1.2.4 Pharmacological treatment options for depression

Antidepressant medication is recommended by NICE as a treatment option for depression (73). There are five main classes of antidepressant agent, categorised by

their mechanism of action – selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), noradrenaline and specific serotoninergic antidepressants (NASSAs), tricyclic and related antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Other antidepressants that do not fit into one of those classes, are known as *atypical*, and include agomelatine, tryptophan, and vortioxetine. A 2018 network meta-analysis by Cipriani et al (77) compared the efficacy (defined as a 50% or greater reduction in depression symptom scores) and acceptability (defined by stopping treatment for any reason) of 21 antidepressant agents used in the treatment of depression. They found that all were more effective than placebo, and all but one (clomipramine) had equal or better acceptability than placebo. However, it is worth noting that the definition of a 50% or greater reduction in depression symptom scores does not necessarily mean that an individual will be depression free, and so, efficacy, as described in the Cipriani review does not equate to remission from depression, but in a short-term reduction of depression symptoms. Heterogeneity variance was assumed to be the same across all treatment comparisons and was reported as 0·044 (95% CIs 0·028–0·063) for efficacy and 0·040 (95% CIs 0·023–0·062) for acceptability, suggesting moderate to-low heterogeneity.

SSRIs are recommended by NICE as first-line drug treatment as they have a good safety profile and are usually well tolerated (73). They include citalopram, escitalopram, fluoxetine, paroxetine and sertraline. The efficacy of individual SSRI antidepressants compared to placebo is similar. Cipriani et al reported odds ratios (ORs) compared to placebo ranging from 1.52 (95% CIs 1.33-1.74) for citalopram, to 1.75 (95% CIs 1.61-1.90) for paroxetine (77). SSRIs may be better tolerated than other antidepressants and are safer in overdose (78). However, common side-effects include anxiety, appetite and weight changes, cardiac rhythm conditions, cognitive impairment, dizziness, drowsiness, dry mouth, excessive sweating, fatigue, fever, gastrointestinal disturbances, haemorrhage, headache, joint stiffness, malaise, myalgia, nausea, sexual dysfunction, skin reactions, sleep, urinary disorders and visual impairment (74,78).

If patients fail to respond adequately to SSRIs or SSRIs are contraindicated, other antidepressant classes, as described below, are recommended (73).

SNRIs include duloxetine and venlafaxine. Both of these, in the Cipriani meta-analysis, had slightly higher odds ratios for efficacy compared to placebo than SSRIs, with ORs 1.85 (95% CIs 1.66-2.07) for duloxetine and 1.78 (95% CIs 1.61-1.96) for venlafaxine (77). SNRIs have a number of similar side-effects to SSRIs (18). However, these agents are cautioned for use by NICE due to the greater possibility of exacerbating cardiac arrhythmias and hypertension, and the risk of overdose (79–81). Common side-effects include anxiety, changes in appetite, cardiac arrhythmias, confusion, depersonalisation, dizziness, dry mouth, fainting, gastrointestinal disturbances, headaches, hypertension, nausea, sedation, sexual dysfunction, skin reactions, sleep disorders, urinary disorders, vision disorders and weakness (79–81).

The TCA amitriptyline had the highest odds ratio for efficacy compared to placebo in the Cipriani meta-analysis, with an OR 2.13 (95% CIs 1.89-2.41) (16). However, TCAs are more sedating, have more antimuscarinic and cardiotoxic side-effects and higher risk of toxicity in overdose than SSRIs (78). Other TCAs include clomipramine, dosulepin, doxepin, imipramine, lofepramine, nortriptyline and trimipramine.

NASSAs include mirtazapine, which had a slightly higher odds ratio for efficacy compared to placebo than SSRIs in the Cipriani meta-analysis (OR 1.89, 95% CIs 1.64-2.20) (77). The side-effect profile of NASSAs are different to that of SSRIs and SNRIs – notably that they are more likely to cause drowsiness and weight gain, but less likely to cause sexual dysfunction (74).

MAOIs were the first discovered antidepressant class, including phenelzine and tranylcypromine, and the more recent moclobemide. However, these agents are rarely prescribed today due to more serious side-effects, and drug and dietary interactions (78). NICE guidelines recommend that MAOIs are only prescribed by a specialist mental health professional (82).

As I have described, there are a number of pharmacological treatment options with depression. These have different mechanisms of action and side-effect profiles. Antidepressant prescribing decisions should include consideration of the side-effect profile, potential interactions with physical health problems and concomitant medication, patient preferences, and the perceived efficacy of any antidepressants previously taken by the patient (82). If antidepressant monotherapy fails to produce an adequate response after trials of two agents for sufficient duration (4-6 weeks),

augmentation with a second antidepressant, the mood stabiliser lithium, or with a second generation antipsychotic may be considered (83). NICE recommends that antidepressant treatment is continued for at least 6 months after treatment response (although what constitutes 'treatment response' is not defined by NICE), which may take 4-6 weeks (73). For people at high risk of depression relapse (again, what constitutes 'high risk' is undefined by NICE), long-term antidepressant treatment may be considered (73).

1.3 Introduction to type 2 diabetes (T2DM)

1.3.1 Description and burden of T2DM

T2DM is a chronic condition where the body cannot effectively use insulin, the hormone that regulates blood sugar levels. Overtime, high blood sugar levels cause damage to many of the body's systems, particularly the vascular and nervous systems. This type of diabetes is largely caused by excess body weight and physical inactivity (84). The global prevalence of T2DM in 2018 was estimated to be over 500 million people, and, like depression, the prevalence is predicted to rise (85). Diabetes was estimated to directly cause 1.6 million deaths in 2016, and is also a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation (84). It is estimated that T2DM costs England up to £18.8 billion each year (86).

1.3.2 T2DM aetiology

1.3.2.1 Insulin resistance

Insulin is the hormone that regulates the conversion of blood sugar into energy and the storage of excess blood sugar as fat. When sugar enters the blood stream, this signals the pancreas to produce insulin. When sugar is converted into either energy or fat, the production of insulin slows down. When large amounts of sugar enter the blood stream, the pancreas produces large quantities of insulin. Over time the body stops responding to the large quantities of insulin being produced – this is known as *insulin resistance.* In insulin resistance the body cannot effectively use the insulin produced. This leads to excessive amounts of sugar in the blood and can eventually progress to type 2 diabetes.

This is distinct from type 1 diabetes (T1DM), which is caused by an autoimmune reaction resulting in a person being unable to produce insulin naturally. While T2DM is largely caused by lifestyle factors, T1DM is a genetic condition.

1.3.2.2 Risk factors for T2DM

In 2018, Bellou et al performed an umbrella review of factors associated with an increased risk of T2DM. They identified a number of different type of risk factors that showed convincing (statistical significance at P $<10^{-6}$, based on >1,000 cases, without large between-study heterogeneity (I2<50%), no evidence of publication or excess significance bias) or highly suggestive (>1,000 cases, P $<10^{-6}$ and largest study presenting a statistically significant effect) evidence of an association with increased risk of T2DM:

Dietary factors: unhealthy dietary pattern; high consumption of processed meat, iron and sugar sweetened beverages; low consumption of whole grains and coffee.

Adiposity factors: high BMI, high waist-hip/height ratios and waist circumference; weight gain; low hip circumference.

Lifestyle factors: low levels of physical activity; high sedentary time; smoking; large proportion of time watching television; high exposure to air pollution; abstinence from alcohol.

Psychosocial factors: low conscientiousness; low educational status.

Biomarkers: high levels of serum gamma-glutamyl transferase (signalling liver disease), alanine aminotransferase (signalling liver disease), serum C-reactive protein (signalling inflammation), and serum uric acid (a range of causes including metabolic syndrome; low levels of serum vitamin D and serum adiponectin (involved in regulating glucose and insulin sensitivity).

Medical history: gestational diabetes; depression; bipolar disorder; psoriasis; metabolic syndrome; late age at menarche.

1.3.2.3 HbA1c, prediabetes and progression to T2DM

Glycated haemoglobin, or HbA1c, measures the average blood sugar levels of a person over the previous two to three months. A normal HbA1c value, known as normoglycaemia, is less than 5.7% . A person is considered to have prediabetes when their HbA1c is between 5.7% to 6.4%. At the prediabetes stage a person's blood sugar levels are raised, but not by enough to be diagnosed with T2DM. People with prediabetes are considered to be at very high risk of developing T2DM. However, it is estimated that approximately 50% of people with prediabetes can prevent or delay T2DM by making changes to their diet, increasing physical activity and losing weight (87). The diagnostic criteria for T2DM is to have at least two HbA1c tests greater than 6.5% (88).

1.3.2.4 Decision to focus on T2DM for this thesis

T2DM is a common and serious condition that has a high burden of disease. It is a distinct condition from T1DM, with a distinct aetiology primarily consisting of lifestyle related risk factors. As I describe in **Section 1.4**, many of these risk factors may be in common with or exacerbated by comorbid depression. This is a relationship that is unique to comorbid depression and T2DM.

1.3.3 Pharmacological management of blood glucose levels

The primary goal of diabetic management is to control blood glucose levels, with significant evidence that doing so reduces the risk of developing complications (85). At an early stage, glycaemic control may be achieved through diet, lifestyle management and weight loss (83,89). When this is not possible, there are a wide range of pharmacological options available. I describe below the NICE recommended treatment strategy for maintaining glycaemic control in people with T2DM (83).

Metformin is internationally recommended as the first-line medication choice for glycaemic control (83,90–92). Common side-effects of metformin include gastrointestinal disturbances, increased appetite and nausea (93). There are a number of contraindications for metformin, in particular renal impairment (94), in which case an alternative oral antidiabetic agent may be prescribed (83). If glycaemic control cannot be maintained (HbA1c level < 7.5%), it is recommended to increase treatment to include up to three different oral antidiabetic medications (83).

Additional oral antidiabetic agents include dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1s (GLP-1s), pioglitazone, sodium-glucose cotransporter-2 (SGLT2) inhibitors and sulfonylureas (95). However, these medications may be associated with more serious adverse effects, such as bladder cancer (pioglitazone), bone fracture (pioglitazone), cardiac conditions (GLP-1s, pioglitazone), hypoglycaemia (GLP-1s, SGLT2 inhibitors, sulfonylureas), infection (DPP-4 inhibitors, pioglitazone, SGLT2 inhibitors), and life threatening ketoacidosis (GLP-1s, SGLT2 inhibitors) (96–100).

If glycaemic control is not achieved with oral antidiabetic medication, insulin treatment is recommended (83). Insulin is administered by injection or insulin pump, and the main adverse effect is hypoglycaemia (101).

1.3.4 Pharmacological prevention and management of diabetic complications

There are a number of complications or conditions associated with T2DM that require pharmacological prevention and/or management. While it is important to prevent and treat these complications, doing so may add to the increased risk of medication side-effects, drug-drug or drug-disease interactions and treatment burden. The most common of these are described below.

1.3.3.1 Hypertension

Ideal blood pressure is usually considered to be between 90/60mmHg and 120/80mmHg. High blood pressure is considered to be from 140/90mmHg (or an average of 135/85mmHg at home). It is estimated that over two thirds of people in the UK with T2DM have high blood pressure, known as hypertension (102). Hypertension is a key risk factor for cardiovascular disease. T2DM and hypertension have a number of shared risk factors, and T2DM causes damage to the vascular system which can cause hypertension (102,103). Subsequently, the combination of hypertension and T2DM leads to increased risk of both macrovascular (cardiovascular) and microvascular (e.g. renal, neuropathic, retinopathic) complications (103).

NICE recommend considering medication for hypertension at an early stage in this patient group (83): Depending on age and ethnicity, initial monotherapy is recommended with one of the following: angiotensin-converting enzyme (ACE)

inhibitor, angiotensin II receptor blocker (ARB), calcium channel blocker or thiazide-like diuretic. If hypertension is not controlled with the use of one of these medications, adding a second and then third medication from this list is recommended.

Common side-effects of all types of antihypertensive medication includes gastrointestinal disturbances, dizziness, headache, and nausea (104–107). Common side-effects for specific drug types also include: for ACE inhibitors, alopecia, cardiac complications, hypotension, pain, sleep disorders, renal impairment rhinitis, skin reactions and weakness (104); for ARBs, renal impairment and hypotension (105); for calcium channel blockers, drowsiness, cardiac complications and skin reactions (106); and for thiazide-like diuretics, electrolyte imbalance, erectile dysfunction, fatigue, hyperglycaemia and skin reactions (46).

1.3.3.2 Cardiovascular disease

Cardiovascular disease (CVD) is a term used to describe conditions affecting the heart or blood vessels – it can include strokes, peripheral arterial disease (a blockage in the arteries leading to the limbs), coronary heart disease and aortic diseases. Coronary heart disease occurs when the flow of blood to the heart is reduced or blocked – this can cause angina, myocardial infarction (when the blood flow is blocked suddenly) and heart failure (when the heart is unable to pump blood around the body properly). Aortic diseases are a group of conditions affecting the aorta (the blood vessel that carries blood from the heart to the rest of the body).

People with T2DM are more than twice as likely to develop cardiovascular disease than healthy people, and CVD is the leading cause of death in people with T2DM (108). It is estimated that CVD affects one third of people with T2DM (109).

Lipid modification therapy with a statin aims to reduce the amount of harmful cholesterol in the blood and is recommended for the primary prevention of CVD for people with T2DM who have increased risk of CVD based on their QRISK2 score (83). The QRISK2 score is a tool used to calculate a person's risk or CVD based on a range of risk factors. According to the QRISK2 tool, those at high risk of CVD includes overweight males over the age of 50 and overweight females over the age of 60, regardless of their cholesterol status (110). Common side-effects of all statins include gastrointestinal disturbances, dizziness, headache, pain, nausea, sleep disorders, thrombocytopenia and weakness (111).

Common medications prescribed in the UK for the secondary prevention of CVD, depending on the type of CVD condition, include the previously mentioned medications for hypertension and lipid modification, as well as antiplatelet mediation, beta blockers and nitrates (112). Common side-effects of antiplatelet medications include haemorrhage (113); for beta blockers, gastrointestinal disturbances, cardiac complications, confusion, depression, dizziness, erectile dysfunction, fatigue, headache, nausea, peripheral vascular disease, skin disorders, sleep disorders, fainting (114); for nitrates, cardiac complications, gastrointestinal disturbances, cerebral ischaemia, dizziness, drowsiness, headache, hypotension and nausea (115).

1.3.3.4 Chronic kidney disease

T2DM is the leading cause of chronic kidney disease (CKD), directly through damage to the blood vessels in the kidneys, and indirectly through damage to the nerves in the bladder, which puts pressure on the kidneys (116). An estimated 10-40% of people with T2DM will eventually suffer from kidney failure (117). There are a number of pharmacological options that have been shown to protect the kidneys from further damage, preventing the progression of CKD and delaying end-stage kidney disease (116). NICE recommends the use of one or more of the following: ACE inhibitors, ARBs, or SGLT2 inhibitors (83). Side-effects of these medications are listed above.

1.3.3.5 Gastroparesis

Up to 50% of people with T2DM have delayed gastric emptying, known as gastroparesis, caused by damage to the nerves to the stomach (118). NICE recommends that vomiting caused by gastroparesis can be treated with erythromycin, metoclopramide or domperidone (83). However, the use of domperidone is cautioned due to its safety profile, particularly its cardiac risk and interaction with other medications (83). Common side-effects of erythromycin include gastrointestinal disturbances, dizziness, headache, hearing impairment, sleep disturbances, nausea, pancreatitis, skin reactions, vasodilation and vision disorders (119); for metoclopramide, depression, drowsiness, gastrointestinal disturbances, hypotension, menstrual cycle irregularities, movement disorders and parkinsonism (120).

1.3.3.6 Painful diabetic neuropathy

Neuropathic pain is present in up to 26% of people with diabetes (121,122). NICE recommends pharmacological treatment with amitriptyline or duloxetine

(antidepressants which are also indicated to treat neuropathic pain), or one of the anticonvulsant medications; carbamazepine or gabapentin (123). Common side-effects of these medications include appetite changes, dizziness, drowsiness, fatigue, gastrointestinal disturbances, headache, movement disorders, nausea, skin reactions, and vision disorders (124).

1.3.3.7 Erectile dysfunction

Erectile dysfunction is thought to occur as a result of nerve and vascular damage. It affects up to 75% of men with T2DM, and men with T2DM are thought to develop erectile dysfunction 10-15 years earlier than men without T2DM (125). NICE recommends phosphodiesterase-5 inhibitors as a treatment option for erectile dysfunction in men with T2DM (83). Common side-effects include alopecia, anaemia, anxiety, dizziness, gastrointestinal disturbances, headaches, infection, sleep disturbances, nausea, pain, skin reactions, vasodilation and vision disorders (65).

1.3.3.8 Diabetic foot infection

Diabetic foot infections can occur in foot wounds resulting from nerve damage and/or impaired circulation, and are the cause of lower limb amputation in T2DM; NICE recommends treatment with a range of potential antibiotics depending on infection type and severity, and patient characteristics (127). Potential antibiotic side-effects are vast and varied, depending on the antibiotic agent prescribed.

1.3.3.8 Other complications of autonomic neuropathy

Autonomic neuropathy occurs when there is damage to the nerves that control automatic body functions. Autonomic neuropathy can cause diarrhoea and impaired bladder emptying leading to urinary tract infections (UTI) (83). Diarrhoea may require treatment with the antimotility medication loperamide (128). Side-effects include gastrointestinal disturbances and nausea (129). There are a range of antibiotic options available for the treatment of UTIs depending on the infection type and location, and patient characteristics (130).

1.3.5 Treatment burden in T2DM

In **Sections 1.3.1-4**, I described a range of serious and disabling effects of T2DM which require management. I also demonstrated that people with T2DM have the potential to require multiple medications. All of these have potential side-effects and

may result in a high treatment burden for this patient group. As well as the pharmacological treatment burden, people with T2DM also have a high burden from necessary self care. This includes diet management, exercise, monitoring of blood glucose and foot care (131).

1.4 When depression and T2DM meet – introduction to comorbid depression and T2DM

1.4.1 The bidirectional relationship between depression and T2DM

There is substantial evidence showing increased prevalence rates of depression in people with T2DM (132,133). A large meta-analysis (6,916 incident cases of T2DM in people with depression and 6,414 incident cases of depression in people with T2DM) reported a risk ratio of 1.6 (95% CI 1.4 to 1.9; Cochrane Q statistic [13 d.f.] 37.63, P < 0.001) for developing T2DM in people with depression, and a risk ratio of 1.2 (95% CI 1.0 to 1.3; Cochrane Q statistic [6 d.f.] 9.17, $P < 0.16$) for developing depression in T2DM, leading them to assume a bidirectional relationship between depression and T2DM (134).

There are a number of theories as to the pathophysiological relationship between depression and T2DM. I have illustrated these in **Figure 1.i** below.

Depression and T2DM are both associated with cortisol-related dysfunction of the hypothalamic-pituitary adrenal (HPA) axis (135). Chronic inflammation which occurs in T2DM can lead to depression symptoms (136). Also, the disrupted sleep patterns and altered circadian rhythms that may occur in depression (137) may lead to increased insulin resistance (138).

Depression can exacerbate the distress associated with T2DM, while the pain, disability and prognosis from T2DM can both cause and exacerbate depression (139,140). While T2DM is predominantly driven by unhealthy lifestyle factors such as inactivity and poor diet (141), depression can both lead to and be driven by such factors (142). Depression can be linked to worsened self-care (142) and has been shown in meta-analysis to decrease adherence of diabetic treatments (143). A large meta-analysis found depression to be associated with poor glycaemic control in people with T2DM (59). Another meta-analysis found a significant association between

depression and the development of diabetic complications, particularly cardiac and renal complications (144).

A number of medications commonly prescribed in T2DM have depression listed as a known side-effect (114,119,120). Antidepressant medication has also been found in meta analysis to be associated with an increased risk of developing T2DM (145). However, there was substantial heterogeneity between studies (I2 = 71%) and the exact mechanism is not known. The authors suggested that the increased risk of T2DM associated with antidepressant use might be due to weight gain, reverse causation, or unmeasured confounding.

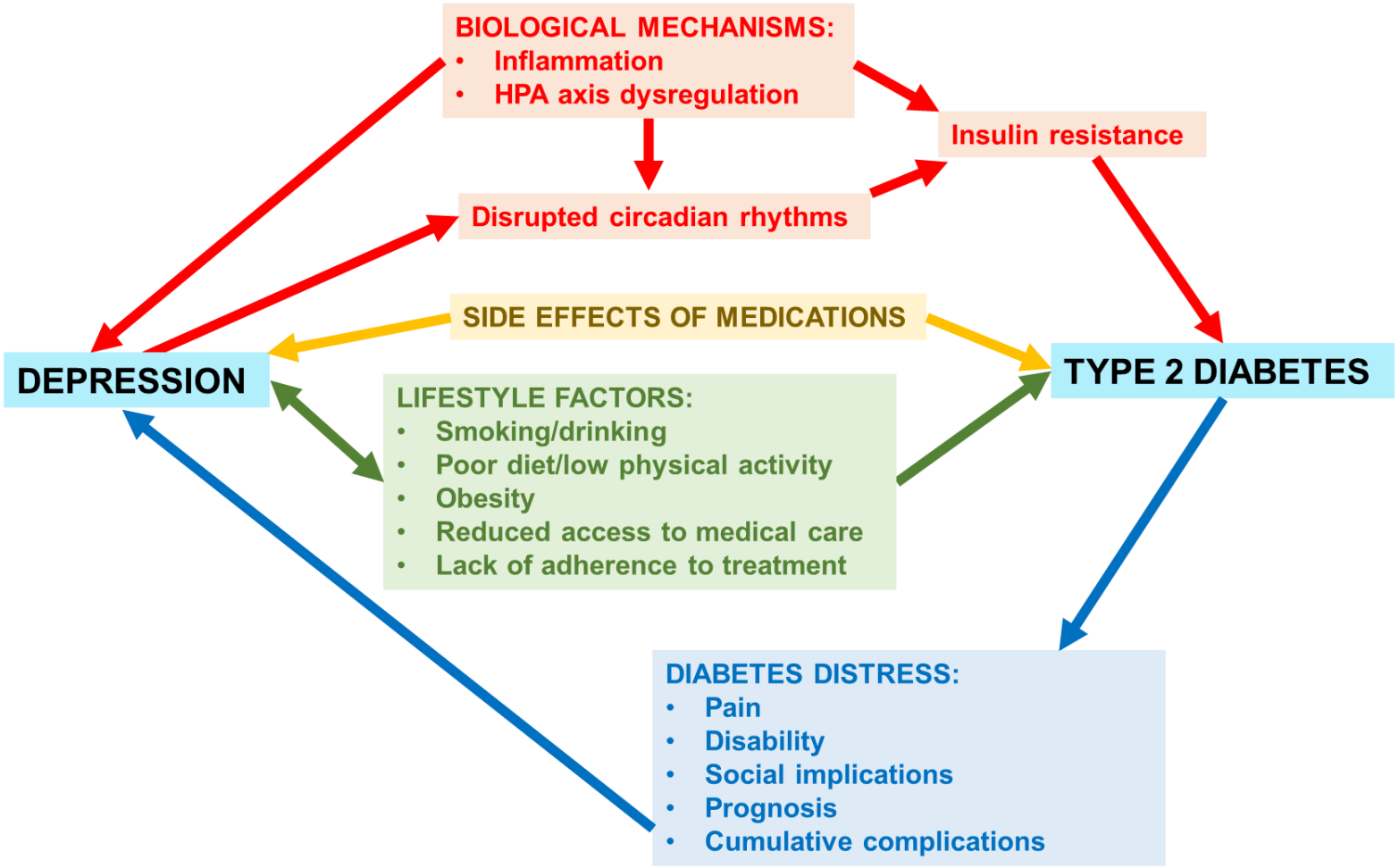
In addition, there are a number of sociodemographic risk factors that both depression and T2DM have in common. People of Black and Asian ethnicities in the UK have been shown to have higher rates of both depression (146) and T2DM (147). Social deprivation, including poor housing, unemployment and poverty are also associated with worse outcomes in T2DM (148–151) and depression (41).

Given this bidirectional relationship, where each condition may worsen the other, the successful treatment of both conditions is crucial to the management of the other, in people with comorbid depression and T2DM.

1.4.2 Insufficient clinical guidelines for the treatment of depression in people with comorbid T2DM

While UK NICE guidelines do address treating depression in people with physical long-term conditions, they are limited and not specific to individual physical conditions (81). The guidelines simply state that care should be patient-centred and collaborative, and that antidepressants should only be used in more severe instances and with care, taking into awareness that the guidelines were written for single conditions (81). A review of UK clinical guidelines with respect to multimorbidity notes the challenges and safety concerns of applying current guidelines to complex patients, who are at risk of drug-disease and drug-drug interactions (152).

Figure 1.i The bidirectional relationship between depression and T2DM



1.4.3 Side-effects of antidepressants which are of particular relevance to people with comorbid T2DM

Given the bidirectional relationship between depression and T2DM, where each condition may worsen the other, the successful treatment of both conditions is crucial to the management of the other. However, there are potential risks as well as benefits associated with antidepressant treatment in people with comorbid depression and T2DM. A number of commonly prescribed antidepressants cause side-effects that potentially exacerbate T2DM and/or its complications, such as weight gain (153), hypoglycaemia, cardiac complications, gastrointestinal disturbances, sexual dysfunction, and visual impairment (154). SSRIs, which are the recommended first-line treatment (82) are cautioned by the British National Formulary for use in people with diabetes (although explanation as to why is not stated) (154). Side effects such as weight gain may contribute to worsening glycaemic control and the progression of T2DM. In addition, cardiac side effects from antidepressants may exacerbate cardiac complications of T2DM, potentially leading to premature mortality. Other side effects such as hypoglycaemia and gastrointestinal disturbances may interact with similar side effects from antidiabetic medication (see **Sections 1.3.3-4**). While side effects such as erectile dysfunction, visual impairment and gastrointestinal disturbances are common complications in T2DM (see **Section 1.3.4**), and so may lead to cumulative drug-disease interactions.

1.4.4 The evidence gap from existing systematic reviews on antidepressant treatment in people with comorbid depression and T2DM

In 2012, a Cochrane review by Baumeister et al synthesised the findings of randomised-controlled trials (RCTs) investigating psychological and pharmacological interventions for depression in people with T2DM (155). They found eight antidepressant vs placebo trials with 377 participants. The follow-up duration of the studies found lasted from three weeks to six months. All trials found an improvement in depression symptoms (assessed by validated self-report questionnaires or standardised interviews) with a standardised mean difference (SMD) in depression score of -0.61 (95% CI -0.94 to -0.27; I2 = 47%) in the group treated with antidepressants compared to those in the placebo group. Three trials showed a short-term increase in depression remission (OR 2.50; 95% CI 1.21 to 5.15; I2 = 0%) in

people treated with antidepressants compared to placebo. Five trials showed a small short-term improvement HbA1c (mean difference -0.36%; 95% CI -0.59 to -0.13; I2 = 0%). There was no medium to long-term evidence beyond six months.

A more recent review in 2016 included both RCTs and a limited search of "other study designs" (156). Beyond the findings of the previous Cochrane review, this review found inconclusive evidence concerning differences between different antidepressant agents and the effect of antidepressants on glycaemic control. Most studies included had small sample sizes or unclear descriptions of methods used. The search of "other study designs" was limited to two clinical trial databases, which by definition will not include observational studies. Therefore a number of relevant observational studies were not included. Again, there was no medium to long-term evidence beyond six months.

I am aware of no existing systematic reviews, prior to my thesis, that investigate other outcomes (beyond those discussed above) of antidepressant treatment in people with comorbid depression and T2DM. These could include long-term outcomes, such as depression relapse, long-term glycaemic control, the development of diabetic complications and mortality.

Prior to my thesis, there was a gap in the existing body of evidence for systematic reviews that investigate "real-world" antidepressant prescribing patterns and outcomes in people with comorbid depression and T2DM, outside of RCTs. This includes a gap in the evidence investigating antidepressant treatment alongside all the other medications that people with comorbid depression and T2DM are taking. In the following section, I describe the potential risks associated with the use of multiple medications at the same time, otherwise known as *polypharmacy*.

1.5 Introduction to the concept of polypharmacy and its associated risks for people with comorbid depression and T2DM

1.5.1 Definition of polypharmacy and relevance to people with comorbid depression and T2DM

Polypharmacy is described by the King's Fund as "the concomitant use of multiple medications by one individual" (157). This is the definition that I shall be adopting for the purpose of my thesis.

The Health Survey for England in 2016 reported that 24% of adults in England are prescribed more than one medication (158). A large survey in England of 7,635 people over the age of 65 found that 49% were prescribed five or more medications (159). The latter survey also found that polypharmacy had quadrupled in the last two decades (159). In T2DM, polypharmacy may be inevitable, with the number of metabolic factors that need to be controlled, plus the number of potential complications that need management. As T2DM progresses, treatment becomes more complex, and thus, polypharmacy levels increase. The addition of depression as a comorbidity can further increase polypharmacy through the use of one, or potentially more, antidepressants (and in more severe cases lithium, anticonvulsants or second-generation antipsychotics).

1.5.1 The concepts of appropriate and inappropriate polypharmacy

Appropriate polypharmacy, for many people, can be essential for extending life expectancy and improving quality of life (160,161). This is particularly the case in people with T2DM who have a number of metabolic factors and/or complications that need to be controlled. Appropriate polypharmacy may also be essential for people with multimorbidity where multiple conditions require pharmacological management (162).

On the other hand, polypharmacy can be problematic when medications are prescribed inappropriately (157). The World Health Organisation (WHO) estimates that more than half of all medicines are prescribed, dispensed or sold inappropriately (163). The UK's Royal Pharmaceutical Society describes four scenarios of inappropriate polypharmacy (164):

1. **Prescribed medicines are no longer appropriate or optimised:**
   Approximately 77% of prescriptions issued in the UK are repeat prescriptions (165). However, in a survey of 1,091 primary care practices in the UK, most revealed that repeat prescriptions were not checked by a clinician (166). For clinicians who did check repeat prescriptions, there was not enough time to do so thoroughly (166). There is also evidence to suggest that patients who are prescribed multiple medications often do not understand why each one is prescribed (167). This may mean that they continue to be prescribed and take medication that they no longer need, or which is no longer appropriate for them. Even when the lack of benefit or potential harm of a medication is realized,

there are still barriers to stopping the inappropriate medication. There may be patient concerns about withdrawal, risk of condition recurrence, impact on other medications, and impact on prescriber relationship (164). Similarly, there may be prescriber concerns about the reaction of the patient or their family from deprescribing (168).

2. **The benefits of prescribed medicines do not outweigh the harms:**
   Adverse drug reactions are a major cause of preventable hospital admissions globally (169). A large study of 18,820 patients admitted to hospital in the North West of England found that 6.5% of these were related to adverse drug reactions, with most of these considered to be preventable (170). Aside from serious adverse reactions that lead to hospitalisation, as I described in **Section 1.2.4** and **Sections 1.3.3-4**, many medications commonly prescribed to people with comorbid depression and T2DM cause side-effects that are potentially uncomfortable, painful or distressing. All medications have both beneficial and harmful effects which must be balanced. It is rare that any medication is effective for a majority of patients (171). One example relevant to people with comorbid depression and T2DM is the use of the medication amitriptyline, although amitriptyline is recommended to treat diabetic neuropathic pain (83), it will fail to provide sufficient pain relief in more than 70% of cases (172). On the other hand, it can commonly cause side-effects of anticholinergic syndrome, drowsiness or QT interval prolongation (173). The extent to which the pain relief benefit experienced from amitriptyline is sufficient to outweigh its harms, may vary according to an individual's tolerability of any side-effects experienced, or according to their risk of harm from a given side-effect. For example, anticholinergic syndrome may be a more serious risk to an older adult who is taking other medications that have anticholinergic effects, as increased anticholinergic burden in older adults can increase the risk of cognitive impairment, falls and mortality (174). In such people, an alternative analgesic medication may be more appropriate. However, the risk-benefit ratio of a given medication is not always immediately apparent. RCTs are the gold standard for evaluating medication benefits and harms. However, the eligibility criteria for such trials usually exclude people for whom the medication would commonly be used, such as older adults, or those with multimorbidity and polypharmacy (175–177). Indeed, NICE guidelines on multimorbidity caution that treatment

recommendations are largely based on evidence from people with single conditions (178).

3. **The combination of medications may cause harm:**
   Interactions between medications can cause unexpected side-effects, or increase or decrease the action of a medication (179). As the number of medications an individual is prescribed increases, the risk of potential drug-drug interactions also increases (180,181). For example, the British National Formulary (BNF) lists 246 individual medications that can interact with the most commonly prescribed antidepressant in the UK, citalopram (182,183). The more medications an individual is prescribed, the more chance they will have of being prescribed medication that interacts. In **Section 1.2.4.** and **Sections 1.3.3-4** I described some of the most common side-effects associated with medications commonly taken by people with comorbid depression and T2DM – these sections clearly demonstrate the potential for cumulative or opposing side-effects. The prescribing of medications that are known to potentially interact occurs when prescribing clinicians do not have time or access to check the other medications that the individual is taking, or where medications are prescribed by different clinicians (184). However, although some medication interactions can be predicted, others may only become apparent after the medication is marketed and interactions have been observed (185).
4. **Practicalities of taking the medication have become unmanageable:** The burden from taking multiple medications can be overwhelming and complex medication regimens confusing, which may lead to non-adherence (186). NICE define adherence to medicines as “the extent to which the patient's action matches the agreed recommendations” (187). A WHO review of adherence to long-term therapies found that 30-40% of people with depression discontinue treatment before the recommended duration and up 85% of people with T2DM regularly did not take their prescribed antidiabetic medication (188). Non-adherence may jeopardise a medication’s effectiveness and lead to worse health outcomes. For example, a study of 11,532 patients with diabetes (type unspecified) found that non-adherence was associated with a 58% increased risk of hospitalisation (OR 1.58, 96% CIs 1.38-1.81) and an 81% increased risk of mortality (OR 1.81, 95% CIs 1.46-2.23) (124). WHO (190) and NICE (191) both declare polypharmacy to be a major risk factor for non-adherence, and

there is some evidence to suggest that the number of medications prescribed is negatively associated with adherence (192,193). Regardless of adherence, a number of studies have found polypharmacy to be associated with worse quality of life (194–196) and depression (197). However, whether this is due to treatment burden, or due to an association with multimorbidity is unclear.

People with comorbid depression and T2DM may be more susceptible to the risks associated with polypharmacy due to an increased likelihood of taking multiple medications at the same time. Depression and T2DM are both long-term conditions, and so, are likely to receive repeat prescriptions. Therefore, they may be at risk of continuing medication that is no longer appropriate, as described above. In **Section 1.2.4.** and **Sections 1.3.3-4** I demonstrated the potential for distressing and potentially dangerous side-effects from medications commonly prescribed to people with comorbid depression and T2DM. The harm of prescribing such medications when there are no longer any benefits is of concern. Furthermore, medications that might be beneficial to relatively healthy participants of clinical trials, may not be appropriate to people with comorbid depression and T2DM, due to drug-disease and drug-drug interactions. People with T2DM already have a high treatment burden which may be made worse by the addition of antidepressants. I described above how high treatment burden may lead to non-adherence. Non-adherence of antidepressant medication jeopardises the successful treatment of depression. Non-adherence to somatic medication jeopardises the successful prevention and treatment of T2DM and its complications. In addition, as I described above, the treatment burden from polypharmacy may worsen depression (197).

As far as I am aware, the relationship between antidepressant treatment, polypharmacy and long-term health outcomes has not been explored in people with comorbid depression and T2DM. This is the research gap that I intend to address in my thesis. In the following section, I identify research priorities in this area.

1.6 Research priorities for antidepressant treatment and polypharmacy in people with comorbid depression and type 2 diabetes

There is increased need for the successful treatment of depression in people with T2DM. However, the risks associated with polypharmacy and the relevant side-effects

from antidepressant medication may make for difficult prescribing decisions. There is a lack of evidence concerning the relationship between antidepressant treatment, polypharmacy and long-term health outcomes in people with comorbid depression and T2DM. This can broadly be addressed with the two overarching research questions:

1) How does polypharmacy influence antidepressant treatment trajectories in people with comorbid depression and T2DM?
2) What is the effect of antidepressant treatment on long-term physical health outcomes in people with comorbid depression and T2DM, who are taking multiple other medications?

In the following sections, I describe these priorities in more detail.

1.6.1 How does polypharmacy influence antidepressant treatment trajectories in people with comorbid depression and T2DM?

Real-world antidepressant prescribing trajectories in people with comorbid depression and T2DM – including starting treatment, stopping treatment, and restarting treatment – could provide important information regarding: inequalities in access to antidepressant treatment, the acceptability of antidepressant treatment, and long-term depression outcomes following antidepressant treatment. I explain these further below in **Sections 1.6.1.1-3**.

1.6.1.1 How do concurrently prescribed medications influence the likelihood of being prescribed an antidepressant for people with comorbid depression and T2DM?

Lack of relevant antidepressant treatment guidelines, increased danger from antidepressant side-effects, and increased risks from polypharmacy make for difficult prescribing decisions in people with comorbid depression and T2DM. Indeed, concern in clinicians of the risks of polypharmacy has been found to lead to under-prescribing (198). It is important to understand whether or not individuals with comorbid depression and T2DM are more likely to be a prescribed an antidepressant according to the concurrent medication they are already prescribed. This could include the individual medications themselves or polypharmacy levels (i.e. the number of different concurrent medications prescribed). This information would highlight whether people with T2DM are being undertreated for depression – for example, if depression was not being treated in people with high levels of polypharmacy. Or, alternatively, whether

they are at increased risk of inappropriate polypharmacy – for example, if antidepressants were being prescribed alongside other medications with which they might interact. I am aware of no studies, prior to my thesis, that investigate this.

1.6.1.2 Does the number of concurrently prescribed medications influence the likelihood of stopping antidepressant treatment before the recommended duration, as a marker of antidepressant acceptability, in people with comorbid depression and T2DM?

In order for antidepressant medication to be effective, NICE guidelines recommend that treatment is continued for 6 months following the initial response (82). In practice, antidepressant treatment is often stopped before the recommended duration (199–201). This may be due to ineffectiveness (lack of beneficial therapeutic action for the individual patient), intolerability (in terms of side effects) and/or patient unwillingness to be treated (due to e.g. overall treatment burden or attitudes towards pharmacological treatment). Lack of adherence to antidepressant treatment guidelines jeopardises the successful treatment of depression. In the meta-analysis by Cipriani et al investigating the effectiveness and acceptability of antidepressant medication in the general population, acceptability is defined as stopping the antidepressant for any reason (77). Thus, stopping antidepressant treatment before the recommended treatment duration can represent antidepressant acceptability, as a combined marker of effectiveness, tolerability and/or non-adherent behaviour. This is the first outcome that I investigate in the original research studies of my thesis.

The simultaneous treatment of both depression and T2DM, in people with comorbid depression and T2DM, is important. However, the use of multiple medications at the same time may increase the risk of drug side effects (184), drug-drug or drug-disease interactions (178–180,184,202), higher treatment burden (184,194–196), and reduced adherence to treatment (186,192,193,203). As such, polypharmacy may impact the acceptability of antidepressant treatment in people with comorbid depression and T2DM. It is important to understand, in people with comorbid depression and T2DM, whether or not higher levels of concurrent medication use reduces the acceptability of antidepressants leading to stopping treatment before the recommended duration. If this is true, polypharmacy could jeopardise the potential reduction of depression symptoms from antidepressant treatment in people with comorbid depression and T2DM.

1.6.1.3 Does the number of medications concurrently prescribed to people with comorbid depression and T2DM influence the likelihood of restarting antidepressant treatment as a marker of clinically identified depression relapse? And does this differ according to the previous duration of antidepressant treatment?

Depression is often chronic, with many patients experience disabling sub-syndromal symptoms for several years, or multiple relapses or recurrences of depression after having initially recovered from an episode (204–206). Depression relapse can be defined as the return of depression symptoms within the expected duration of the current episode of depression (up to 12 months) (207). In the general population, almost half of people who stop antidepressant treatment subsequently relapse (207). Evidence shows that the risk of depression relapse during the course of antidepressant treatment is increased in people with a higher burden from physical comorbidities (208). One type of burden from multimorbidity can come from polypharmacy. The use of five or more medications has been found in systematic review to be associated with a 73% higher risk of depression (OR = 1.73 (95% CIs 1.39-2.14) (197). Therefore, polypharmacy may place people at higher risk of depression relapse due to the burden of living with multiple long-term conditions and taking complex medication regimes (209), or the potential adverse effects of the medications themselves and interactions between them (180,202). The effect of polypharmacy on depression relapse specifically in people with comorbid depression and T2DM is unknown.

In the general population, individuals who discontinue antidepressant treatment are 2.1 times more likely to experience depression relapse compared to those who continue treatment (207). However, the optimum duration of treatment for the prevention of depression relapse is unknown. NICE guidelines recommend longer durations of antidepressant treatment – at least 2 years – in people with higher risk of relapse (82). The guidelines do not define who might be included in this higher risk of relapse group. If individuals with comorbid depression and T2DM who are prescribed higher numbers of concurrent medications are at higher risk of relapse compared to those prescribed lower numbers of concurrent medications, then these individuals may benefit from longer durations of antidepressant treatment. On the other hand, there have been a number of systematic reviews of RCTs in the general population, that show that people who discontinue antidepressants are more likely to relapse than

those who remain on antidepressant treatment (210–212). As such, the optimum duration of antidepressant treatment to prevent depression relapse in individuals with comorbid depression and T2DM who are taking multiple medications and may be at high risk of depression relapse, is unknown.

It is important to understand whether polypharmacy renders people with comorbid depression and T2DM at higher risk of depression relapse so that these individuals can receive enhanced support. It is also important to understand whether longer durations of antidepressant treatment would benefit people with comorbid depression and T2DM who have higher levels of polypharmacy. This is the second outcome that I investigate in the original research studies of my thesis.

1.6.2 What is the effect of antidepressant treatment on long-term physical health outcomes in people with comorbid depression and T2DM, who are taking multiple other medications?

Both depression and T2DM are long-term conditions. Many adverse physical health outcomes in T2DM can take a long time to occur. Overtime, uncontrolled blood sugar levels in people with T2DM cause damage to many of the body's systems. Therefore, understanding factors that influence long-term glycaemic control in people with comorbid depression and T2DM is important. Ultimately, both depression and T2DM can result in premature mortality. Understanding factors that increase or reduce premature mortality is therefore also important.

1.6.2.1 What is the effect of antidepressant treatment on long-term glycaemic control in people with comorbid depression and T2DM?

The primary goal of diabetic management is to control blood glucose levels, with significant evidence that doing so reduces the risk of developing complications (85). As such, the long-term management of blood glucose levels is crucial to preventing diabetic complications and worsening physical health. Antidepressants have been shown to have a small effect on improving glycaemic control in the short term (155). However, the effect of antidepressant treatment on long-term glycaemic control is unknown. Depression is a chronic and often recurring condition, and so, many people with depression may receive antidepressant treatment for long durations (an estimated 90% of antidepressant prescriptions in UK primary care are chronic (213)). It is

important to understand the long-term effect of antidepressant treatment on glycaemic control in people with comorbid depression and T2DM.

There are a small number of studies investigating the association between antidepressant treatment and long-term glycaemic control. These studies have conflicting findings. A large cohort study in Taiwan of 26,746 people with diabetes (type unspecified) and depression found that long-term antidepressant use prior to baseline was associated with a reduction in hyperglycaemic crisis episodes over time (214). Conversely, a cross-sectional study of 5,592 people in the Netherlands found that people who were prescribed SSRIs were more likely to also be prescribed insulin (suggesting worse glycaemic control) compared to those who were not prescribed SSRIs (215). Another study investigating reports listed in the WHO Adverse Drug Reaction database found that antidepressants were associated with both hyperglycaemia and hypoglycaemia (216). Thus, the effect of antidepressant medication on long-term glycaemic control in individuals with comorbid depression and T2DM remains unclear.

If antidepressants improve glycaemic control in the long-term, this could be an effective intervention to prevent the decline of diabetic health in people with comorbid depression and T2DM. On the other hand, if antidepressants are associated with worse long-term glycaemic control, issues of safety may need to be investigated. Long-term glycaemic control is the third outcome that I investigate in the original research studies of my thesis.

1.6.2.2 What is the effect of antidepressant treatment on mortality in people with comorbid depression and T2DM?

In 2019, diabetes (type unspecified) was the eighth leading cause of death globally, affecting 1.55 million people (217). Cardiovascular disease, which can be caused by T2DM, was the leading cause of death globally, affecting 18.56 million people (217). Suicide was the fifteenth leading cause of death, affecting 759,028 people (217). The reduction of preventable mortality in people with comorbid depression and T2DM is a serious unmet need.

The evidence concerning the association between antidepressant treatment and mortality in people with comorbid depression and T2DM is sparse and conflicting. There are two studies that investigate the impact of antidepressant treatment on all-

cause mortality in people with comorbid depression and diabetes. The first, including 155,647 male veterans in the USA with T2DM, found that antidepressant treatment had no impact on the association between depression and mortality (218). The second, a Taiwanese population-based study including 53,412 people with comorbid depression and diabetes (type unspecified), found that most antidepressants significantly reduced mortality rates (219). I am aware of no studies that investigate the association between antidepressant treatment and cause-specific mortality.

Depression can lead to suicide. It is known to be associated with worse diabetic health outcomes (220,221) and with non-suicide premature mortality (13). Therefore, if antidepressants successfully treat depression in people with comorbid depression and T2DM, they should also decrease rates of mortality. In the general population, a protective effect of antidepressants on suicide has also been observed (222).

However, antidepressants can cause a number of side effects that can be dangerous to people with comorbid depression and T2DM. These include weight gain (153), hypoglycaemia and cardiac complications (154).

It is important to understand the association between antidepressant treatment and mortality specifically in people with comorbid depression and T2DM. If antidepressants are protective against mortality through the successful treatment of depression, improving access to antidepressant treatment could be an effective intervention to reduce preventable mortality in this patient group. If antidepressants increase the risk of mortality, potential issues of safety or unmet patient need would need to be further investigated. Cause-specific mortality is the fourth outcome that I investigate in the original research studies of my thesis.

1.7 Limitations of randomised controlled trials to explore outcomes of antidepressant treatment and polypharmacy in comorbid depression and type 2 diabetes

"At its best a trial shows what can be accomplished with a medicine under careful observation and certain restricted conditions. The same results will not invariably or necessarily be observed when the medicine passes into general use."

– Austin Bradford Hill, 1984

RCTs are the gold standard for evaluating medication efficacy and safety. However, they are not necessarily optimal for evaluating outcomes of “real-world” medication use in complex populations. Studies using electronic health record (EHR) data may usefully augment RCTs and fill some gaps in our understanding of the relationship between depression, T2DM and their drug treatments. This is the approach I take for the original research studies included in my thesis.

1.7.1 Exclusion of complex populations in RCTs

RCTs are the gold standard for evaluating medication outcomes and often have strict inclusion criteria, thereby enabling case definition and intervention effect certainty. However, the strict inclusion criteria also often excludes complex populations with comorbidities and concurrent polypharmacy (223,224).

Eight out of the eleven RCTs included in the Cochrane review of antidepressant treatment in people with comorbid depression and T2DM had inclusion criteria available to access in the English language (155). Of these:

- All excluded the most severe cases of depression (225–233);
- Six of the eight excluded people taking certain commonly prescribed medications (225–227,229,231,232);
- Six of the eight excluded people with common diabetic complications/comorbidities (225–228,231,232).

Thus, RCTs of antidepressant efficacy in comorbid depression and T2DM have not been representative of this patient group who commonly have diabetic complications, comorbidities and polypharmacy, and are more at risk of severe depression. Subsequently, the results of such trials may only be applicable to the healthiest people with comorbid depression and T2DM, with earlier stage T2DM and milder depression.

1.7.2 Understanding “real-world” antidepressant prescribing

Predefined interventions and end-points prevent RCTs from investigating real-world medications use, where decisions to start and stop medications, as well as the choice between different pharmaceutical agents, depend largely on clinician and patient preference (223,224,234). Sociodemographic characteristics, such as gender (235), age (236), ethnicity (237), cultural taboos (238), language barriers (238), deprivation (239) and physical health status (239), may impact “real-world” help seeking behaviour

or access to treatment. In addition, clinician and primary care practice characteristics, such as clinician gender, age and training; or practice location, size and proportion of elderly patients, have been shown to impact the choice of pharmaceutical agent prescribed (234). Reasons for stopping medication in clinical trials may be different to those in clinical practice. For example, a participant in an RCT may be more likely to continue a medication that is not effective due to altruism, increased health monitoring and/or motivation from trial staff (240). If a medication is not effective or is intolerable, in clinical practice a patient may switch to an alternative pharmaceutical agent (82) – this may not be available or captured in an RCT. Thus, RCTs are not appropriate for investigating "real-world" antidepressant prescribing patterns.

1.7.3 Limited follow-up times in RCTs

The follow-up times of the RCTs included in the Cochrane review of antidepressant treatment in people with comorbid depression and T2DM ranged from three weeks to six months (155). I explained the importance of understanding what affects long-term physical and mental health outcomes in people with comorbid depression in **Section 1.6.2-4**. RCT follow-up times typically do not allow enough time for long-term outcomes to develop. It is rarely feasible to continue clinical trials for longer follow-up periods due to attrition and high costs (223,224). RCTs are often funded by pharmaceutical companies with the aim of demonstrating the efficacy of their product, therefore, such RCTs typically focus on short-term efficacy and safety (223). As such, study designs that are better suited to longer follow-up periods are required to investigate long-term outcomes.

1.7.4 Small sample sizes

The sample sizes of the RCTs included in the Cochrane review on antidepressant treatment in people with comorbid depression and T2DM ranged from 15 to 89 participants (155). People with comorbid depression and T2DM are a complex and heterogeneous patient group – there are many combinations of complications, comorbidities and polypharmacy regimens that it would not be possible to represent or have the statistical power to investigate as either direct exposures or confounding factors in small samples (241). Thus, larger sample sizes are required to explore outcomes of antidepressant treatment and polypharmacy in individuals with comorbid depression and T2DM.

1.7.5 The use of electronic health record data to overcome the limitations of RCTs to explore outcomes of antidepressant treatment and polypharmacy in people with comorbid depression and T2DM

EHRs record information on health problems, investigations and treatments as they occur in day-to-day clinical practice. Each patient that comes into contact with a health service will have a record that contains information about them and each encounter with the service. Their main purpose is for the case management of patients in clinical practice. It is estimated that approximately 98% of people in the UK are registered with a primary care practice (242,243). Each of these will have a primary care EHR record that contains longitudinal information on their medical history within primary care. Most depression (74) and T2DM (244) cases in the UK are treated through primary care, which includes the issuing of medication prescriptions. Therefore, primary care EHRs contain rich information concerning "real-world" prescribing patterns and outcomes for people prescribed antidepressants and other concurrently prescribed medications. Pseudonymised extracts of EHR data can be shared with researchers, making it easier to access large-scale, longitudinal clinical data for research. In addition, EHR studies do not require expensive and time consuming participant recruitment and data collection.

In my thesis, I will explore outcomes of antidepressant treatment and polypharmacy, as they occur in the "real world" in people with comorbid depression and T2DM. For the original research studies included in my thesis, I will use UK-based primary care EHR data from the Clinical Practice Research Datalink (CPRD). I discuss this data source in detail in my **Methods Chapter 3**.

In the following section, I set out the aims and objectives addressed by my thesis.

1.8 Aims of my thesis and objectives of the studies included in my thesis

My thesis includes two overarching aims, with three objectives in each aim, informed by the evidence gaps outlined above:

Aim 1: In people with comorbid depression and T2DM, to explore differences in antidepressant prescribing trajectories according to concurrent medication prescribing:

Objective 1: To perform a systematic review of existing observational literature reporting the prevalence of antidepressant prescribing in people with comorbid depression and T2DM, and whether concurrent medication prescribing effects the likelihood of receiving an antidepressant in this patient group.

Objective 2: To perform a UK-based EHR study examining whether the number of concurrent medications prescribed to people with comorbid depression and T2DM at the time of starting antidepressant treatment increases their risk of stopping antidepressant treatment before the recommended treatment duration.

Objective 3: To perform a UK-based EHR study examining whether the number of concurrent medications prescribed to people with comorbid depression and T2DM at the time of stopping antidepressant treatment increases their risk of subsequently restarting antidepressant treatment, and whether this differs by the previous duration of antidepressant treatment.

Aim 2: In people with comorbid depression and T2DM, to explore the association between antidepressant treatment and long-term physical health outcomes:

Objective 4: To perform a systematic review of existing observational literature comparing long-term physical health outcomes in people with comorbid depression and T2DM who were treated with antidepressants compared to those who were not treated with antidepressants.

Objective 5: To perform a UK-based EHR study examining whether people with comorbid depression and T2DM who were prescribed antidepressants were more likely to subsequently start insulin, as a marker of the long-term decline in diabetic health, compared to those who were not prescribed antidepressants.

Objective 6: To perform a UK-based EHR study examining whether people with comorbid depression and T2DM who were prescribed antidepressants had higher rates of all-cause and cause-specific mortality than those who were not prescribed antidepressants.

Chapter 2: Systematic Reviews of the Prevalence and Long-term Outcomes Associated with Antidepressant Treatment in People with Comorbid Depression and Type 2 Diabetes

Modified versions of the studies included in this chapter are published as:

Jeffery A, Maconick L, Francis E, Walters K, Wong ICK, Osborn D, Hayes JF. Prevalence and characteristics of antidepressant prescribing in adults with comorbid depression and type 2 diabetes mellitus: A systematic review and meta-analysis. Health Sci Rev (Oxf). 2021;1. doi: 10.1016/j.hsr.2021.100002

And preprinted as:

Jeffery A, Buckman JEJ, Francis E, Walters K, Wong ICK, Osborn D, Hayes JF. A Systematic Review of Long-term Antidepressant Outcomes in Comorbid Depression and Type 2 Diabetes. medRxiv 2022.04.11.22273519; doi: https://doi.org/10.1101/2022.04.11.22273519.

2.1 Introduction

In this chapter, I describe the two systematic reviews that I did summarising existing evidence from observational studies to answer the following questions in people with comorbid depression and T2DM:

i) What is the prevalence of antidepressant prescribing? And does concurrent medication prescribing effect the likelihood of receiving an antidepressant prescription?

ii) What are the long-term outcomes associated wii antidepressant treatment?

I used one search strategy for both systematic reviews, separating articles by research question at the screening stage. For this reason, I report the two reviews together in this chapter. In the sections below, I explain why it was necessary to perform these two reviews as part of my thesis.

2.1.1 Systematic review 1: What is the prevalence of antidepressant prescribing? And does concurrent medication prescribing effect the likelihood of receiving an antidepressant prescription?

In **Chapter 1.4**, I explained that people with comorbid depression and T2DM have increased need for the successful treatment of depression. However, as I explained in **Chapters 1.4-5**, the lack of specific treatment guidelines, side-effects of antidepressant medication and risks associated with polypharmacy make for difficult prescribing decisions. The effect that concurrent medication prescribing has on the likelihood of being prescribed an antidepressant in people with comorbid depression and T2DM is currently unknown. There are no other systematic reviews that report the prevalence of antidepressant prescribing in people with comorbid depression and T2DM, or factors that are associated with antidepressant prescribing.

This systematic review addresses the first aim of my thesis – to explore differences in antidepressant prescribing trajectories according to concurrent medication prescribing.

2.1.2 Systematic review 2: Long-term health associated with antidepressant treatment

Depression and T2DM are both long-term conditions that may require long-term treatment. However, as I described in **Chapter 1.4**, the maximum duration of any previous study investigating antidepressant treatment in this patient group was 6 months (155,156,245). This time frame is not sufficient for many long-term outcomes to develop.

RCTs typically have short follow-up times, as they are usually designed to evaluate initial treatment response (223). Observational studies, therefore, may be better suited to finding evidence for long-term outcomes (224). Two of the three previous systematic reviews investigating antidepressant treatment in T2DM only included RCTs in their search (155,245). The third systematic review, by Roopan et al (156) included “other study designs”. However, they did not specify which study designs were included and they only searched clinical trial databases. Roopan et al found one observational study (246) using routinely collected data over a period of 11 years, which found long-term antidepressant treatment (3+ years) to be associated with higher risk of

hypoglycaemia. However, it was not a requirement for participants to be diagnosed with depression or present with depressive symptoms, and the reason for prescribing the antidepressants were unknown. In addition, I described a number of relevant observational studies in **Chapter 1.6.2** that would have met Roopan et al's inclusion criteria. This demonstrates the limitations of the databases searched for identifying observational studies.

Thus, there is the need for an up to date systematic review with a wider search of observational studies investigating the association between antidepressant treatment and long-term health outcomes in individuals with comorbid depression and T2DM.

This systematic review addresses the second aim of my thesis – to explore the long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM.

2.2 Methods

I performed two systematic reviews in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA), and registered the reviews on PROSPERO prior to the commencement of screening (CRD42020182581 and CRD42020182788, respectively). The search and first stage of screening (title and abstract) were undertaken together for both reviews, with studies for inclusion under each research question separated for full text screening. Quality checks were performed by the following collaborators: Emma Francis (title and abstract screening; both reviews), Lucy Maconick (full text screening, data extraction, risk of bias analysis, and meta-analysis calculations; first review), Josh Buckman (full text screening; second review). If disagreements arose, these were resolved by consensus, or by consulting PhD supervisor, Joseph Hayes.

2.2.1 Study inclusion criteria

2.2.1.1 Types of study

For both reviews I included observational studies including cohort studies, case-control studies, case series and cross-sectional studies. I excluded RCTs, quasi-experimental trials where patients receive an antidepressant as part of the study, systematic reviews, case studies/reports, editorials, letters and opinion pieces.

Observational studies do not prescribe the intervention (i.e. antidepressant treatment) as part of the study, and so, are an appropriate design to investigate real-world prescribing patterns.

Where more than one study used data from the same dataset, I included the study with the most generalisable population, larger sample size (as larger sample sizes allow for more precise effect estimates (247) and lowest risk of bias.

2.2.1.2. Patient inclusion criteria

For both reviews I included studies investigating adults (18+ years) with comorbid depression and T2DM.

Depression could be identified by clinician diagnosis, medical record, standardised interview, or self-report. Where diagnostic criteria were not available, I used the authors' definition of depression, provided depression was explicitly stated for all participants or the subgroup being used for analysis. I did not include studies where definition of depression was the prescription of an antidepressant alone (as antidepressant prescribing was either the outcome or the intervention of interest).

Type 2 diabetes could be defined as an in-study clinician diagnosis, medical record, or self-report. The type of diabetes should have been explicitly verified as type 2, and I did not include studies where the diabetes type was ambiguous or mixed.

2.2.1.3. Comparison group

For both reviews I used people with depression and T2DM who received no antidepressant prescription as the comparison group.

2.2.1.4. Outcome and exposures for the first review on the prevalence of antidepressant prescribing and effect of concurrent medication prescribing

For the first review, investigating the prevalence of antidepressant treatment in people with comorbid depression and T2DM, the outcome of interest was the prescription of any antidepressant medication. I included studies where the prevalence of antidepressant prescribing could be calculated, as the proportion of total participants with comorbid depression and T2DM who received any antidepressant prescription.

The exposure was concurrent medication prescribing. I extracted any information on concurrent medication use or prescribing where these could be compared between

people who did and did not receive an antidepressant prescription. This could include treatment with a specific medication, or medication class, or a count of the number of medications prescribed.

2.2.1.5 Exposure and outcomes for the second review investigating long-term outcomes associated with antidepressant treatment

For the second review, investigating long-term outcomes associated with antidepressant treatment, the exposure of interest was the prescription of any antidepressant medication. As the review focused on long-term outcomes, I required a minimum antidepressant treatment duration of 7 months, which is recommended by NICE as the minimum course of treatment required for effectiveness (6 months following response, which may take 4-6 weeks) (82). I included antidepressant prescriptions defined through self-report, prescription records or clinician report. I excluded antidepressant prescriptions explicitly indicated for conditions other than depression. I defined antidepressant medication as any medication listed in BNF Chapter 4.3 (248) or ATC Chapter N06A (249).

The outcome of interest was any long-term outcome occurring after a minimum follow-up time of 7 months. This time frame was specified as existing reviews already covered follow-up times up to 6 months. I did not limit the potential outcomes that could be measured in association with antidepressant treatment. These could include: depression severity, remission, relapse or recurrence; glycaemic control or other markers of diabetic health; diabetic comorbidities; other measures of physical morbidity; mortality; health service utilization and costs; quality of life; socio-economic outcomes; patient reported outcomes.

2.2.2 Search strategy

I used the same search strategy for both reviews. This enabled me to perform one search. I then separated studies into the two separate reviews according to the research question for full text screening.

I used the following sources from inception to 10-May-2021 for the identification of studies:

- MEDLINE
- EMBASE

- Scopus
- CINAHL Plus
- Web of Science
- PsychInfo
- PsycExtra
- Open Grey

I identified four search domains from the research questions:

1) Depression;

2) T2DM;

3) Antidepressants;

4) Observational study.

I did not include the exposures related to concurrent medication prescribing from the first review and the long-term outcomes from the second review in the search domains. This was because I did not want to limit inclusion of the studies to particular medication exposures or long-term outcomes. I did not use a search domain for “long-term”, as I considered that studies investigating different long-term durations would not specifically use this, or similar searchable phrases. Thus, the search domains that I identified enabled me to combine the search and first stage of screening for both reviews.

I established synonyms and related words for each domain, and then mapped these to appropriate medical subject headings (MeSH) for each database. For the antidepressants domain, I included drug classes such as “SSRI” (in full and abbreviated) and drug names such as “fluoxetine”. I also included free text search terms for each term, using wildcards for spelling variations and truncation. I included brand names such as “Prozac” in the free text search terms. I validated my choice of search terms by checking terms used in the existing systematic reviews concerning antidepressant treatment in people with T2DM (155,156,245) and wider systematic reviews for separately for each domain of depression (250,251), T2DM (252), antidepressants (77,253) and observational studies (254). Full search terms are included in Appendix A. I separated terms within domains using “OR” and between domains using “AND”.

I accepted articles in the following languages: English, French, Spanish, Italian, Portuguese, Greek.

In addition, I reviewed references of all studies screened at full text stage and all relevant systematic reviews found during the search.

2.2.3 Data screening and extraction

I entered details of all identified studies into one Excel spreadsheet and screened these for eligibility in two stages. In the first stage, I screened the title and abstracts (where required), and categorised studies according to whether they were eligible for inclusion in the first review, the second review, or both. I then prepared two Excel spreadsheets with the potentially eligible studies for each review separately. I screened the full texts of the studies included in each spreadsheet to confirm their eligibility for inclusion in each review. At each stage of screening, 100% of articles were independently screened by a second reviewer.

For each review, I designed a separate Excel spreadsheet for data extraction. Both spreadsheets included the following: study design/setting, study population, study aim, study size, country, case definition, demographics (age, gender, ethnicity, education), depression severity, how antidepressant prescribing was defined, antidepressant prescription prevalence, medication, proportion of people treated with insulin.

For the first review (concerning the prevalence of antidepressant prescribing and concurrent medication exposure), I also included details of concurrent medication exposure in the spreadsheet.

For the second review (concerning long-term outcomes associated with antidepressant use) I also included any details of long-term outcomes in the spreadsheet.

2.2.3 Risk of bias

I used an adapted version of the Newcastle-Ottawa Scale (255) to assess the risk of bias for each study. I adapted the scale by combining criteria from both the cohort and case-control scales, to be generically appropriate for the design of the included studies (included in Appendix B). I decided not to exclude studies with higher risk of bias from

the meta-analysis due to the strict inclusion criteria of the review; however, I considered the risk of bias in the interpretation of the results.

2.2.4 Statistical analysis

For the first review:

I calculated prevalence estimates and 95% CIs based on the percentage of eligible participants who were reported as having been prescribed an antidepressant. For the effect of concurrent medication exposures on the likelihood of being prescribed an antidepressant, I extracted the odds ratio (OR) and 95% CIs. Where measures of effect were not included in the paper, if possible, I calculated these from the data provided.

Where three or more studies that were sufficiently similar reported the same exposure of interest, I conducted random effects meta-analyses for each exposure to calculate a pooled effect size with 95% confidence intervals. Otherwise, I synthesised the results narratively.

I assessed statistical heterogeneity by visual inspection of forest plots and by the I^2 statistic quantifying inconsistency across studies, where $I^2 > 75\%$ indicates considerable inconsistency (256). Where I found considerable heterogeneity between studies, I performed sensitivity analyses, stratifying by study design, case and outcome identification, population setting, country and year.

I did not perform any analysis for the second review – I discuss reasons for this below in my **Results Section 2.3**.

2.3 Results – study inclusion and exclusion

My search yielded 14,389 unique abstracts. For the first review, concerning the prevalence of antidepressant prescribing, I assessed 96 full-text articles for eligibility, and selected seven for inclusion in the review (257–263). For the second review, concerning the long-term outcomes associated with antidepressant prescribing, I assessed 64 full-text articles for eligibility. However, I found no studies that met my inclusion criteria. A PRISMA flow chart of study inclusion and reasons for exclusion is shown in **Figure 2.i.**

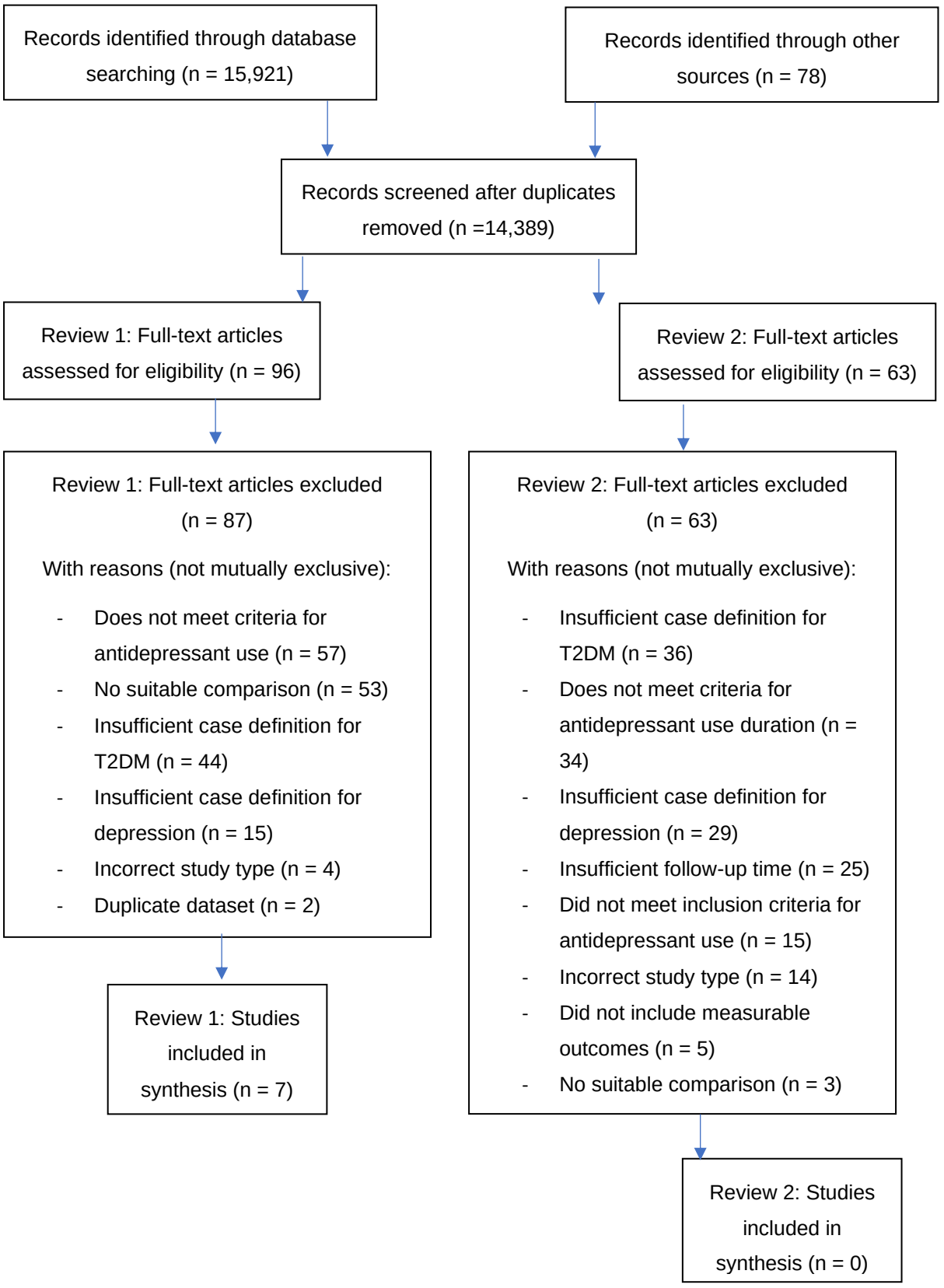
2.4 Results – first systematic review investigating the prevalence of antidepressant prescribing and the effect of concurrent medication prescribing on the likelihood of being prescribed an antidepressant in people with comorbid depression and T2DM

2.4.1 Description of included studies

I included 7 studies with a total of 13,674 participants. I report a summary of study characteristics and exposures in **Table 2.i** and a summary of participant characteristics in **Table 2.ii**.

Two studies were retrospective EHR cohort studies (258,260) and one study was a cross-sectional analysis of insurance claims data (261). All three of these identified depression and T2DM through clinical coding and antidepressant exposure through prescriptions data. One study was a prospective cohort study that identified depression using a validated symptom scale questionnaire and T2DM through clinical diagnosis; however, the identification of antidepressant exposure was unclear (263). Two studies were cross-sectional surveys that identified depression using a validated symptom scale questionnaire; one of these identified both T2DM and antidepressant exposure through self-report (257); the other identified T2DM through linkage to medical records, however, their method of identification of antidepressant exposure was unclear (262). The final study was a secondary analysis of a diabetes education programme evaluation; they identified depression through self report, however, the method of identification of T2DM and antidepressant exposure was unclear (259).

Figure 2.i PRISMA flow chart of study inclusion and reasons for exclusion



All participants were community dwelling, with average ages ranging from 45 – 64. All studies were set in populations from the USA, with the exception of the prospective cohort study which was Australian (262). All studies had higher numbers of female compared to male participants, except one of the EHR studies which included only male veterans (260). All studies, with the exception of the study using insurance claims data, reported ethnicity (261). The proportion of individuals of black and minority ethnicities (BME) ranged from 14.8-60.0%. The studies with the lowest prevalence of people from BME were the EHR study including veterans (260) and the study including people from the diabetes education programme (259). The study with the highest prevalence of people from BME was the prospective cohort study which specifically aimed to investigate differences in antidepressant prescribing according to ethnicity (262).

Only the cross-sectional surveys (257,262) and the prospective cohort study (263) reported depression severity. These studies all included people whose depression severity ranged from mild to severe. However, only one of the cross-sectional studies accounted for depression severity when estimating the prevalence of antidepressant prescribing (262). Only three studies reported information on educational attainment (257,259,263). The proportion of people included in these studies who had not completed high school ranged from 10-13.6%.

Six studies reported the proportion of individuals being prescribed insulin (257–259,261–263). Only the EHR study of male veterans did not report this (256). The study using insurance claims data excluded people who were prescribed insulin (261). Within the other studies, the proportion of people who were prescribed insulin ranged from 20%-55.4%. The studies with the highest rates of insulin prescribing (where this was reported and not excluded) were those that used medical record data (258,262). Only three of the studies that reported the rates of insulin prescribing, did so stratified by people who did or did not receive an antidepressant (257–259). These three were included in my meta-analysis in **Section 2.3.3** investigating the effect of concurrent medication prescribing on the likelihood of being prescribed an antidepressant in people with comorbid depression and T2DM.

Risk of bias scores ranged from 0 to 5 out of 7, with 0 being highest risk of bias. The EHR and claims data studies had the lowest risk of bias, whilst the secondary analysis

of the diabetes education programme had the highest risk of bias. I report a risk of bias summary in **Figure 2.ii**.

Table 2.i Design of included studies

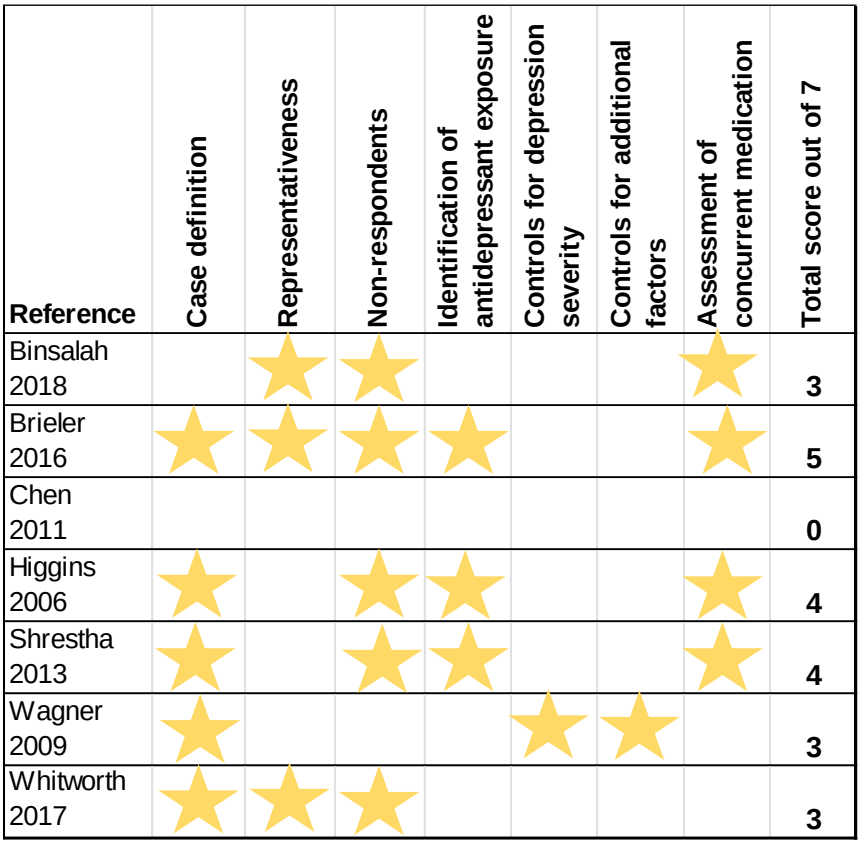
Reference	Study Design/Setting	Study Aim	Study Size	Case definition	Identification of antidepressant	Polypharmacy exposures
Binsalah 2018 (257)	NHANES cross-sectional survey; home interviews and research centre assessment	Evaluate association of antidepressants with healthcare utilization	955	PHQ-9; self-reported T2DM	Self-report	Insulin use vs oral antidiabetics
Brieler 2016 (258)	Retrospective cohort study; electronic medical records	Evaluate association of antidepressants with glycaemic control	265	ICD codes	Prescription	Insulin use vs oral antidiabetics
Chen 2011 (259)	Secondary analysis of programme evaluation; data recorded by diabetes educator	Evaluate association of depression and antidepressants on goal setting	271	Self-reported depression; T2DM unclear	Unclear	Insulin use
Higgins 2006 (260)	Retrospective cohort study; electronic medical records	Evaluate association of heart disease with depression and the impact of antidepressants	691	ICD codes	Prescription	None
Shrestha 2013 (261)	Cross-sectional; insurance claims	Evaluate association of depression and excess medical expenditures	10,881	Primary/secondary inpatient or outpatient encounters	Prescription	None
Wagner 2009 (262)	Cross-sectional; phone interviews and research centre assessment	Evaluate association of ethnicity and depression treatment	56	PHQ-9; ICD code or prescription for T2DM	Unclear - possible self-report	None
Whitworth 2017 (263)	Prospective cohort study; research centre assessment	Describe the long-term trajectories of depression symptom severity and associates of these trajectories	178	PHQ-9; clinical diagnosis	Unclear - possible self-report	None

Table 2.ii Participant characteristics in included studies

Reference	Study population	Country	Age (years)*	Female %	Ethnicity	Education	Depression severity	Insulin treated %
Binsalah 2018 (257)	Community dwelling	USA	58 ± (12-13)	66.1	Black (17.8%); Hispanic (17.1%); other (6.5%); white (58.6%)	< high school 10.8%	Mild (60.6%); moderate-severe (39.4%)	20.0%
Brieler 2016 (258)	Community dwelling; urban location	USA	61-62 ± (11-12)	72.8	White (51.3%)	Not available	Not available	40.4%
Chen 2011 (259)	Community dwelling; in diabetes education programme	USA	55-57	72	BAME (14%); white (85.2%) [study reporting is missing 0.8%]	< high school 10%; > high school 41%	Not available	29.5%
Higgins 2006 (260)	Community dwelling military veterans	USA	42% > 60	0	White (85.2%)	Not available	Not available	Not available
Shrestha 2013 (264)	Community dwelling; with employee insurance; not taking insulin	USA	51.3-52.2	56.7	Not available	Not available	Not available	0%
Wagner 2009 (262)	Community dwelling; with private insurance; urban location	USA	55.7 ± 7.2	56.6	White (40%)	Not available	Mean PHQ-9 = 11	55.4%
Whitworth 2017 (263)	Community dwelling	Australia	58-63 ± (11-12)	56.7	White (51.1%)	< high school 13.6%	Mild (49.4%); moderate-severe (50.6%)	29.7%

* Age when in format "a ± b" is mean and standard deviation; otherwise most common range given

Figure 2.ii Risk of bias summary for studies included in review on the prevalence of antidepressant prescribing in people with comorbid depression and T2DM



Reference	Case definition	Representativeness	Non-respondents	Identification of antidepressant exposure	Controls for depression severity	Controls for additional factors	Assessment of concurrent medication	Total score out of 7
Binsalah 2018		★	★				★	3
Brieler 2016	★	★	★	★			★	5
Chen 2011								0
Higgins 2006	★		★	★			★	4
Shrestha 2013	★		★	★			★	4
Wagner 2009	★				★	★		3
Whitworth 2017	★	★	★					3

Stars represent 1 point towards the total score, where studies met the criteria to have low risk of bias in each category. The higher the total score, the lower the risk of bias.

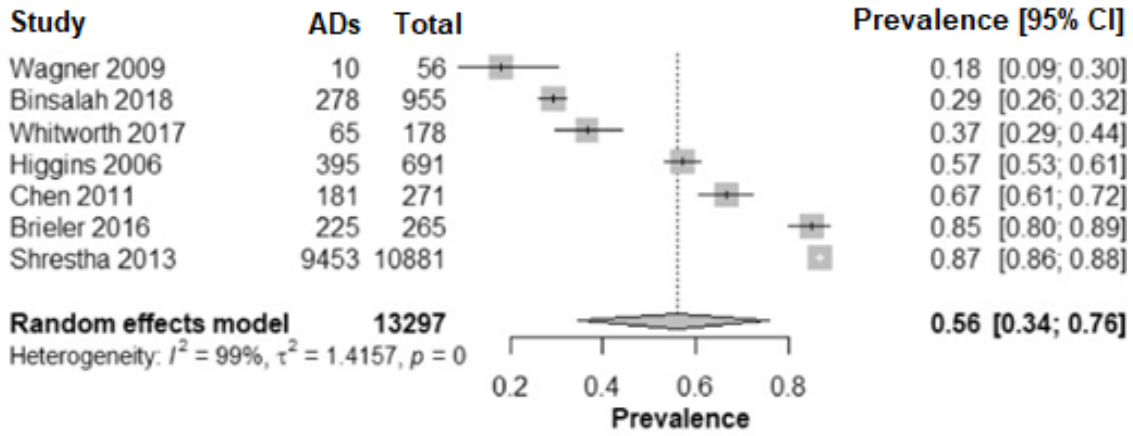
Case definition, ascertainment of exposure and assessment of outcome all accepted in-study clinician diagnosis, validated questionnaires, medical records or prescriptions as meeting the criteria for low risk of bias.

Self-report or no description did not meet the criteria for low risk of bias. Studies were considered to meet the criteria for low risk of bias if they made a reasonable attempt to manage non-respondents and described this.

2.4.2 Prevalence of antidepressant prescribing in people with comorbid depression and T2DM

There was considerable variation in the prevalence of antidepressant prescribing across studies, which ranged from 18% - 87%. The pooled prevalence estimate from the random effects meta-analysis was 56% (95% CIs 34 – 76%), however, statistical heterogeneity was considerable, at I^2 = 99% (**Figure 2.iii**). I performed sensitivity analyses according to study design, case and outcome identification, population setting, country and year. Three studies identified depression through clinical coding in EHR or insurance records – two of these studies had the highest prevalence rates of antidepressant prescribing at 85% and 87% (258,261); the third had a lower prevalence rate of 57%, however, this was recorded in a population of all-male military veterans (256). The three studies with the lowest prevalence rates of antidepressant prescribing, ranging from 18% to 37% all identified depression as part of the research study either through self-administered questionnaires or self-report (257,262,263). When combined in meta-analysis, these studies gave a pooled antidepressant prevalence estimate of 29% (23% – 37%) and I^2 of 62%.

Figure 2.iii Forest plot for the results of the random effects model meta-analysis of the prevalence of antidepressant prescribing in adults with comorbid depression and T2DM



ADs = number of people prescribed an antidepressant

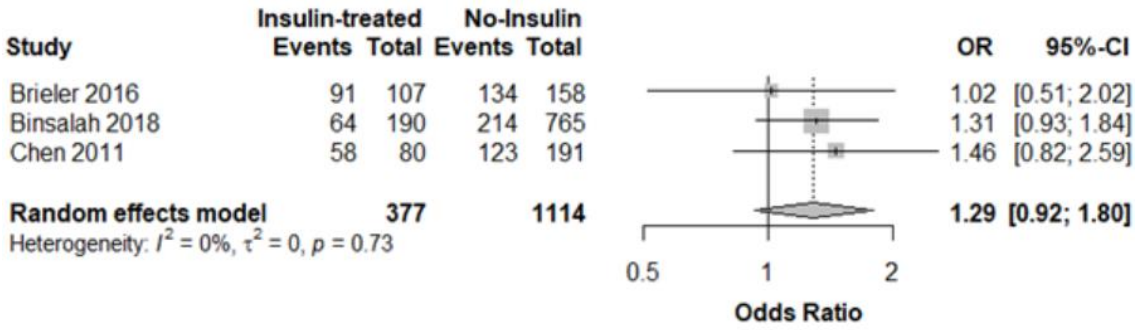
2.4.3 Concurrent medication prescribing associated with antidepressant prescribing in people with comorbid depression and T2DM

Three studies reported the prevalence of antidepressant use in participants who were treated with insulin, compared to those who were not (257–259). None of the studies showed evidence of a difference in the odds of being prescribed an antidepressant in participants with insulin controlled T2DM, with a pooled OR estimate of 1.29 (95% CIs 0.92-1.80) (**Figure 2.iv**). There was no evidence of statistical heterogeneity between studies (I^2 of 0%).

One study reported antidepressant prevalence in those prescribed oral antidiabetic medication compared to those not prescribed any antidiabetic medication, with no evidence of a difference (258).

No studies reported if there were differences in antidepressant prescribing because of other medications prescribed, other than antidiabetic medications described above.

Figure 2.iv Forest plot for the results of the random effects model meta-analysis of the association between insulin use and antidepressant prescribing in adults with comorbid depression and T2DM



2.5 Results – second systematic review investigating the long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM

I found no studies that found that met my inclusion criteria for this review.

2.5.1 Further detail on reasons for exclusion

In Table 2.iii I list all the studies that I screened at the full-text stage of screening (185,208,214–216,218,246,260,265–319) with details of whether or not they met each

of my inclusion criteria. The reasons for exclusion were not mutually exclusive – a study could be excluded for more than one reason.

Table 2.iii Studies screened at full-text for my systematic review on the long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM with details of each inclusion criteria (page 1 of 3)

	Diabetes type 2 specified and disctinct	Participant meets criteria for depression	Antidepressant use specified and distinct	Antidepressant treatment duration at least 7 months	Suitable comparison group	Measurable outcome	Outcome measured at least 12 months after start of treatment	Observational study
Abrahamian 2009 (194)	Y	Y	Y	Y	Y	Y	N	N
Abrahamian 2012 (195)	Y	Y	Y	Y	Y	Y	N	N
Acee 2012 (196)	Y	N	Y	N	Y	Y	N	Y
Alenzi 2016 (197)	N	Y	Y	N	Y	Y	Y	Y
Amital 2012 (198)	N	Y	Y	N	N	N	NA	Y
Arya 2017 (151)	N	Y	Y	N	Y	Y	Y	Y
Bhattacharya 2016 (199)	Y	Y	Y	N	Y	Y	Y	Y
Bryan 2010 (200)	N	Y	Y	N	Y	Y	N	N
Caughey 2013 (201)	N	N	Y	N	Y	Y	N	Y
Danhauer 2018 (202)	Y	N	Y	N	Y	Y	N	Y
Derijks 2008A (149)	N	N	Y	Y	Y	Y	Y	Y
Derijks 2008B (178)	N	N	Y	Y	Y	Y	Y	Y
Filipcic 2010 (203)	Y	Y	Y	Y	Y	Y	N	N
Hazuda 2019 (204)	Y	N	Y	N	Y	Y	Y	Y
Higgins 2006 (189)	Y	Y	Y	N	Y	Y	N	Y
Iosifescu 2004 (142)	N	Y	Y	Y	N	Y	N	N
Kammer 2016 (205)	N	N	Y	N	Y	Y	N	Y
Kammer 2016 (206)	N	N	Y	N	Y	Y	N	Y
Kammer 2017 (207)	N	Y	Y	N	Y	Y	N	Y
Katon 2008A (208)	NA	NA	NA	NA	NA	NA	NA	N
Katon 2008B (209)	N	Y	N	NA	NA	Y	NA	N

Y indicates that the study met inclusion criteria; N indicates that the study did not meet inclusion criteria. NA indicates not applicable for the intervention or comparison criteria, if the study did not specify antidepressant use, or for the outcome criteria if no suitable outcome was investigated.

Table 2.iii cont. Studies screened at full-text for my systematic review on the long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM with details of each inclusion criteria (page 2 of 3)

Reference	Population		Intervention		Comparison	Outcome		Study Design
	Diabetes type 2 specified and disctinct	Participant meets criteria for depression	Antidepressant use specified and distinct	Antidepressant treatment duration at least 7 months	Suitable comparison group	Measurable outcome	Outcome measured at least 12 months after start of treatment	Observational study
Katon 2011 (210)	NA	NA	NA	NA	NA	NA	NA	N
Katon 2012 (211)	Y	N	N	NA	NA	Y	NA	Y
Katon 2015 (212)	N	N	N	NA	NA	Y	NA	Y
Keating 2018 (213)	Y	N	N	NA	NA	Y	NA	Y
Keitner 1991 (214)	N	Y	N	NA	NA	Y	NA	Y
Knol 2008 (215)	N	N	Y	Y	Y	Y	Y	Y
Labad 2012 (216)	Y	N	Y	N	Y	Y	N	Y
Lee 2017 (217)	N	N	Y	N	Y	Y	Y	Y
Lee 2020 (147)	N	N	Y	N	Y	Y	Y	Y
Lin 2009 (218)	N	Y	N	NA	NA	Y	NA	Y
Lunghi 2017A (219)	Y	Y	N	NA	NA	Y	NA	Y
Lunghi 2017B (220)	Y	Y	N	NA	NA	Y	NA	Y
Lustman 1997 (221)	N	Y	Y	N	Y	Y	Y	N
Lustman 2007 (222)	Y	Y	Y	Y	Y	Y	N	N
Miller 1996 (223)	N	Y	Y	Y	Y	Y	N	N
Moulton 2019 (224)	Y	N	N	NA	NA	Y	NA	Y
Nicolau 2013 (225)	Y	Y	Y	Y	Y	Y	N	N
Noordamn 2016 (148)	Y	N	Y	N	Y	Y	Y	Y
Novak 2016 (226)	N	N	N	NA	NA	Y	NA	Y
Osborn 2010 (227)	N	Y	Y	N	Y	N	NA	Y
Pan 2011 (228)	Y	N	N	NA	NA	Y	NA	Y

Y indicates that the study met inclusion criteria; N indicates that the study did not meet inclusion criteria. NA indicates not applicable for the intervention or comparison criteria, if the study did not specify antidepressant use, or for the outcome criteria if no suitable outcome was investigated.

Table 2.iii cont. Studies screened at full-text for my systematic review on the long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM with details of each inclusion criteria (page 3 of 3)

Reference	Population		Intervention		Comparison	Outcome		Study Design
	Diabetes type 2 specified and disctinct	Participant meets criteria for depression	Antidepressant use specified and distinct	Antidepressant treatment duration at least 7 months	Suitable comparison group	Measurable outcome	Outcome measured at least 12 months after start of treatment	Observational study
Passamonti 2015 (229)	Y	Y	Y	N	Y	Y	N	Y
Peyrot 1999 (230)	N	Y	N	NA	NA	Y	NA	Y
Popkin 1985 (231)	N	Y	Y	N	Y	Y	N	Y
Radojkovic 2016 (232)	Y	Y	Y	Y	Y	Y	N	N
Rivich 2019 (233)	N	N	Y	N	Y	Y	N	Y
Rizvi 2014 (234)	N	Y	Y	N	N	N	NA	Y
Rubin 2013 (235)	Y	N	Y	N	Y	Y	Y	Y
Rush 2008 (236)	N	Y	Y	N	Y	Y	Y	Y
Sambamoorthi 2006 (237)	N	Y	Y	N	Y	N	NA	Y
Shen 2013 (238)	N	Y	Y	N	Y	Y	Y	Y
Simon 2005 (239)	N	N	Y	N	Y	N	NA	Y
Song 2014 (240)	N	Y	Y	Y	Y	Y	N	Y
Tatonetti 2011 (119)	N	N	Y	N	Y	Y	N	Y
Tuncel 2015 (241)	Y	N	Y	N	Y	Y	N	Y
Unutzer 2009 (242)	N	N	N	NA	NA	Y	NA	Y
Viscogliosci 2020 (243)	N	N	Y	N	Y	Y	N	Y
Wami 2013 (244)	Y	N	Y	N	Y	Y	Y	Y
Wickstrom 1964 (245)	N	Y	Y	N	Y	Y	N	N
Williams 2010 (246)	N	N	N	NA	NA	Y	NA	Y
Xing 2018 (247)	Y	Y	N	NA	Y	Y	NA	Y
Yekta 2015 (248)	Y	N	Y	Y	Y	Y	Y	Y

Y indicates that the study met inclusion criteria; N indicates that the study did not meet inclusion criteria. NA indicates not applicable for the intervention or comparison criteria, if the study did not specify antidepressant use, or for the outcome criteria if no suitable outcome was investigated.

2.6 Discussion

2.6.1 Summary of findings for my first systematic review on the prevalence of antidepressant prescribing in people with comorbid depression and T2DM, and the effect of concurrent medication on the likelihood of being prescribed an antidepressant in this patient group

This was the first systematic review to investigate the prevalence of antidepressant prescribing in people with comorbid depression and T2DM.

When all eligible studies were synthesized in meta-analysis, the prevalence of antidepressant prescribing in individuals with comorbid depression and T2DM was 56% (95% CIs 34-76%). However, between studies this ranged from 18-87% and there was considerable heterogeneity (I^2 = 99%). The two highest prevalence rates of antidepressant prescribing in people with comorbid depression and T2DM (87% and 85%) were from studies where depression was identified through clinical coding (258,261). Whereas the lowest three prevalence rates of antidepressant prescribing (18%, 29% and 37%) were in community screened populations (257,262,263). Populations with depression identified through clinical coding may have more severe depression than those identified through community screening because more severe depression may make them more likely to access care (320). Indeed, the only study that accounted for depression severity when estimating the prevalence of antidepressant prescribing, was the study with the lowest prevalence rate (262). Additionally, the decision to prescribe may drive the coding of depression diagnoses resulting in a tendency to see falsely high prevalence rates of prescribing using clinical data sources (321,322). Thus, the prevalence estimate of 29% from the studies which identified depression through community screening, may be more representative and is in line with estimates in the general UK population (323). However, none of the studies included were set in the UK, so these findings may not represent UK practice in people with comorbid depression and T2DM.

Higher odds of antidepressant prescribing may have been expected in people who were prescribed insulin compared to those who were not. Insulin users represent people with more complex T2DM who may be more likely to have increased contact time with healthcare services (324). This could provide increased opportunity to commence antidepressant treatment. They would also be more likely to have worse

overall health which is a risk factor for depression (325). However, I did not find this to be the case. I found no difference in the prevalence of antidepressant prescribing between people with comorbid depression and T2DM who were prescribed insulin, compared to those who were not. However, all these studies were set in the USA, and so, this finding may not represent UK or international clinical practice.

I found no studies that reported information on any other concurrent medication use or prescribing in people with comorbid depression and T2DM. As such, there is a considerable evidence gap concerning the effect of concurrent medication on the likelihood of being prescribed an antidepressant in this population.

2.6.2 Explanations for the lack of findings in my second systematic review on the long-term outcomes of antidepressant treatment in people with comorbid depression and T2DM

I found no studies suitable for inclusion in my second systematic review investigating long-term outcomes associated with antidepressant treatment in people with comorbid depression and T2DM.

The most common reason for exclusion (n=36) was the insufficient case definition for T2DM. The majority of these studies (n=27) did not adequately specify the diabetes type as T2DM. Historically, the classification of diabetes types has been blurred. For example, in the USA, prior to the implementation of ICD-10 in 2015, the International Classification of Diseases grouped diabetes codes by complication, with the diabetes type included only as an optional add on (326). Therefore, USA studies which relied on clinical coding entered prior to this date may be unable to identify the diabetes type. In addition, a report on the classification of diabetes type in UK healthcare noted that patients were commonly unaware of their diabetes type (327) – if this is the case, it may also make the identification of diabetes type through self-report challenging or unreliable. Another option to identify diabetes type may be based on assumptions made from the medications prescribed (272). The introduction of “type 2” diabetes in 1998, replaced “non-insulin dependent diabetes” (328) – a term which is still used today (329,330). However, this terminology may lead to unreliable definitions of diabetes type. Many individuals with T2DM progress to insulin therapy (83), and other diabetes types, such as gestational diabetes mellitus may not use insulin (331). Thus,

the identification of diabetes type may be challenging in observational studies due to the use of different nomenclature over time.

More than one third of the studies (n=29) that I excluded at the full-text stage of screening did not specify whether participants had a diagnosis or symptoms of depression. Most of these studies did not investigate depression outcomes. Amongst those that did investigate depression outcomes, a number of studies (n = 8) using routinely collected data used antidepressant prescribing to identify depression. However, I could not include these studies as there would be no suitable comparison group to compare antidepressant treatment as the intervention of interest. Also, antidepressants can be used for conditions other than depression, such as neuropathic pain (173,332) (particularly relevant to this population), sleep disorders (79,173) or anxiety (154). Therefore, the prescription of antidepressants does not necessarily indicate depression.

More than one third of the studies that I excluded at the full-text stage of screening did not meet my criteria for the minimum follow-up time (7 months). This was usually due to the study design. Cross-sectional designs were often used to measure the associations between current antidepressant use and factors of interest. Where I identified longitudinal studies, many of these only had short follow-up times as they were intended to measure short-term outcomes. In addition, more than half the studies that I excluded (n=34) did not meet my criteria for the minimum duration of antidepressant treatment (7 months, in line with NICE guidelines (333)). Many of these did not report information regarding the duration of antidepressant treatment – they measured either “any antidepressant prescription” during the follow-up or “current use” at a baseline date. However the purpose of these studies was not to assess long-term outcomes of a full course of antidepressant treatment. My review has shown that there is a lack of studies specifically aiming to investigate the long-term outcomes associated with medium-to-long term (7+ months) antidepressant use.

2.6.3 Strengths and limitations

These reviews were the first ever systematic reviews in adults with comorbid depression and T2DM, to address:

i) The prevalence of antidepressant prescribing and concurrent medication use;

ii) Long-term outcomes associated with antidepressant treatment.

Previous systematic reviews investigating antidepressant treatment in people with comorbid depression and T2DM have focused on RCTs. As I explained in my **Introduction Chapter 1**, RCTs cannot investigate "real-world" antidepressant prescribing and outcomes since, by design, they have predefined interventions and end points. Therefore, the two systematic reviews included in this thesis are the first to investigate antidepressant prescribing and outcomes as they occur in the "real-world".

The search terms that I used were broad. I did not include terms for concurrent medication exposures or long-term outcomes. I included a wide range of terms to represent depression, T2DM and antidepressants. I also searched seven databases to provide a wide range of coverage. This resulted in a large number (14,389) of references being screened.

However, my inclusion/exclusion criteria were strict, resulting in the exclusion of the vast majority of studies identified in the search. For my second review, investigating the long-term outcomes associated with antidepressant treatment, my strict inclusion criteria meant that I found no studies suitable for inclusion. For both reviews, I required precise case definitions T2DM and depression. If I had not done this, studies would have been included that were not specific to my patient group of interest. While terms for diabetes type in clinical practice have historically been varied, the relationship between T2DM and depression is distinct due to its shared risk factors and bidirectional relationship(334). Therefore, I considered it necessary to place specific focus on this patient group. I only included studies that specifically identified patients as having depression (this could include major depressive disorders, depressive episodes, and self-reported depressive symptoms), excluding those that made this assumption based on antidepressant prescription. As antidepressant prescription was the outcome of interest for the first review and the intervention of interest for the second review, this would not have been appropriate for participant inclusion criteria.

I explained in my **Introduction Chapter 1** that previous RCTs investigating antidepressant treatment in people with comorbid depression and T2DM had excluded people with the most severe depression and complex physical health needs. The observational studies included in my first review investigating the prevalence of

antidepressant prescribing, on the other hand, were set in a range of populations, three of which were considered to be representative. However, none of the studies found were set in the UK – all but one (set in Australia (263)) were set in the USA. Therefore, the findings may not be generalizable to a UK population, or global populations. I did not put any language restrictions on the literature searches and no studies were excluded based on language. However, search terms were in the English language and the databases searched primarily contain research in European languages, therefore this review may not have identified studies outside these limits. Caution should also be taken when drawing conclusions from the results of this review due to the high risk of bias of the included studies. In particular, only one of the included studies adjusted any of the findings by depression severity or other factors related to overall health. This study had the lowest prevalence rate of antidepressant prescribing.

As I explained above in **Section 2.5.1**, antidepressants can be used for conditions other than depression, such as neuropathic pain (particularly relevant to this population), sleep disorders or anxiety. While I excluded any studies where antidepressants were explicitly prescribed for a condition other than depression, the indication of the antidepressant prescription was not always known (the exceptions being Binsalah 2018 (257) and Chen 2011 (259)). For individuals with T2DM, this is particularly relevant as a number of antidepressants could be indicated for diabetic neuropathic pain, as well as other comorbidities. Insulin users typically have more advanced and complex T2DM and so are more likely to experience neuropathic pain. This could lead to more non-depression related prescription of antidepressants. However, this only applied to one of the studies included in the meta-analysis (258) and all of the participants included in this study met my criteria of having depression. Furthermore, there was no evidence of an association between insulin use and antidepressant prevalence.

For my second review investigating the long-term outcomes associated with antidepressant prescribing, I required a minimum of 7 months antidepressant treatment duration, based on NICE treatment guidelines for antidepressants to be effective (82). I deemed this criteria to be essential, as my outcomes of interest were long-term, rather than focusing on initial response to treatment. In medical record studies, “any” or “current” antidepressant use, based on the identification of 1+

antidepressant prescription(s) may include individuals who had been prescribed an antidepressant once, without ever having taken it. I aimed to assess long-term outcomes in people with comorbid depression and T2DM who had received a full antidepressant treatment course. It should be noted, however, that no studies were excluded on this basis alone.

Although no studies met my inclusion criteria for long-term outcomes associated with a full course (7+ months) of antidepressant treatment in people with comorbid depression and T2DM, the exploration of why potentially eligible studies were not suitable for inclusion highlights important limitations of existing observational studies. I discuss my approach to these limitations throughout the observational studies included in my thesis in my **Conclusions and implications Section 2.6.4** below.

2.6.4 Conclusions and implications

My first review found considerable variation in the prevalence of antidepressant prescribing in this patient group. The highest prevalence (85-87%) was found in studies using routinely collected medical record or insurance claims data. While studies that surveyed populations in the community had much lower pooled prevalence rate of antidepressant prescribing (29%). These vastly different prevalence rates of antidepressant prescribing suggest that there are important differences in accessing antidepressant treatment between people who have clinically identified and recorded depression, compared to people in the general population who meet diagnostic criteria for depression. It is important to bear this in mind in the interpretation of observational studies using routinely collected data. I continue to refer to this difference in the interpretation of all four observational studies that I did as part of this thesis, throughout **Chapters 4-7** and in my **Discussion Chapter 8**.

The only concurrent medication that was reported for people who were prescribed antidepressants, compared to those who were not, was insulin treatment. I found no evidence of a difference in the likelihood of being prescribed an antidepressant between people with comorbid depression and T2DM who were prescribed insulin and those who were not prescribed insulin. People who are prescribed insulin typically represent those with worse diabetic health and increased healthcare needs which may lead to increased contact with healthcare services. As such, my review finds no evidence to suggest that these factors influence the likelihood of being prescribed an

antidepressant in people with comorbid depression and T2DM. However, all of the studies included in this meta-analysis were set in the USA. Therefore, this may not be generalisable to other countries, such as the UK.

I found no studies that investigated any other concurrent medication use and its effect on the likelihood of being prescribed an antidepressant in people with comorbid depression and T2DM. This topic, therefore, remains poorly understood. In my **Methods Chapter 3**, I discuss the difficulty of addressing this using routinely collected data. However, in the first two observational studies of my thesis, in **Chapters 4-5**, I report the extent to which people with comorbid depression and T2DM are exposed to polypharmacy. I then examine the association between the number of concurrent medications prescribed at the time of starting antidepressant treatment and antidepressant acceptability (**Chapter 4**); and the association between the number of concurrent medications prescribed at the time of stopping antidepressant treatment and depression relapse (**Chapter 5**).

I found no studies investigating long-term outcomes associated with antidepressant treatment in people with comorbid depression and T2DM. I address this evidence gap in **Chapters 5- 7**, where I used EHR data to investigate depression relapse after stopping antidepressant treatment **(Chapter 5)**, and the associations between antidepressant prescribing and insulin initiation **(Chapter 6)** and mortality **(Chapter 7)**.

The reasons for exclusion of many of the studies screened at full-text in my second systematic review, investigating long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM, has also highlighted some key methodological issues that I attempt to address in the observational studies included in my thesis. I explain how I do so in my **Methods Chapter 3**. The key issues were:

- Unclear case definitions for T2DM and depression (addressed in **Methods Chapter 3.3.3**);
- Short follow up times (addressed in **Methods Chapter 3.2.1**);
- Unclear exposure periods to antidepressants (addressed in **Methods Chapter 3.6.3**);

- Failure to adjust for potentially confounding patient characteristics (addressed in **Methods Chapter 3.6.4**).

Chapter 3: Overview and Justification of the Methods Used in the Electronic Health Record Studies of This Thesis

3.1 Introduction

In order to address the gaps in evidence highlighted by my two systematic reviews in **Chapter 2**, and described in **Chapter 1**, I performed 4 observational studies using electronic health record (EHR) data. In this chapter, I provide rationale for the decisions made about how to complete the four observational studies in my PhD. I identify and describe the UK Clinical Practice Research Datalink (CPRD) as a suitable data source. I then describe the steps taken in developing study designs and analysis plans; whilst aiming to draw conclusions related to causality, whilst minimizing confounding and bias. Where these decisions are only relevant to a single study/chapter only, I discuss this in detail in the relevant chapter. I discuss the study specific limitations of chosen approaches in the discussion sections of each individual chapter, and more general limitations in **Chapter 8**.

3.2 Description of the UK Clinical Practice Research Datalink (CPRD) and rationale for using it as a data source

In my Introduction Chapter 1.7.3 I explained that EHR data is ideal for the investigation of “real-world” antidepressant prescribing trajectories and long-term health outcomes in a complex population such as people with comorbid depression and T2DM. As part of my thesis, I performed four observational studies using EHR data from the CPRD. In the following sections, I describe my the UK CPRD and explain why it is an ideal data source to meet the objectives of the studies included in my thesis.

3.2.1 Description of the UK CPRD

The CPRD is a large electronic dataset of longitudinal clinical records from UK primary care. It is owned by the UK Department of Health and operates within the Medicines and Healthcare Regulatory Agency. Data from the CPRD have been used to produce over 3,000 peer reviewed research publications (335). It is used to inform clinical

practice and drug safety guidance (335). A bibliography of CPRD studies is maintained on the CPRD website (335).

The CPRD contains pseudonymised primary care records for over 60 million people, across 2000 primary care practices in the UK (335). It is estimated that approximately 98% of people in the UK are registered with a GP and the CPRD has been found to be representative of the general population in regards to gender, age and ethnicity (242,243). Most depression (74) and T2DM (244) in the UK is treated through primary care, which includes the issuing of medication prescriptions. A systematic review of the validity of diagnoses in CPRD showed good levels of validity for mental health conditions, endocrine and metabolic conditions and circulatory conditions (336). As such, the CPRD is an ideal data source for accessing a large representative sample of individuals with clinically identified comorbid depression and T2DM.

The CPRD includes two separate databases: CPRD Gold and CPRD Aurum, each based on different computer software packages used for the EHRs (Vision for CPRD Gold, and Egton Medical Information System (EMIS) for CPRD Aurum). The CPRD collects routine data each month from general practices using these EHR who have agreed to participate. Unless they have individually requested to opt out, all patients registered at participating practices are included in the dataset, from their date of registration until their last contact with the participating practice. The content of the two databases are similar; including all demographic information, diagnoses, symptoms, laboratory tests and other health indicators recorded by the general practitioner in the patient's electronic records, as well as all prescriptions issued. Data dictionaries are available on the CPRD website, www.CPRD.com/data. I combined both databases (Gold and Aurum) throughout this thesis.

At the time of data extraction, the median follow-up time for patients included in the CPRD was 5-6 years (335,337). This makes it suitable for investigating long-term outcomes. The CPRD is also linked to the Office for National Statistics (ONS) death registrations, enabling validation of death dates and causes (230). Death registrations are mandatory by law in the UK (338). As such, ONS death registration data is a reliable source of information on mortality.

In CPRD primary care practices, prescriptions are issued electronically and automatically recorded on a patient's record. Therefore, the EHR will match exactly

the prescriptions issued. Thus, CPRD data accurately represents “real-world” primary care prescribing. This is ideal for investigating “real-world” antidepressant prescribing and concurrent medication prescribing.

Thus, the CPRD is an ideal data source for conducting valid, representative and generalisable research into the outcomes of antidepressant treatment and polypharmacy in people with comorbid depression and T2DM.

3.2.2 CPRD data recording

3.2.2.1. CPRD Gold

The database structure separates information into demographic, clinical, referral, immunisation, test and therapy data, recorded against unique identifiers for each patient. All entries to a patient record are considered as ‘consultations’ (though these may not represent face-to-face encounters). Within each consultation multiple ‘events’ may be recorded, each with an associated date.

For clinical coding, CPRD Gold uses version 2 Read codes – a clinical classification system containing over 96,000 codes (339). Read codes are used to describe a patient’s condition, including diagnoses, tests, medical history, lifestyle measures and therapies offered. Numerical data can also be recorded, with an associated Read code, on clinical measures such as weight or HbA1c. Prescriptions issued are automatically recorded with a product code, name, dosage instructions, and quantity. Results of laboratory tests are also commonly fed back to the primary care record electronically. Data from other sources, such as diagnoses made in secondary care, may be entered manually into the patient record by the primary care practice staff.

3.2.2.2 CPRD Aurum

The database structure separates information into demographic, clinical, and therapy data, recorded against unique identifiers for each patient. Referral, immunization and test data are recorded within the clinical or the therapy tables. As with CPRD Gold, all entries to a patient record are considered as ‘consultations’, and within each consultation multiple ‘events’ may be recorded, each with an associated date. Data recording and coding is similar to CPRD Gold. CPRD Aurum uses Read codes and SNOMED codes – another clinical classification system, containing over 350,000 codes (340).

3.2.2.3 Data validation

Data included in the CPRD undergo three levels of validation checks (242,341). At collection level, electronic health record software performs automated validation of data integrity and duplication. At transformation level where data leaves the primary care practice record and enters the CPRD, data are validated for referential integrity between records. Finally, within the CPRD, research-quality-level validation for the completion and internal consistency of key variables is performed.

3.2.2.4 Linkage to Office for National Statistics mortality data

A subset of English primary care practices have consented to participate in CPRD data linkage, using the unique identifier for each patient, with secondary and specialist care, disease registries, deprivation data and mortality data from the Office for National Statistics (335). While CPRD primary care practices record patient dates of death, they do not record the cause of death, which is available from the ONS mortality data.

3.2.3 Comparison of the CPRD with other UK electronic health records

There are three large primary care EHR databases in the UK: CPRD, The Health Improvement Network (THIN) and QResearch (342). CPRD and THIN both began extracting pseudonymised patient records from the Vision EHR system in 1987, as part of the Value Added Information System (343). There is an overlap between CPRD Gold and THIN, whereby approximately 60% of CPRD Gold practices contribute to both (344). QResearch extracts patient records from the EMIS EHR system (345). There are a number of studies that suggest high level of similarity between the three databases (346,347).

I chose the CPRD as the data source for the studies in this thesis due to the large coverage, the combination of two different EHR systems, the ability to link to ONS mortality data, and because of the extensive expertise existing within the UCL Division of Psychiatry, Department of Primary Care and Population Health and School of Pharmacy. Benefits of using CPRD as a data source include the large sample size, long duration of follow-up time, breadth of coverage and representativeness, and data quality.

3.2.4 Ethical approval and consent

The use of data for the studies included in thus thesis was approved by the Independent Scientific Advisory Committee of CPRD (protocol no. 21_001648). The letter of approval is included in Appendix C.

All data sent to the CPRD is anonymised and therefore consent is not required. More information on CPRD data protection can be found: https://cprd.com/safeguarding-patient-data.

3.3 Inclusion Criteria for Electronic Health Record Studies

All of the observational EHR studies in my thesis included adults with comorbid depression and type 2 diabetes. I describe my inclusion criteria in detail below, in **Sections 3.3.1-3**.

3.3.1 Dataset inclusion criteria

Data were received from the CPRD for individuals with a diagnosis, symptom or process of care code for depression (see below, **Section 2.3.2 Case definition for depression)** and anxiety, as part of CPRD protocol no. 18_288R which covered a wider range of studies than those included in this thesis. The studies in this thesis were added to the original CPRD data request as an amendment (protocol no. 21_001648). All individuals registered at a primary care practice included in CPRD Gold or Aurum (see **Section 3.2.1**) and who met the following criteria were included in the dataset received from the CPRD:

- Year of birth was recorded
- Registration date was recorded
- Registration date was less than the practice's last collection date
- Registration date was greater than or equal to 01/01/1900
- Registration date was greater than or equal to the registration end date
- Registration date was prior to the birth year
- Gender was male or female
- Age was less than 115 at the end of follow-up (based on registration end date, death or last collection date)
- At least one recorded health care episodes dated during the follow-up period of 01/01/2000 – 31/12/2018 (or the last practice collection date) and after the patient's birth year

- Patient was permanently registered at practice

EHR records for a total of 6,365,025 people meeting these criteria were received from the CPRD. This included 2,225,657 from CPRD Gold and 4,139,368 from CPRD Aurum.

From this dataset, I excluded people who did not have at least 365 days follow-up aged 18+ between the dates 01/01/2000 – 31/12/2018. I set this limitation on the minimum follow-up duration to ensure that I would be able to identify incident prescribing and baseline characteristics for each person that I included in my studies.

3.3.2 Case definition and identification of people with depression

I included people who had at least one depression diagnosis, symptom or process of care code recorded during the follow-up period. Symptom codes could include terms such as, “low mood”. Process of care codes could include terms such as, “depression monitoring letter sent”. I excluded people who only had codes for depression related to dementia, maternity, schizophrenia or bipolar disorder, as these are distinct subtypes of depression from major depressive disorder.

The code list for depression was developed, based on codes considered to be representative of major depressive disorder, prior to the commencement of my PhD by the UCL Division of Psychiatry and UCL Research Department of Primary Care and Population Health, using the method described by Davé and Petersen (348). I include this code list in Appendix D.

I included people with depression based on codes related to symptoms and processes of care, as well as diagnostic codes (e.g. “depressive disorder”). This was based on evidence that these types of code are increasingly being used to record depression in primary care instead of diagnostic codes (349). Primary care practitioners may avoid using diagnostic codes for depression, potentially due to the stigma associated with diagnosis (350) or following the introduction of performance indicators based on the number of individuals receiving diagnostic codes (351).

3.3.3 Case definition and identification of people with T2DM

3.3.3.1 Challenges in identifying people with T2DM from UK primary care EHR data

Studies on the validation of T2DM clinical codes in UK primary care data have shown that the use of clinical coding alone has limited sensitivity and specificity (352,353). These studies found that there was significant misclassification of T2DM in the use of clinical codes. Also, not all patients with T2DM were detectable using clinical coding.

A number of recent studies involving people with T2DM and using CPRD data (354–357) identified people with T2DM based on antidiabetic prescriptions alone. However, I considered this approach to be too exclusive as it would exclude people with early stage T2DM who were not yet prescribed antidiabetic medication and controlled their diabetes through lifestyle management. In addition, the most commonly prescribed antidiabetic medication, metformin, may also be used to prevent T2DM or to treat polycystic ovary syndrome (93). As such, treatment with antidiabetic medication does not necessarily indicate T2DM.

It may be possible to identify people with blood glucose levels above the threshold to diagnose T2DM using data on diagnostic testing. However, I am not aware of any other studies that use this method alone for T2DM case definition.

Given these challenges, I designed a stepwise inclusion and exclusion process to identify people with T2DM, using clinical codes, antidiabetic medication and confirmatory diagnostic testing. I describe and provide rationale for each of the following stages in more detail below:

Step 1 – Identify people with potential T2DM through clinical coding or antidiabetic medication prescriptions;

Step 2 – Confirm diabetic status with blood/serum glucose/HbA1c results above the diagnostic threshold;

Step 3 – Exclude remaining participants who may have type 1 diabetes (T1DM) or gestational diabetes.

3.3.3.2 Step 1 – Identify people with potential T2DM through clinical coding or antidiabetic medication prescriptions

I developed my own clinical code list for T2DM aiming to optimise sensitivity and specificity. I reviewed three published code lists of T2DM Read codes – from Elixhauser (358), Charlson (358) and CALIBER (359). There was variation between each list and terms relating to earlier stage T2DM (describing, for example, lifestyle

and diet management support) were missing. In addition, these lists contained codes related to gestational and T1DM, which were necessary to exclude. Therefore, I combined the codes specific to T2DM from each of the published code lists. I then searched the medical code dictionary from CPRD Gold and Aurum for any additional codes related to T2DM using established search techniques (348). This code list is provided in Appendix E.

I developed a code list for antidiabetic medication by searching the CPRD product dictionary for drug substances listed in the antidiabetic medication chapters of the British National Formulary (BNF) and the Anatomical Therapeutic Chemical (ATC) Classification System. This code list is provided in Appendix F.

3.3.3.3 Step 2 confirm diabetic status with blood/serum glucose/HbA1c results above the diagnostic threshold

I developed a list of codes to identify blood/serum glucose/HbA1c tests. To do this I reviewed the published code lists from CALIBER (359) for relevant terms in CPRD Gold and used these to search for matching terms in CPRD Aurum. I also used established search techniques (348) to search for any additional relevant terms. This code list is provided in Appendix G. For each type of test, I set a cut off value that is used in clinical practice to identify T2DM, and included only participants who had at least 2 tests with results recorded above the set value. The requirement for two or more tests is in line with T2DM diagnostic criteria (328).

It may be that I excluded some individuals who had diagnostic testing performed prior to or separate from the period of care covered by their EHR. However, I prioritised specificity in this instance to ensure confidence that all participants included had T2DM. This was especially necessary as I had chosen to include individuals with earlier stage T2DM who may have less definitive clinical coding and no antidiabetic medication.

3.3.3.4 Step 3 exclude remaining participants who may have T1DM or gestational diabetes

People with T1DM may also be identified using the above diagnostic criteria or antidiabetic medication prescriptions. In addition, the misclassification of diabetes type using clinical coding has been shown in previous research (352,353).

Insulin treatment is required for all individuals with T1DM (360). Therefore, I excluded people with possible T1DM, identified by less than 6 months between the date of the first recorded oral antidiabetic prescription and the first recorded insulin prescription.

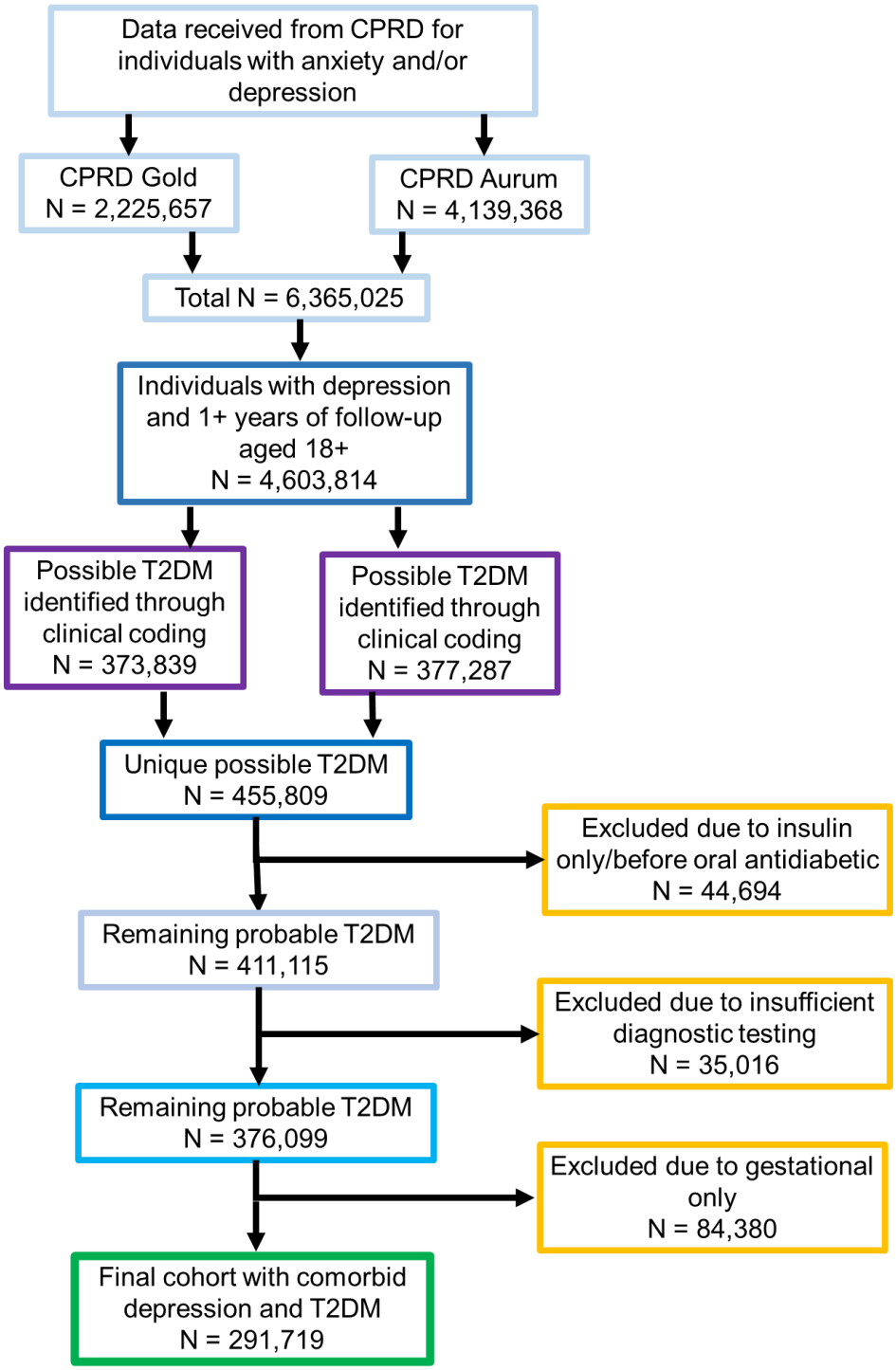
People with gestational diabetes may also be identified using the above diagnostic criteria or antidiabetic medication prescriptions. In addition, the misclassification of diabetes type using clinical coding has been shown in previous research (352,353).

I excluded people who were likely to only ever have had gestational diabetes only, identified when codes for T2DM and antidiabetic medication were only present during periods of pregnancy.

To identify periods of pregnancy in order to exclude individuals who only had gestational diabetes mellitus: I used the CALIBER (359) code list for pregnancy in CPRD Gold and searched for matching terms to develop a code lists for pregnancy in CPRD Aurum.

I demonstrate the inclusion/exclusion of people with comorbid depression and T2DM in a flowchart in **Figure 3.ii**.

Figure 3.ii Flowchart showing selection of people with comorbid depression and T2DM



3.4 Definition of outcomes and exposures

In this section, I explain my rationale for selecting prescriptions-based outcome and exposure variables. Some aspects of both physical and mental health may not be well recorded in a patient's primary care EHR, which is designed for clinical management, rather than research. This may include key variables of interest, such as depression severity, regular measurements of HbA1c, or reasons for initiating or discontinuing treatment. Proxy variables are measured variables that are associated with an unmeasured variable of interest. They can be used to estimate variables of interest where the exact variable itself is not well recorded. Prescriptions data in EHRs are ideal candidates for proxy variables as they are highly accurate and complete. At the primary care practices included in the CPRD, prescriptions are issued electronically and automatically recorded on a patient's record. Therefore, the EHR matches exactly the prescriptions issued.

3.5.1 Use of prescription-focused outcomes

In this section, I introduce the use of prescriptions data as proxy variables in **Chapters 4-6** to estimate antidepressant acceptability, depression relapse and the long-term decline of diabetic health.

3.4.1.1 Stopping antidepressant treatment before the recommended duration as a proxy for antidepressant acceptability

My first observational study aimed to investigate the association between the number of concurrent medications prescribed and antidepressant acceptability. Antidepressant acceptability is a combined marker of effectiveness (beneficial therapeutic action for the individual patient), tolerability (in terms of side effects) and/or patient willingness to be treated (due to e.g. overall treatment burden or attitudes towards pharmacological treatment). The ideal measure of antidepressant effectiveness, would be the change in depression symptom severity before and after treatment. However, the type of depression coding used in the CPRD (i.e. symptom, diagnosis, severity scales) is inconsistent and not recorded in regular intervals in relation to antidepressant treatment (see **Table 3.i and Figure 3.iii** below). Only 0.85% of my cohort of people with comorbid depression and T2DM had a recorded symptom severity score from a validated scale prior to starting antidepressant treatment, and only 0.54% in the following 6 month period. Depression symptoms or

diagnoses are occasionally recorded with accompanying severity category of mild, moderate or severe, however, this may be assigned subjectively by the clinician, and still was only recorded in 4.53% of participants prior to starting antidepressant treatment and 3.98% in the following 6 month period. Medication side effects, aside from those which result in hospitalization, are also difficult to estimate using CPRD data as these are often under-recorded and under-reported (361). In addition, patient willingness to be treated and the reasons for this are not recorded in EHR data. Therefore, a proxy for antidepressant acceptability is required. In the widely-cited meta-analysis by Cipriani et al investigating the effectiveness and acceptability of antidepressant medication in the general population, acceptability is defined by stopping the antidepressant for any reason (77). As such, stopping antidepressant treatment is a widely accepted proxy for antidepressant acceptability. I adopted this approach for my study investigating the association between the number of concurrent medications prescribed and antidepressant acceptability, in **Chapter 4**. In this study, I investigated that rate of stopping antidepressant treatment before the NICE recommended treatment duration (6 months, following an initial response window of 1 month = 7 months total) (82) as a marker of antidepressant acceptability.

3.4.1.2 Restarting antidepressant treatment as a proxy for depression relapse

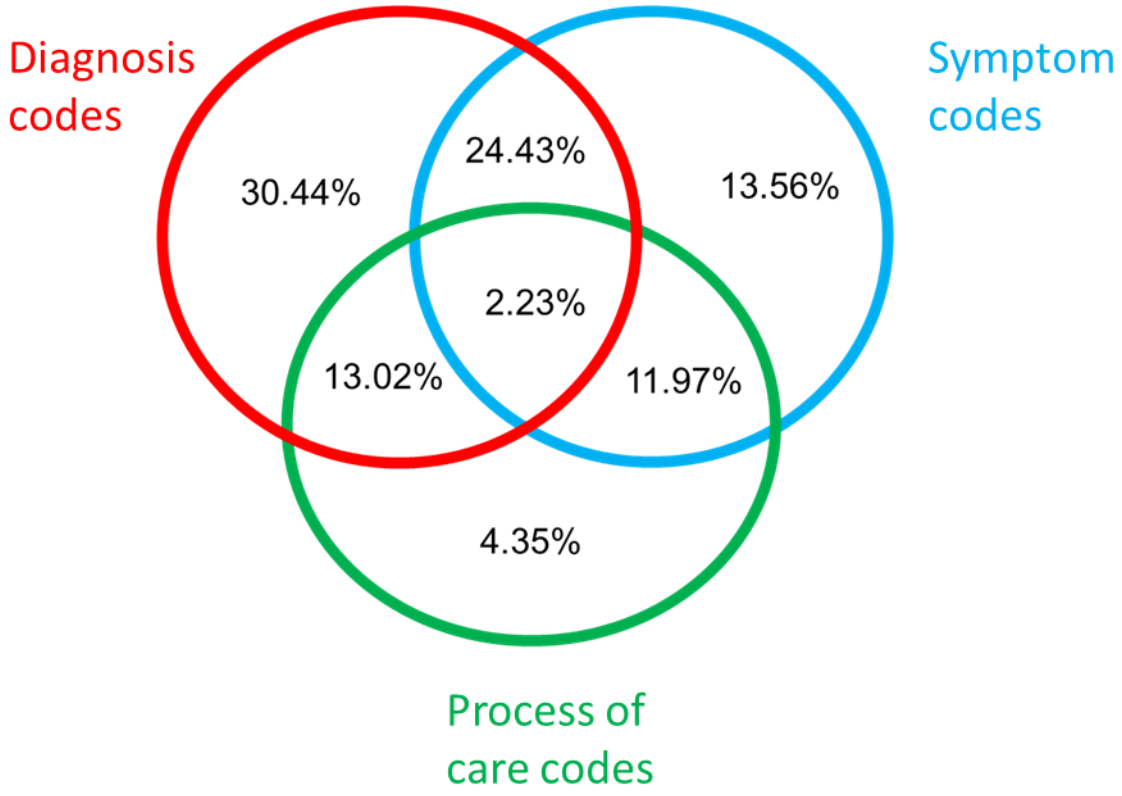
My second observational study aimed to investigate the association between the number of concurrent medications prescribed and depression relapse. Depression relapse can be defined as the return of depression symptoms within the expected duration of the current episode of depression (up to 12 months) (207). However, as I explained above in **Section 3.5.1.2** and demonstrate below in **Table 3.i** and **Figure 3.iii**, depression symptoms and symptom severity are not consistently or regularly recorded in EHRs. Therefore, again, a proxy variable is required to estimate depression relapse. I used the outcome of restarting antidepressant treatment within 12 months after stopping as a marker of clinically identified depression relapse. I considered this to be a suitable proxy measure because it indicates that the clinician and patient have identified a need to restart treatment for depression. Furthermore, all participants had previously sought help for depression from primary care and received antidepressants (as they were restarting antidepressant treatment as opposed to starting for the first time).

Table 3.i Proportion of patients with different types of depression code at intervals related to depression treatment

	Proportion of participants* with type of depression code (%)		
	At any time	**<6 months before antidepressant**	**<6 months after antidepressant**
Any depression code	73,808 (100.00)	45,881 (62.16)	29,289 (39.68)
Symptom score from validated scale	3,361 (4.55)	630 (0.85)	395 (0.54)
Subjective severity code	5,676 (7.69)	3,342 (4.53)	2,939 (3.98)
Diagnosis codes	48,080 (65.14)	34,744 (47.07)	38,364 (51.98)
Symptom codes	38,523 (52.19)	20,903 (28.32)	15,178 (20.56)
Symptom codes without diagnosis	18,841 (25.53)	16,539 (22.41)	12,958 (17.56)
Process of care codes	23,298 (31.57)	2,796 (3.79)	13,740 (18.62)
Process of care codes only	3,214 (4.35)	623 (0.84)	7,328 (9.93)

*Participants with comorbid depression and T2DM identified as starting antidepressant treatment for the first time

Figure 3.iii Venn diagram representing proportion of patients with comorbid depression and type 2 diabetes, prescribed antidepressants for the first time in their EHR follow-up, with records for different types of depression code



3.4.1.3 Starting insulin treatment as a proxy for the long-term decline of diabetic health

My third observational study aimed to investigate the association between antidepressant treatment and the long-term decline of diabetic health. HbA1c is a biological marker routinely used to measure glycaemic control and assess the risk of developing complications in individuals with T2DM (362,363). However, HbA1c may not be regularly recorded in a patient's EHR, and sometimes, alternative measures of glycaemic control, such as blood/serum glucose may be recorded, which do not map directly onto HbA1c levels. Indeed, only 19.19% of individuals starting oral antidiabetic medication for the first time, when their glycaemic control would be measured as an indication to start treatment, had a recorded value for HbA1c within 6 months before starting treatment included in CPRD. Therefore, a proxy variable was required to estimate the long-term decline of glycaemic control.

If an individual cannot control their HbA1c levels through diet and physical activity, oral antidiabetic medications are prescribed. When oral antidiabetic medications are no longer able to control an individual's HbA1c below their individually agreed threshold, insulin therapy may be started (83). Thus, starting insulin therapy represents the long-term decline of glycaemic control and the failure of oral antidiabetic medication. Starting insulin is a definitive outcome which can easily be measured in CPRD with prescriptions data. Therefore, it is an ideal proxy measure for the long-term decline of diabetic health.

3.4.2 Use of prescription-focused exposures

The first aim of my thesis, including the first two observational studies in **Chapters 4-5**, was to investigate the association between concurrent medication prescribing and antidepressant treatment trajectories. The exposure in both these studies was the number of concurrent medications prescribed at a baseline date. I describe in detail my definition and identification of the number of concurrent medications prescribed as an exposure in the relevant **Chapters 4-5**.

The second aim of my thesis, including the second two observational studies in **Chapters 6-7**, was to investigate the association between antidepressant treatment and long-term physical health outcomes. I describe in detail my definition and identification of antidepressant prescribing as an exposure in the relevant **Chapters 6-7**.

3.4.3 Development of medication code lists

I developed a code list for antidepressant medication (included in Appendix H) by searching the CPRD product dictionary for drug substances listed in the antidepressant chapters of the BNF and the ATC Classification System. I only included antidepressants that have been licensed to treat depression in the UK during the study period. The specific antidepressant medications included are listed in the relevant chapters.

I developed code lists for all concurrent medications by extracting all therapeutical product codes recorded within the specified time point for each study. I then manually categorised each individual drug substance name to a drug and drug class. I excluded therapeutical products that were not medications (e.g. bandages, syringes, etc.), topical medications, supplements and vaccinations. This list was reviewed by my primary supervisor, Dr Joseph Hayes (psychiatrist), and collaborator, Dr Cini Bhanu (GP). I have not included this code list as an appendix as it is tens of thousands of items long, however, it is available on request.

3.5 Study Design

3.5.1 Cohort studies examining the association between polypharmacy and antidepressant treatment trajectories

Cohort studies follow-up two or more different groups over time to compare a subsequent outcome(s) of interest. For the studies included in my first aim investigating the association between polypharmacy and antidepressant treatment trajectories, I used cohort study designs, whereby people with comorbid depression and T2DM who had different levels of polypharmacy were followed up from a specific time point to compare different antidepressant treatment trajectories (stopping treatment, switching drugs, restarting treatment). I describe the study designs in more detail in the relevant **Chapters 4-5**.

3.5.2 Nested case-control studies for the association between antidepressant treatment and physical health outcomes (starting insulin and mortality)

For the studies included in my second aim, investigating the association between antidepressant prescribing and physical health outcomes included in **Objective 2**, I used matched nested case-control study designs, whereby prior antidepressant prescribing was compared in cases with the specific physical health outcome to controls without the specific physical health outcome.

Nested case-control studies are nested within a defined cohort, and so, have the same benefit as cohort studies in that they follow-up participants from the point of study entry until they reach a subsequent outcome or not. I chose the nested case-control approach, as this is an efficient alternative to cohort analysis when studying time-varying exposures (such as antidepressant treatment), as it has superior computational efficiency to Cox regression and has been found to yield similar results (364). Cohort studies typically assess an exposure at pre-defined baseline and compare people with and without the exposure over a follow-up period during which an outcome can occur at any time; case-control studies on the other hand assess an outcome at a pre-defined index date, and then compare people with and without the exposure during a retrospective follow-up period during which an exposure can occur at any time – this is a preferable design for outcomes that are time varying in nature (364–366), such as antidepressant treatment (due to the time varying nature of depression itself). While cohort studies do allow for the investigation of time-varying exposures, this is computationally complex, and typically suited to exposures that vary only a small number of times during the follow-up, whereas antidepressant prescribing may vary a considerably number of times over longer follow-up periods. Furthermore, case-control studies allow for the investigation of more than one exposure, enabling the investigation of multiple different types of antidepressant prescribing patterns during the follow-up period, including whether an individual had ever been prescribed an antidepressant, the cumulative duration of antidepressant treatment, the number of different antidepressant agents prescribed and the timing of the antidepressant prescribing relative to the outcome.

3.6 Approach to confounding

Confounding may occur when groups in which outcomes are being compared differ in other ways than the exposure alone. These differences may include sociodemographic factors, medical conditions and clinical characteristics, behaviours

or treatments. When these differences influence both the exposure and the outcome, they cause a false association, known as confounding.

Confounding may be controlled for using matching, restriction, multivariable adjustment and stratification. In all studies, I address confounding through multivariable modelling, matching and/or stratification. I describe study specific approaches, rationale for and descriptions of the covariates included as potential confounders in the relevant chapters. Directed acyclic graphs (DAGs) map proposed causal relationships between an exposure, outcome and confounding variables. They enable the identifications of different types of bias to causal effects. For each study, I provide a DAG to identify potential confounding factors that could be adjusted for in my analysis. DAGs were created using the dagitty tool (367).

As a minimum, in each study I adjusted for the following confounding variables: age, gender, ethnicity and GP practice. Age may effect a person's response and tolerance (in terms of side-effects) to medication (368); the likelihood of being prescribed multiple medications due to the increasing number of comorbidities that come with ageing (369); the symptomology of depression (370,371); and the development of long-term physical health outcomes due to ageing. There are well established differences in medication use according to gender (372–374); gender differences in the risk factors and symptoms of depression (23); and known gender differences in the risk, pathophysiology and complications of T2DM (375). There are known ethnic differences in the UK for depression (376), T2DM, health risk factors and access to healthcare (377). Socioeconomic deprivation also is known to effect both physical (378) and mental health (41). CPRD does contain linkage to practice-level deprivation scores for a number of participating practices in England, however, this only includes approximately 35% of individuals. As this would significantly reduce my sample size, I decided not to include it. Instead, throughout all studies, I accounted for clustering by GP practice, by including the GP practice ID as a stratum term in my models. In this way, I accounted for practice level deprivation and prescribing trends.

I describe my approach to addressing missing data in confounder variables for each study in the relevant chapters.

3.7 Analytic Approach

3.7.1 Cox proportional hazards regression

For the cohort studies included as part of my first aim (investigating the association between polypharmacy and antidepressant treatment trajectories), I used Cox proportional hazards regression. This type of model is commonly used to test differences in the time to which an event occurs between two or more groups of interest, allowing for the adjustment of confounders (379). They are preferable to use in time-to-event analysis, as they have more statistical power than logistic regression (380,381) due to their taking account of the time until an event occurs (382). Cox regression models also appropriately handle censoring of individuals who leave the study (e.g. due to death or de-registration with the primary care practice) before the end of the follow-up period. Time-to-event analysis is the most appropriate type of analysis for both studies in my first aim – the first being interested in the amount of time a participant takes to stop or switch antidepressant treatment (**Chapter 4**), and the second in the amount of time before a participant experiences depression relapse (**Chapter 5**). Furthermore, Cox regression models are semi-parametric, and so, do not require a parametric distribution of the outcome.

Cox regression usually requires a linear relationship between the main exposure and outcome. However, given the suspected non-linear relationship between the number of concurrent medications (my exposure in both cohort studies) and antidepressant treatment trajectories (stopping treatment, switching agents, and restarting treatment), it was necessary to transform the main exposure variable. I used a penalised B-splines term in the univariable and multivariable analysis for the main exposure variable (number of concurrent medications). Spline functions enable the use of the linear Cox proportional hazards model where linear assumptions are not met, by fitting a number of linear functions to a non-linear relationship to provide interval estimates. Spline functions provide more flexibility in estimating nonlinear relationships than algebraic functions (383). B-splines specifically are piecewise-defined, thereby overcoming numerical instability, and therefore are ideal for modelling and interpreting relationships with integer exposures. While user-selected splines can introduce bias, I used a penalised method to fit the splines, which balances flexibility against overfitting (384). The penalised fit defines the range of each spline, at which the interval estimates are made.

3.7.2 Conditional logistic regression

For the matched case-control studies that I did as part of my second aim (investigating the association between antidepressant prescribing and the physical health outcomes of starting insulin and mortality), I used conditional logistic regression models to estimate incident rate ratios for the association between antidepressant prescribing and the risk of physical health outcomes. As I used a nested case-control design, with incident rate sampling and individual matching, the odds ratios computed by conditional logistic regression are unbiased estimates of incident rate ratios with little or no loss in precision (364). This is an appropriate method to compare the incidence of physical health outcomes in participants with different exposures to antidepressant treatment. Although logistic regression does not take time into account, as the study design allowed multiple exposures, I was able to do this by the investigation of antidepressant prescriptions at different time points in relation to the outcome. Conditional logistic regression takes into account the matching of cases and controls, which causes each matched set to be statistically dependent, by using a stratum term to estimate unobserved factors specific to each matched set (385).

3.7.3 Statistical software

All analysis was performed using R version 4.0.5.

Chapter 4: The Association Between Concurrent Medication Prescribing and Antidepressant Acceptability

An abridged version of this study is published as:

Jeffery A, Bhanu C, Walters K, Wong ICK, Osborn D, Hayes JF. *Polypharmacy and antidepressant acceptability in comorbid depression and type 2 diabetes: a cohort study using UK primary care data.* British Journal of General Practice 9 January 2023; BJGP.2022.0295. DOI: 10.3399/BJGP.2022.0295

4.1 Introduction

In this chapter, I report and discuss the cohort study that I did using CPRD data to examine the association between concurrent medications prescribing and stopping or switching antidepressants in people with comorbid depression and T2DM. As I explained in my **Methods Chapter 3**, I took the approach of Cipriani et at (77) where I used stopping antidepressants as a proxy for antidepressant acceptability.

In my **Introduction Chapter 1**, I defined antidepressant acceptability as a combined marker of effectiveness (beneficial therapeutic action for the individual patient), tolerability (in terms of side effects) and/or patient willingness to be treated (due to e.g. overall treatment burden or attitudes towards pharmacological treatment). Antidepressant acceptability may influence a person's decision to continue or stop treatment. Stopping antidepressants before the recommended minimum duration (7 months) could jeopardise the effectiveness of depression treatment (333). Therefore, understanding predictors of antidepressant acceptability is important. I explained in my **Introduction Chapter 1** how the increased treatment burden from polypharmacy may negatively impact antidepressant acceptability and increase the risk of non-adherence to antidepressant treatment. However, prior to this study the relationship between polypharmacy and antidepressant acceptability or adherence in people with comorbid depression and T2DM had not been explored.

The main aim of this study was to understand whether people with comorbid depression and T2DM were more or less likely to stop antidepressant treatment before

the recommended duration (primary outcome), the more concurrent medications they were prescribed at the start of antidepressant treatment. I hypothesised that people who were prescribed more concurrent medications would be more likely to stop antidepressant treatment before the recommended duration. I hypothesised that the increased burden from polypharmacy would negatively impact antidepressant acceptability.

I also aimed to explore whether stopping antidepressant treatment was related to the acceptability of the antidepressant agent itself, or due to patient acceptability of antidepressant treatment overall. To do this, my second aim was to understand whether people prescribed more concurrent medications were more or less likely to switch antidepressant agents (within 7 months) (secondary outcome). People may switch to a different antidepressant agent, if the first antidepressant agent was ineffective or intolerable, but they still wanted to attempt pharmacological treatment. On the other hand, people may stop antidepressants completely if they are unwilling to adhere to antidepressant treatment generally. This could be due to a number of reasons, including ineffectiveness, intolerability, early alleviation of symptoms, or non-adherent behaviour. I hypothesised that people who were prescribed more concurrent medications at the start of antidepressant treatment would be more likely to switch antidepressant agents within 7 months. This was based on evidence that polypharmacy is associated with increased risk of medication side effects and interactions (180,202). I also hypothesised that there would be a greater increase in the risk of stopping antidepressants completely than of switching antidepressant agents, as people were prescribed more concurrent medications. This was based on the added risk of non-adherent behaviour associated with polypharmacy (186,192,193,203).

My third aim was to examine whether different antidepressant drug classes were more or less acceptable to people with comorbid depression and T2DM who were taking multiple other medications. I hypothesised that people who were prescribed SSRIs would have the lowest increase in risk of stopping antidepressant treatment before the recommended duration associated with higher numbers of concurrent medications. This was based on the relatively better tolerated side-effect profile of SSRIs compared to other antidepressant drug classes (333).

4.2 Methods

4.2.1 Study design and setting

I completed a cohort study using EHR data from the UK CPRD. I show a graphical representation of the study design in **Figure 4.i,** after describing the patient inclusion criteria and study outcomes.

The study period ran from 1 January 2000 to 31 December 2018. These dates were selected based on data availability (see **Chapter 3.3.1**). However, I used data from earlier years (pre-2000) to select the cohort and to identify some of the confounders required in my study.

4.2.2 Patient inclusion criteria

I included in the cohort all adults (age 18+) with comorbid depression and T2DM who were prescribed antidepressants for the first time during the study period. I described how I identified people with comorbid depression and T2DM within the CPRD in detail in my **Methods Chapter 3.4.2-3**. I chose to include individuals who were prescribed antidepressants for the first time to capture the antidepressant treatment trajectory in people with newly treated depression. Prescribing decisions in such individuals are not subject to previous antidepressant response/tolerability which would bias the studies' findings.

To only include people who were starting antidepressant treatment for the first time, I identified first antidepressant prescriptions using the following criteria:

- At least 6 months of antidepressant prescription-free data after the individual's date of registration – to identify incident prescribing;
- First antidepressant prescription recorded during the individuals EHR follow-up period, aged 18+ and between the years 2000 to 2018;
- First antidepressant prescription was for one of the following agents: citalopram, escitalopram, fluoxetine, mirtazapine, paroxetine, sertraline, venlafaxine;
- No other antidepressant medications (as listed in the antidepressant chapters of the BNF and the ATC Classification System) recorded on the date of the first antidepressant prescription.

The indication for drug prescriptions are not routinely recorded in CPRD data. Therefore, I chose the above antidepressant agents because they are the most commonly prescribed antidepressants for the initial treatment of depression in the UK (386). I could not be confident that other antidepressants were being prescribed to treat depression – particularly those commonly prescribed for diabetic neuropathic pain, such as duloxetine.

I started follow-up on the date of the first antidepressant prescription. I ended follow-up after 224 days (7 months). I censored participants if they stopped or switched antidepressants (the outcome), at their date of death, end of registration with their primary care practice, end of the study period (31 December 2018), or after 224 days whichever was first.

4.2.3 Outcomes

4.2.3.1 Primary outcome – stopping antidepressant treatment before the recommended duration (7 months)

NICE recommendations state that antidepressant treatment should be maintained for 6 months after the remission of an episode of depression, allowing for 4-6 weeks for remission to be achieved (82) – this gives a total minimum duration of 7 months. I defined stopping antidepressants as a gap of at least 60 days without an antidepressant prescription. I specified a gap of 60 days to account for a 1 month prescription (the median duration of antidepressant prescription in the study dataset/cohort), plus a maximum of 1 month to issue the subsequent prescription. This is in line with other research investigating stopping antidepressants in primary care data (387,388).

4.2.3.2 Secondary outcome – switching antidepressant agents

My secondary outcome was switching antidepressant agents. I defined this as having a new record of a prescription for any other antidepressant (i.e. different to the first antidepressant agent) within the first 60 days after the date of the last antidepressant prescription (when the first antidepressant agent was stopped).

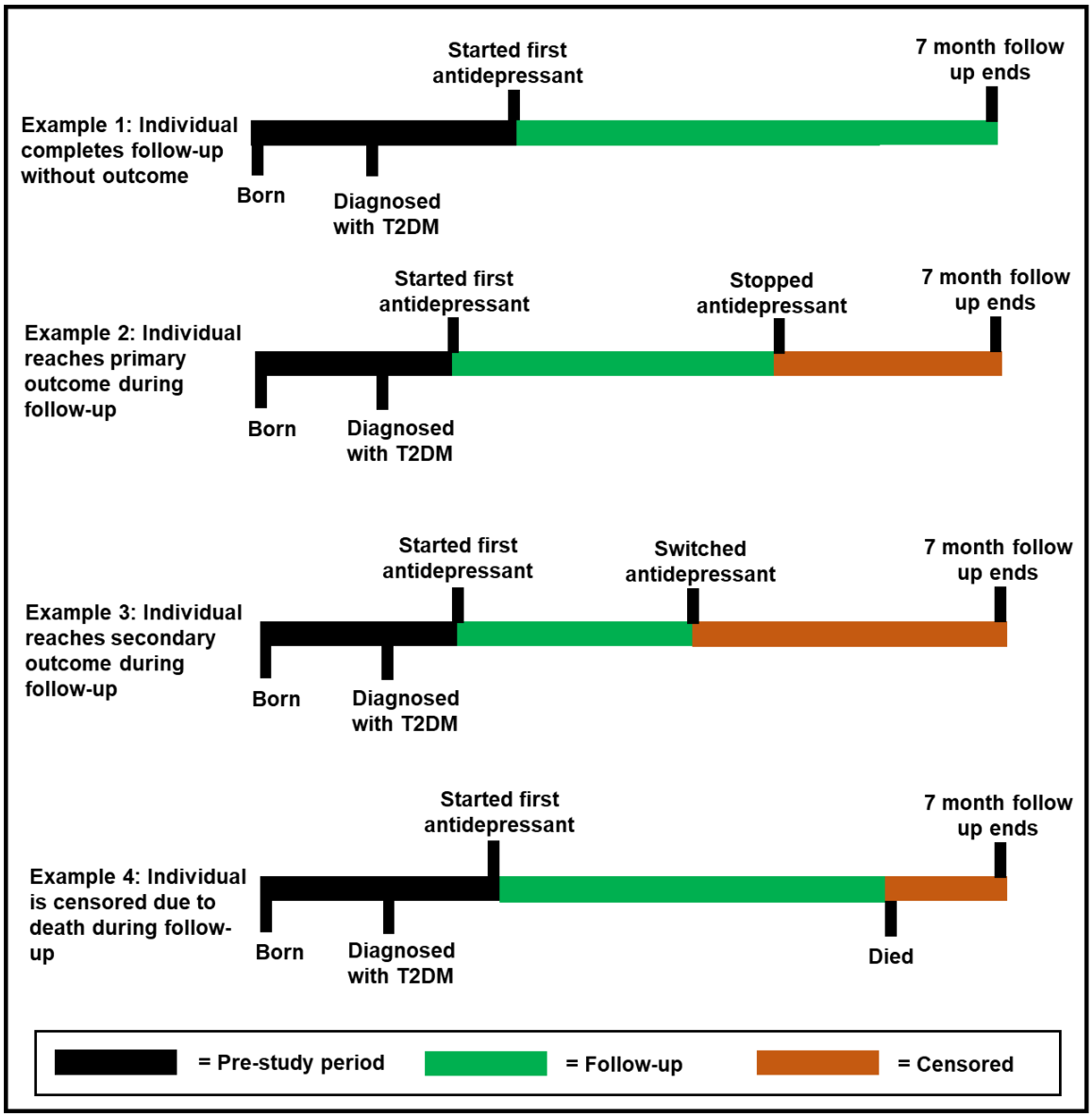
The second antidepressant agent prescribed could be any of the following: SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (duloxetine, venlafaxine), TCAs (amitriptyline >= 50mg, amoxapine, clomipramine,

dosulepin, imipramine, lofepramine, maprotiline, nortriptyline >= 50mg, trimipramine,), MAOIs (isocarboxazid, moclobemide, phenelzine, tranylcypromine) or other antidepressant agents (agomelatine, mianserin, mirtazapine, nefazodone, oxitriptan, reboxetine, trazodone, tryptophan).

I only included antidepressants that have been licensed to treat depression in the UK during the study period. I assumed that a prescription for a second antidepressant agent would be likely to treat depression, when it was dated immediately after the first-line antidepressant to treat depression was stopped. This is why I included a wider range of antidepressant agents, than the first-line drugs described in the patient inclusion criteria. For amitriptyline and nortriptyline, I included only prescriptions that were issued at a dosage >= 50mg, which is indicated for depression.

I show a graphical representation of follow-up time in which the outcomes may occur in **Figure 4.i**.

Figure 4.i Graphical representation of study design



4.2.4 Exposure definition: the number of concurrent medications prescribed at the time of starting antidepressant treatment

The study exposure was the number of concurrent medications prescribed to an individual at the time of the first antidepressant prescription or up to 90 days prior. This did not include the antidepressant itself. I specified 90 days to capture prescriptions which are issued for longer durations, which may be commonplace for long-term conditions. I excluded topical medications, supplements and vaccinations. I described the creation of the code list for all medications in the my **Methods Chapter 3.5.3**.

Some people do not receive concurrent medications for T2DM, so the reference group was zero concurrent medications (not including the antidepressant).

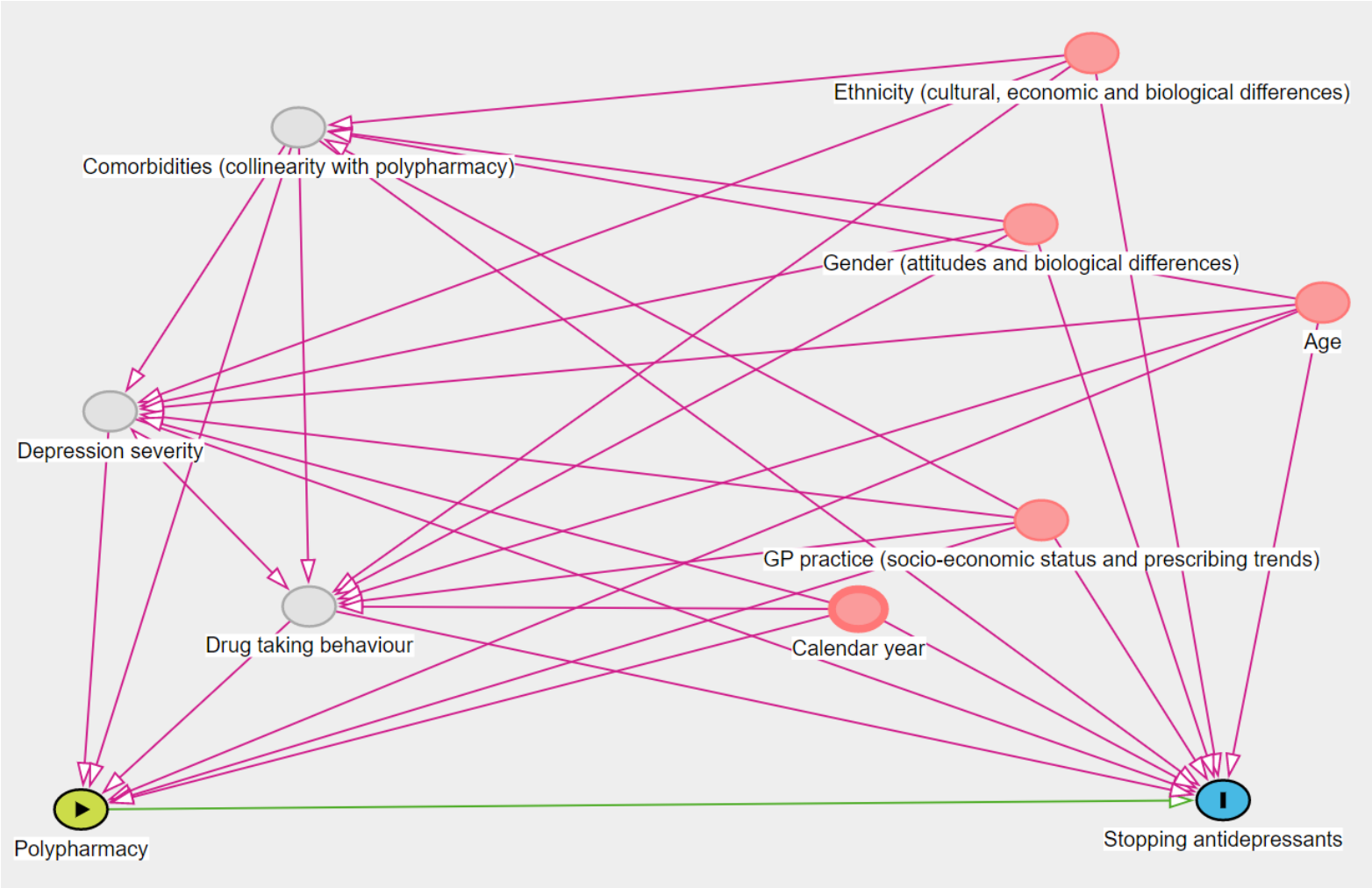
4.2.5 Confounders

I included calendar year, age, gender, ethnicity and GP practice (as a stratum term) as potential confounders, as demonstrated in **Figure 4.ii**. I did not include comorbidities or the stage of the diabetes as confounders because they were highly collinear with the main exposure. Where ethnicity was missing, I recoded this as "White" – as the CPRD population has been found to be representative of the UK population in terms of ethnicity (242,243), 93% of more individuals with missing ethnicity would be expected to be of White ethnicity. This approach is in line with other research studies using the CPRD (389).

4.2.6 Interaction test to examine whether the association between the number of concurrent medications prescribed and stopping antidepressant treatment differs by specific antidepressant drug class

My third aim was to examine whether different antidepressant drug classes were more or less acceptable to people with comorbid depression and T2DM who were taking multiple other medications. To do this, I tested for a multiplicative interaction between the antidepressant class prescribed as first-line treatment and the main exposure (number of concurrent medications prescribed at the time of starting antidepressant treatment), with regards to the primary outcome (stopping antidepressants before the recommended duration). I categorised antidepressant classes as SSRIs (including citalopram, escitalopram, fluoxetine, paroxetine, sertraline), mirtazapine or venlafaxine.

Figure 4.ii DAG showing the relationship between confounders, exposure and outcome



*Green circle = exposure; blue circle = outcome; red circle = potential confounder; grey circle = unmeasured; direction of arrow shows potential causal effect – red arrow = confounding relationship, green arrow = causal pathway

4.2.7 Sensitivity analyses

4.2.7.1 Sensitivity analysis restricting the exposure to ongoing concurrent medication (repeat prescriptions)

One off prescriptions do not necessarily mean that an individual is taking a medication. To account for this, I performed a sensitivity analysis to distinguish ongoing treatment with concurrent medications (repeat prescriptions) from one-off prescriptions. To do this, I redefined the primary exposure variable (number of concurrent medications), by recalculating the total number of concurrent medications. I only included medications with at least two prescriptions up to 180 days prior to the index date, and at least one of the prescriptions within 90 days of the index date.

4.2.7.2 Sensitivity analysis including only individuals with complete ethnicity data

I performed a second sensitivity analysis to investigate the effect of coding individuals with missing ethnicity as “White”. To do so, I repeated the main analysis including only individuals with completed ethnicity.

4.2.9 Statistical analyses

I used Cox regression to estimate hazard ratios for the association between the number of concurrent medications and the two outcomes relating to antidepressant treatment trajectories namely 1) stopping antidepressants and 2) switching to different antidepressant agents. As the relationship between the number of concurrent medications and stopping/switching antidepressants was not linear, I used a penalised B-splines term to transform the exposure variable (number of concurrent medications). I described this method in detail in my **Methods Chapter 3.6.1**.

I first performed a univariable analysis to determine the association between each outcome and the number of concurrent medications. I then included the main exposure with all confounders in multivariable analyses. I included the primary care practice as a stratum term, whereby separate baseline hazard functions were fitted for each stratum, to account for the clustering effect of each primary care practice.

I repeated the above analysis for each sensitivity analysis described in **Section 4.2.7**.

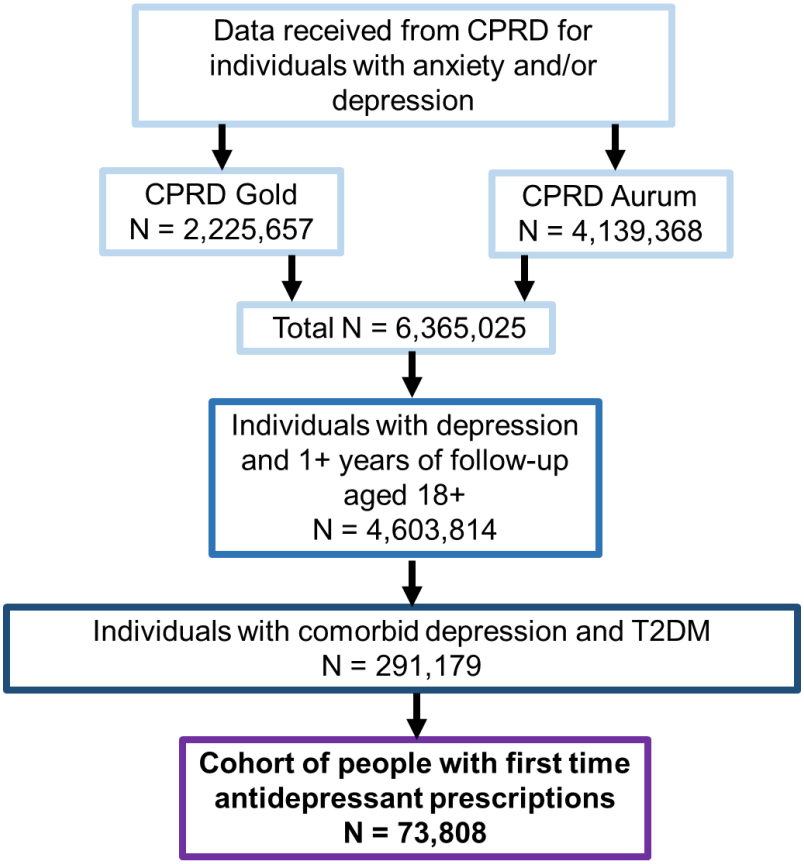
I also tested for a multiplicative interaction between the antidepressant drug class (SSRIs, mirtazapine and venlafaxine) and the main exposure (the number of concurrent medications), with regards to stopping antidepressants.

4.3 Results

4.3.1 Characteristics of individuals included in this study

I identified 73,808 individuals with comorbid depression and T2DM, who started antidepressant treatment for the first time during the study period. I demonstrate the number of individuals included or excluded in a flow diagram, **Figure 4.iii**.

Figure 4.iii Flow diagram of inclusion and exclusion



People with comorbid depression and T2DM who started antidepressants during their EHR follow-up were 52% female and had a median age of 63 (IQR 52-75). In terms of diabetes severity, 12.27% were at an early stage in that they were receiving no concurrent anti-diabetic treatments, 28.57% were receiving the first-line treatment (metformin) alone, 44.75% were receiving second-line oral antidiabetic treatments and

14.41% were at the later stage of diabetes where they were receiving insulin therapy. The median number of concurrent medications prescribed at the time of starting antidepressant treatment (including anti-diabetic medication but excluding the antidepressant itself) was 7 (IQR 4-10). When I restricted to ongoing medications (repeat prescriptions), the median was 5 (IQR 3-8. I describe the full characteristics of participants in **Table 4.i**.

The 5 most commonly prescribed concurrent medications when people with comorbid depression and T2DM started antidepressant treatment (other than antidiabetic medications) were: statins (54.86% of participants), non-steroidal anti inflammatory drugs (NSAIDS) (38.29%), ACE inhibitors (36.84%), opioids (29.84%) and proton pump inhibitors (PPIs) (28.60%).

People with comorbid depression and T2DM continued their first antidepressant treatment for a median of 4.57 months (IQR 0.92-19.22). Within 7 months of starting antidepressant treatment, 44.26% stopped treatment completely and 11.75% switched antidepressant agents.

4.3.2 Results for the association between polypharmacy and discontinuing antidepressants

4.3.2.1 Main analysis

I found that the more medications people were receiving, the less likely they were to completely stop antidepressant treatment before the recommended treatment duration (**Figure 4.ii**). Individuals had a reduced rate of stopping antidepressants before the recommended duration if they were prescribed 2 concurrent medications (HR 0.76, 95% CI 0.61-0.92) and this rate reduced further until individuals were prescribed 18 concurrent medications (HR 0.20, 95% CIs 0.05-0.84). When people with comorbid depression and T2DM were prescribed the median number of 7 concurrent medications the rate of stopping antidepressant treatment before the recommended duration was 65% lower than individuals taking no medications other than their antidepressant (HR 0.45, 95% CI 0.37-0.55). Adjustment for confounders had a minimal effect on the model (for example changing from HR 0.39 to HR 0.45 for 7 concurrent medications). I report the hazard ratio point estimates and 95% CIs in **Table 4.ii.**

Table 4.i – Participant characteristics and descriptive analysis

	All participants (n = 73,808)
Median age (years)	63 (IQR 52-75)
Female, n (%)	38,402 (52.00)
Ethnicity group, n (%):	
Asian	4,413 (5.98)
Black	1,805 (2.45)
Missing (imputed as White)	25,098 (34.00)
Mixed	366 (0.50)
Other	519 (0.70)
White	41,607 (56.37)
Diabetes treatment stage:	
Early stage (no pharmacological treatment)	9,057 (12.27)
Metformin only	21,088 (28.57)
Second-line oral-antidiabetics	33,028 (44.75)
Insulin	10,635 (14.41)
Median number of concurrent prescriptions*	7 (IQR 4-10)
Median number of concurrent repeat prescriptions*	5 (IQR 3-8)
Median duration in months of first antidepressant course	4.57 (IQR 0.92 – 19.22)
Stopped antidepressants before the recommended duration (%)	32,665 (44.26)
Switched antidepressant agent (%)	8,672 (11.75)
Censored < 224 days (%)	3,854 (5.22)

* I measured concurrent prescriptions at/90 days prior to the first recorded antidepressant medication; I included in these anti-diabetic medications but excluded the antidepressant itself

Figure 4.ii – Hazard ratios for the changing rate of discontinuing antidepressant treatment, by the number of concurrent medications prescribed at the start of antidepressant treatment (adjusted for confounders)

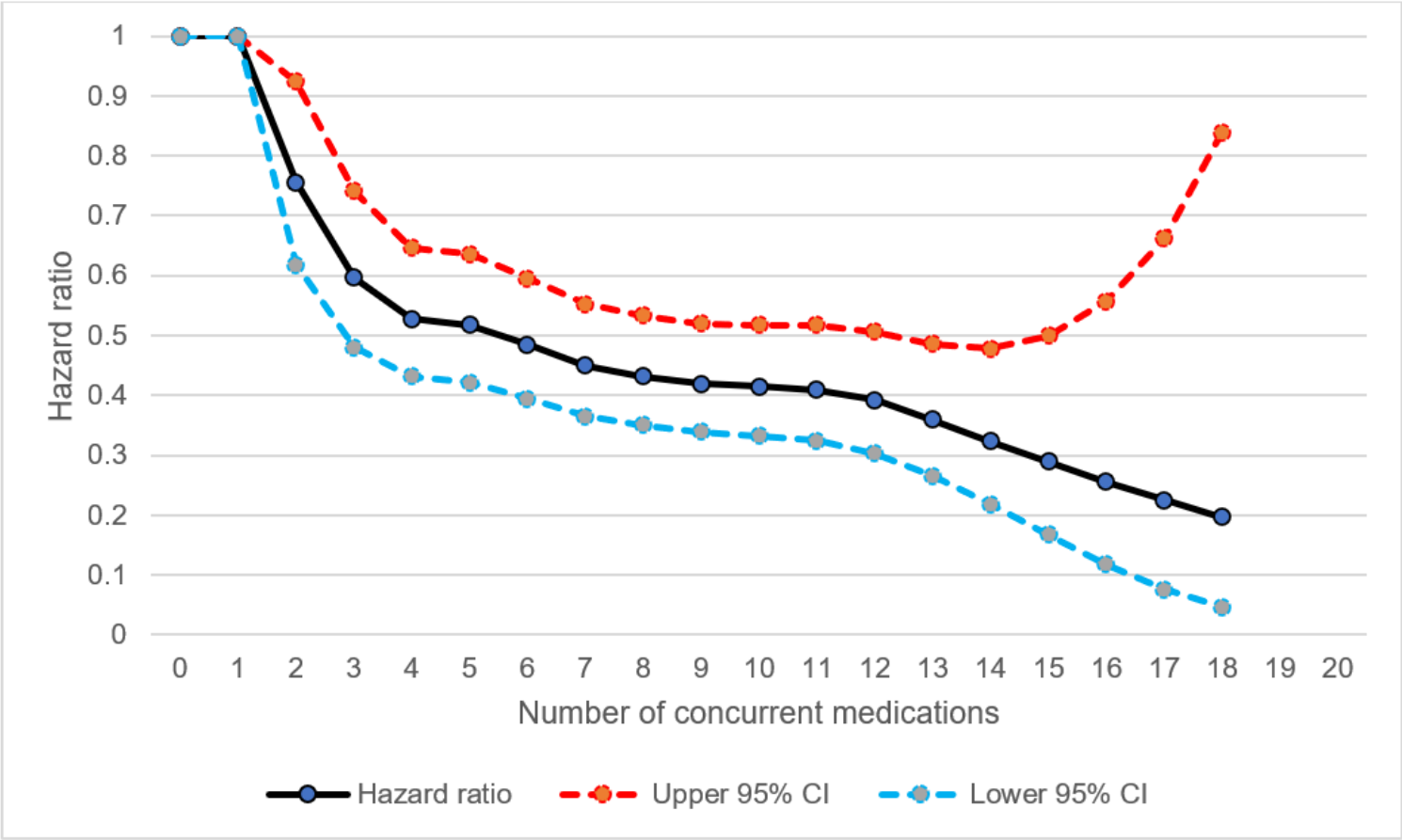


Table 4.ii Main analysis results for the association between the number of concurrent medications and stopping antidepressant treatment before the recommended duration

	Univariable HRs (95% CI)	Multivariable HRs (95% CI)
Number of medications*:		
0	1	1
2	0.60 (0.31-1.18)	0.76 (0.61-0.92)
3	0.53 (0.31-0.91)	0.60 (0.48-0.74)
4	0.45 (0.25- 0.81)	0.53 (0.43-0.65)
5	0.46 (0.26- 0.82)	0.52 (0.42-0.64)
6	0.43 (0.24-0.76)	0.48 (0.39- 0.60)
7	0.39 (0.22-0.68)	0.45 (0.37-0.55)
8	0.38 (0.21-0.68)	0.43 (0.35-0.53)
9	0.36 (0.20-0.65)	0.42 (0.34-0.52)
10	0.35 (0.19-0.63)	0.42 (0.33-0.52)
11	0.35 (0.19-0.65)	0.41 (0.32-0.52)
12	0.35 (0.19- 0.66)	0.39 (0.30-0.51)
13	0.30 (0.15- 0.59)	0.36 (0.27- 0.49)
14	0.25 (0.11- 0.54)	0.32 (0.22- 0.48)
15	0.24 (0.09-0.61)	0.29 (0.17-0.50)
16	0.19 (0.05-0.77)	0.26 (0.12-0.56)
17	0.13 (0.01-1.30)	0.22 (0.08-0.66)
18	0.09 (0.00-3.59)	0.20 (0.05-0.84)

*Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

4.3.2.2 Sensitivity analysis: exposure to ongoing medications (repeat prescriptions) only

In my sensitivity analysis, I restricted the exposure variable to include ongoing medications (repeat prescriptions) only. People who were prescribed more ongoing concurrent medications were still less likely to stop antidepressant treatment before the recommended duration compared to those who were not prescribed any ongoing medications other than the antidepressant itself. However, the size of the association was reduced compared to any concurrent medications. When people with comorbid depression and T2DM were prescribed the median number of 5 ongoing (repeat) concurrent medications the rate of stopping antidepressant treatment before the recommended duration was 30% less compared to individuals taking no medications other than their antidepressant (HR 0.70, 95% CIs 0.64-0.75). Adjustment for confounders had a minimal effect on this model as well (from HR 0.69 to HR 0.70 for 5 ongoing concurrent medications). I report the hazard ratio point estimates and 95% CIs in **Table 4.iii.**

4.3.2.3 Interaction test: whether the association between the number of concurrent medications and stopping antidepressant treatment differed according to the antidepressant class prescribed

There was no evidence of an interaction between the antidepressant class prescribed and the number of concurrent medications prescribed at the start of antidepressant treatment, with regards to stopping antidepressants before the recommended duration (p-value > 0.1).

Table 4.iii Sensitivity analysis results for the association between the number of repeat concurrent medications and stopping antidepressants before the recommended duration

	Univariable HRs (95% CI)	Multivariable HRs (95% CI)
Number of medications*:		
0	1	1
2	0.85 (0.47-1.55)	0.89 (0.85-0.94)
3	0.73 (0.46-1.15)	0.80 (0.75-0.87)
4	0.71 (0.42-1.18)	0.74 (0.69-0.80)
5	0.69 (0.42-1.13)	0.70 (0.64-0.75)
6	0.59 (0.36-0.98)	0.65 (0.60-0.70)
7	0.59 (0.36-0.97)	0.62 (0.57-0.67)
8	0.54 (0.32-0.89)	0.59 (0.54-0.64)
9	0.54 (0.32-0.90)	0.56 (0.52-0.61)
10	0.49 (0.29-0.83)	0.54 (0.49-0.60)
11	0.47 (0.27-0.82)	0.52 (0.47-0.59)
12	0.44 (0.24-0.80)	0.51 (0.44-0.58)
13	0.47 (0.25-0.89)	0.49 (0.41-0.59)
14	0.56 (0.27-1.14)	0.48 (0.38-0.61)
15	0.49 (0.19-1.28)	0.46 (0.34-0.63)
16	0.31 (0.07-1.34)	0.45 (0.31-0.66)
17	0.16 (0.02-1.75)	0.43 (0.27-0.69)
18	0.09 (0.00-3.65)	0.42 (0.24-0.74)

*Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

4.3.2 Results for the association between polypharmacy and switching antidepressant agents

I found no evidence of a difference, according to the number of concurrent medications prescribed at the time of starting antidepressant treatment, in the rate of switching to a different antidepressant agent in people with comorbid depression and T2DM. This was the case in the main analysis reported in **Table 4.v** (including any concurrent

medications) and the sensitivity analysis reported in **Table 4.vi** (including ongoing concurrent medications only).

Table 4.v Main analysis results for the association between the number of concurrent medications and switching antidepressant agents

	Univariable HRs (95% CI)	Multivariable HRs (95% CI)
Number of medications*:		
0	Reference	Reference
2	0.95 (0.89-1.02)	1.00 (0.99-1.02)
3	0.91 (0.82-1.01)	1.00 (0.97-1.03)
4	0.88 (0.77-0.99)	1.00 (0.96-1.04)
5	0.85 (0.75-0.97)	1.00 (0.95-1.06)
6	0.84 (0.74-0.96)	1.04 (0.94-1.07)
7	0.84 (0.73-0.95)	1.01 (0.93-1.09)
8	0.84 (0.73-0.96)	1.01 (0.92-1.10)
9	0.84 (0.73-0.96)	1.01 (0.91-1.11)
10	0.84 (0.73-0.97)	1.01 (0.90-1.13)
11	0.84 (0.71-0.99)	1.01 (0.89-1.15)
12	0.84 (0.70-1.02)	1.01 (0.88-1.16)
13	0.85 (0.68-1.08)	1.01 (0.87-1.18)
14	0.87 (0.65-1.16)	1.02 (0.86-1.20)
15	0.88 (0.62-1.26)	1.02 (0.85-1.22)
16	0.90 (0.58-1.39)	1.02 (0.84-1.24)
17	0.91 (0.54-1.54)	1.02 (0.83-1.26)
18	0.93 (0.50-1.72)	1.02 (0.82-1.28)

*Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

Table 4.vi Sensitivity analysis results for the association between the number of concurrent repeat medications and switching antidepressant agents

	Univariable HRs (95% CI)	Multivariable HRs (95% CI)
Number of medications*:		
0	1	1
2	0.98 (0.97-1.00)	0.99 (0.98-1.01)
3	0.97 (0.94-0.99)	0.99 (0.96-1.02)
4	0.95 (0.91-0.99)	0.98 (0.94-1.02)
5	0.93 (0.89-0.98)	0.98 (0.93-1.03)
6	0.92 (0.86-0.98)	0.97 (0.91-1.04)
7	0.90 (0.84-0.97)	0.97 (0.90-1.04)
8	0.89 (0.82-0.97)	0.96 (0.88-1.05)
9	0.88 (0.80-0.97)	0.96 (0.87-1.06)
10	0.86 (0.78-0.96)	0.95 (0.85-1.07)
11	0.85 (0.75-0.96)	0.95 (0.83-1.07)
12	0.84 (0.73-0.96)	0.94 (0.82-1.08)
13	0.83 (0.71-0.95)	0.94 (0.80-1.09)
14	0.81 (0.69-0.95)	0.93 (0.79-1.10)
15	0.80 (0.67-0.95)	0.93 (0.77-1.11)
16	0.79 (0.65-0.95)	0.92 (0.76-1.12)
17	0.78 (0.63-0.95)	0.92 (0.74-1.13)
18	0.77 (0.61-0.95)	0.91 (0.73-1.15)

*Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

4.4 Discussion

4.4.1 Main findings

In this study, I examined whether people with comorbid depression and T2DM were more likely to stop antidepressant treatment before the recommended duration (7 months) or switch antidepressant agents within this time, if they were prescribed more concurrent medications at the time of starting antidepressant treatment.

I found that the majority of people with comorbid depression and T2DM (55%) stopped the first antidepressant prescribed before the recommended duration of treatment (median duration 4.57 months) – 44% of these stopped antidepressant treatment completely (defined as a gap of 60 days after the last prescription) and 11% switched antidepressant agents. I had hypothesised that people with comorbid depression and T2DM would be more likely to stop antidepressants before the recommended duration the more concurrent medications they were prescribed. However, my findings were the opposite to this. The more medications that people were taking at the time of starting antidepressant treatment, the less likely they were to stop antidepressants before the recommended duration. However, people were no more or less likely to switch antidepressant agents according to the number of concurrent medications prescribed. There was also no difference between different antidepressant agents with regards to stopping treatment before the recommended duration.

4.4.2 Comparison to existing literature

This was the first study that I am aware of to investigate antidepressant acceptability or stopping antidepressant medication in people with comorbid depression and T2DM, or according to the number of concurrent medications prescribed in any population.

The median duration of treatment for the first antidepressant prescribed (4.57 months) was shorter than what is reported for the UK general population (6 months) (201). This suggests that antidepressants may be less acceptable to people with comorbid depression and T2DM.

In the general population, there is a growing body of literature suggesting that the treatment burden from polypharmacy negatively affects medication acceptability and adherence (184,186,192–196). However, the findings of my study may suggest the opposite, as the more concurrent medications prescribed, the less likely an individual with comorbid depression and T2DM was to stop antidepressant treatment before the recommended duration. This is based on the assumption that stopping antidepressant treatment is a proxy for antidepressant non-adherence, one explanation for which may be antidepressant acceptability. The findings of my study are in line with other studies specifically in people with T2DM. Several studies investigating adherence to somatic medication in people with T2DM have also reported that the more medications people were prescribed, the more likely they were to adhere to antidiabetic medications (390–

393). One study suggests that this may be due to increased contact with healthcare services (394). However, reasons for the difference between studies in people with T2DM and in the general population are unclear.

4.4.3 Potential explanations for these findings

The reasons for starting and stopping medication are not captured within CRPD EHRs. An individual may switch antidepressant agents if they did not respond to or could not tolerate the first antidepressant tried, but still wish to continue treatment. On the other hand, stopping antidepressant treatment completely (my primary outcome for this study – described above) represents an unwillingness to continue pharmacological treatment. People with comorbid depression and T2DM were less likely to stop antidepressant treatment completely the more medications they were prescribed, but no more or less likely to switch antidepressant agents. One explanation for this is that people who were prescribed more medications were more willing to adhere to antidepressant treatment.

People who take more medications may be more accepting of pharmaceutical treatment generally. They may find it easier to adhere to treatment because of additional support (such as more frequent GP or nurse appointments, or dosette boxes) or pre-existing medication taking habits. This could make them more likely to continue antidepressants for the recommended duration. On the other hand, people who take more medications may (by implication) have worse overall health. Both worse overall health (325) and polypharmacy (197) have been shown to be associated with more severe depression. Therefore, people with comorbid depression and T2DM who take more concurrent medications, may have more severe depression, whereby antidepressant treatment is less likely to be stopped by the patient or the clinician. Similarly, individuals who were taking less concurrent medications may have had less severe depression. These individuals may have felt better sooner (whether due to the antidepressant treatment or due to spontaneous remission) and therefore stopped antidepressant treatment early. Alternatively, the antidepressant may have had no benefit and therefore been stopped.

However, reasons for antidepressant discontinuation are not available in CPRD data. As such, there are a number of alternative explanations for early antidepressant discontinuation. For example, the decision to stop antidepressant treatment may have

been made by the clinician, if the antidepressant prescribed was not appropriate for the patient – this could particularly be the case for people prescribed more concurrent medications who may have more contraindications than those prescribed less concurrent medications. In addition, it is not possible to see whether patients who are continuing to be issued antidepressant medication are indeed taking the medication. It may be that the prescriptions are being issued but not taken. This could increasingly be the case for patients who have multiple prescriptions being issued.

To see whether any particular class of antidepressant was more or less acceptable to people with comorbid depression and T2DM taking multiple medications, I compared the risk of stopping antidepressant treatment according to the number of concurrent medications prescribed, between people who were prescribed different antidepressant classes as their first antidepressant agent. Different antidepressant classes have different side effect profiles. For example, SSRIs may commonly cause cardiovascular disturbances; mirtazapine may commonly cause weight gain; venlafaxine may commonly cause hypertension. If differences in antidepressant acceptability were due to antidepressant side effects, I would have expected to observe differences across the different classes of antidepressant agents. However, this was not the case.

My sensitivity analysis restricted exposure to concurrent medications to include only ongoing medications (repeat prescriptions). The inverse association between the number of medications prescribed at the time of starting antidepressant treatment and the risk of subsequently stopping before the recommended duration remained. However, the size of the association was smaller. Ongoing medications represent an ongoing treatment burden. One off medications are likely to represent acute health events or newly worsened health issues. This suggests that experiencing acute health events or newly worsened health may be further associated with a reduction in the risk of stopping antidepressants early. This may be related to the psychological distress experienced from acute health events (395,396), increasing the need for antidepressant treatment.

4.4.4 Strengths and limitations

This is the first study to investigate depression relapse or restarting antidepressant treatment after stopping in people with comorbid depression and T2DM. It is also the first study in any population to compare differences in depression relapse or restarting

antidepressant treatment, according to the number of concurrent medications prescribed.

With a sample size of 73,808, this study is over 200 times larger than all studies combined in the 2012 Cochrane meta-analysis of antidepressant treatment outcomes in people with comorbid depression and T2DM. All RCTs included in the Cochrane review excluded individuals with severe depression, and the majority excluded individuals with comorbidities common in T2DM, or prescribed medications common in T2DM. In this study, I included people with comorbid depression and T2DM who had started antidepressant treatment for the first time, regardless of depression severity, comorbidities or concurrent medication use. The findings of this study provide a representative view of real world antidepressant treatment trajectories in people with comorbid depression and T2DM in the UK.

I considered stopping antidepressants before the recommend duration of treatment to be an indicator of antidepressant acceptability. This is in line with a large meta-analysis by Cipriani et al investigating the effectiveness and acceptability of antidepressant medication in the general population, in which acceptability was defined as stopping the antidepressant agent for any reason (77). I adapted Cipriani et al's definition of antidepressant acceptability to UK NICE guidelines, where the period of time where stopping antidepressants could be considered reflected the minimum recommended duration of antidepressant treatment. The European Medicines Agency define the acceptability of a pharmaceutical product as 'the ability and willingness of a patient to use and its caregiver to administer the medicine as intended' (397). The reasons for starting and stopping medications are not included in CPRD data. Therefore, I performed a secondary analysis examining rates of switching antidepressant agents. An individual may switch antidepressant agents if they did not respond to or could not tolerate the first antidepressant tried, but still wish to continue treatment. On the other hand, stopping antidepressant treatment completely (my primary outcome for this study) represents an unwillingness to continue pharmacological treatment. By doing this I was able to hypothesise as to potential reasons for stopping antidepressant treatment early. However, without the explicit recording of reasons for stopping treatment, these hypotheses could only be speculative.

As described above, all prescriptions issued in primary care are done so electronically, and so, are automatically recorded. Therefore, I have high confidence in the

completeness and accuracy of my primary exposure variable – which was the count of concurrent medications prescribed at the time of starting antidepressant treatment. Other studies investigating polypharmacy have typically done so as a binary or categorised outcome (162,192,194,197,393,398). With the large sample size of this study, I was able to more precisely model the relationship between polypharmacy and stopping antidepressant treatment and polypharmacy as a continuous count of concurrent prescriptions using spline functions. This means that I was able to identify the minimum number of concurrent medications that an individual needed to be more likely to stop antidepressant treatment. I was also able to observe the increasing effect size of each additional medication prescribed, compared to the reference value of zero.

I used the reference value of zero concurrent medications (other than the antidepressant itself) as the comparison group to which all other values for the count of concurrent medications were compared. While individuals taking 1 or more medications may be more representative of individuals with T2DM (83), the model did not fit a spline point at the value of 1 concurrent medication, showing that there was no evidence of a difference between 1 and 0 concurrent medications. Thus, I made comparisons to the group of individuals who were not being prescribed any concurrent medications.

The definition of concurrent medication only required one prescription of each exposure medication in the 90 days prior to the index date. This could mean that it included one-off prescriptions that the patient did not take, or failed trials of multiple medications to treat the same issue. However, I addressed this with my sensitivity analysis, by including only ongoing repeat prescriptions only. The association between the number of concurrent medications prescribed at the time of starting antidepressant treatment and subsequently stopping remained.

I was unable to directly account for the severity of people's depression, as there was no consistently recorded variable in the dataset to account for this directly. Therefore, as discussed above in **Section 4.4.3**, I suspect that the findings of this study were confounded by the indication of depression severity. This would mean the decreased risk of stopping antidepressant treatment seen in people with comorbid depression and T2DM who were prescribed more medications, were attributable to these people being more severely depressed and therefore having a greater need to continue

treatment. However, with no direct way to account for depression severity, this hypothesis can only be speculative.

I adjusted for the following demographic variables: age, gender, ethnicity, calendar year and GP practice. There was very little difference in any of the results after confounder adjustment. There was a large amount of missing data for ethnicity, however, the findings did not differ when I only included individuals with completed ethnicity. It was not possible to account for patient-level deprivation, as this was not available for most individuals. However, deprivation was accounted for at GP practice level, by the inclusion of the GP practice ID as a stratum term in the model. The inclusion of GP practice as a stratum term accounted for clustering at practice level by fitting baseline hazard functions for each GP practice. In this way, I was able to account for geographical differences, and practice-level prescribing trends. Thus, my findings were robust in that they were not confounded by area-level sociodemographic factors.

I performed a range of analyses, including the investigation of my secondary outcome (switching antidepressant agents), sensitivity analysis (repeat prescriptions only), and subgroup analyses (antidepressant class). This has enabled me to hypothesise that the association between polypharmacy and early antidepressant discontinuation is due to improved adherence behaviour and is confounded by depression severity. However, as the rationale behind prescribing decisions is not captured by EHR data, again, the full interpretation of these results can only be speculative.

4.4.5 Implications

In people with comorbid depression and T2DM, it is common to stop antidepressants before the recommended duration of treatment. However, the more concurrent medications an individual in this patient group was taking, the more likely they were to adhere to the recommended duration of antidepressant treatment. This may be because they had worse overall health, resulting in more severe depression requiring the continuation of treatment. These individuals may have derived the most benefit from antidepressant treatment. Alternatively, it may be because individuals who were prescribed more concurrent medications were more accepting of pharmaceutical treatment generally. These individuals may find it easier to adhere to treatment because of increased levels of support or pre-existing medication taking behaviours.

Failure to adhere to antidepressant treatment recommendations could jeopardise the successful treatment of depression in these individuals. If this is indeed what is happening, increased monitoring and support for antidepressant adherence in people with comorbid depression, particularly who are taking fewer concurrent medications, may be beneficial. I discuss this in more detail in my **Discussion Chapter 8**.

While there was no evidence from my findings in this study that the number of concurrent medications adversely effected antidepressant acceptability, the long-term safety of antidepressant treatment in people with comorbid depression and T2DM who are taking multiple medications are still unknown. I address this later in my thesis, in **Chapters 6-7**, which investigate the association between antidepressant treatment and long-term physical health outcomes in people with comorbid depression and T2DM.

In the following **Chapter 5**, I look at what happens to people with comorbid depression and T2DM after they stop antidepressant treatment. I examine whether the number of concurrent medications prescribed at the time of stopping antidepressant treatment affects the likelihood of restarting antidepressants, which I use as a proxy for depression relapse. The findings of this next study could help to disentangle whether people with comorbid depression and T2DM who are prescribed more concurrent medications are more severely depressed, or whether they are more accepting of pharmaceutical treatment generally. In addition, in **Chapter 5**, I will also explore whether shorter durations of antidepressant treatment, as seen in people taking fewer concurrent medications, jeopardise the successful treatment of depression in people with comorbid T2DM.

Chapter 5: The Association between Polypharmacy and Depression Relapse in Adults with Comorbid Depression and Type 2 Diabetes

An abridged version of this study is published as:

Jeffery, A., Bhanu, C., Walters, K., Wong, I., Osborn, D., & Hayes, J. (2023). *Association between polypharmacy and depression relapse in individuals with comorbid depression and type 2 diabetes: A UK electronic health record study.* The British Journal of Psychiatry, 222(3), 112-118. doi:10.1192/bjp.2022.160

5.1 Introduction

In the previous **Chapter 4**, I looked at what happened to people with comorbid depression and T2DM after starting antidepressant treatment in terms of subsequently stopping or switching antidepressants. In this chapter, I look at what happens to people with comorbid depression and T2DM after they stop antidepressant treatment. Specifically, rates of restarting antidepressant treatment as a marker of clinically identified depression relapse.

Depression relapse can be defined as the return of depression symptoms within the expected duration of the current episode of depression (up to 12 months) (207). In the general population, it is estimated that approximately 41% of people who stop antidepressant treatment, subsequently relapse (210). As I described in detail in my Introduction **Chapter 1.4.1**, T2DM is associated with an increased risk of depression symptoms. Therefore, individuals with comorbid depression and T2DM may be at increased risk of depression relapse. Understanding predictors of depression relapse in this patient group is important. A recent meta-analysis Palapinyo et al showed that polypharmacy was associated with increased depression symptoms (197). In **Chapter 4**, I found that people with comorbid depression and T2DM who were prescribed more medications, were more likely to continue having antidepressant prescriptions issued – I suggested that this may be due to them having worse overall health, and consequently more severe depression. If people who take more concurrent

medications are more likely to be more severely depressed, this could also mean they have a higher risk of depression relapse.

In my Introduction **Chapter 1.6.1.3**, I explained that the optimum antidepressant treatment duration is unknown – on one hand, studies show that people who stop antidepressant treatment are more likely to relapse than those who continue treatment (207); on the other hand, some studies show that people who stop antidepressants after longer durations are more likely to relapse than those who were taking antidepressants for shorter durations (212). NICE guidelines recommend longer durations of antidepressant treatment – at least 2 years – in people with higher risk of relapse (82). However, the guidelines do not define who might be included in this higher risk of relapse group. If people with comorbid depression and T2DM who are prescribed larger numbers of concurrent medications are at higher risk of relapse compared to those prescribed fewer concurrent medications, then these individuals may benefit from longer durations of antidepressant treatment.

There are no studies that I am aware of investigating the association between polypharmacy or the previous duration of antidepressant treatment and depression relapse or the risk of restarting antidepressants in people with comorbid depression and T2DM.

The main aim of this study was to understand whether people with comorbid depression and T2DM were more or less likely to restart antidepressants within 12 months, the more concurrent medications they were prescribed at the time of stopping antidepressant treatment. I hypothesised that people who were prescribed more concurrent medications at the time of stopping antidepressant treatment, would be more likely to restart antidepressants within 12 months, as a marker of clinically identified depression relapse. This was based on evidence that people who take more medications are more likely to be depressed (197).

I also aimed to understand whether being prescribed antidepressants for longer durations before stopping would attenuate the risk of restarting antidepressants in the future. NICE guidelines recommend longer antidepressant treatment durations for people at higher risk of relapse. I had previously hypothesised people with comorbid depression and T2DM taking more concurrent medications would be in this group.

Therefore I hypothesised that being prescribed an antidepressant for a longer duration would attenuate the risk of restarting antidepressants in the future.

5.2 Methods

5.2.1 Study design and setting

I completed a cohort study using EHR data from the UK CPRD. I show a graphical representation of the study design in **Figure 5.i**, after describing the patient inclusion criteria and study outcomes.

The study period ran from 1 January 2000 to 31 December 2018. However, I used data from earlier years (pre-2000) to select the cohort and to identify some of the confounders required in my study.

5.2.2 Patient inclusion criteria

I included individuals with comorbid depression and T2DM who had both started and subsequently stopped antidepressant treatment during the study period.

I took the sample of individuals for this study from the cohort of individuals included in the study described in the previous **Chapter 4** (investigating the association between polypharmacy and stopping antidepressants). These were adults (18+ years) with comorbid depression and T2DM who had started antidepressant treatment for the first time. Individuals entered this base cohort when they commenced antidepressant treatment, which I considered to signify a clinically identified episode of depression.

From this base cohort, I identified individuals who stopped antidepressant treatment at any time during their EHR follow-up. I defined stopping antidepressants as a gap of at least 60 days without an antidepressant prescription, after the expected duration of the last antidepressant prescription. To do this, I calculated the likely duration for each antidepressant prescription using data on the number of tablets issued, recorded frequency and/or duration, length of previous prescriptions. I specified a gap of 60 days to account for the antidepressant washout period, individuals who may collect their prescription at irregular intervals, who may have left over medication from previous prescriptions, or who may restart antidepressants due to withdrawal symptoms rather than depression relapse (399). I excluded individuals with less than

60 days follow up after the expected duration of the last antidepressant prescription before stopping.

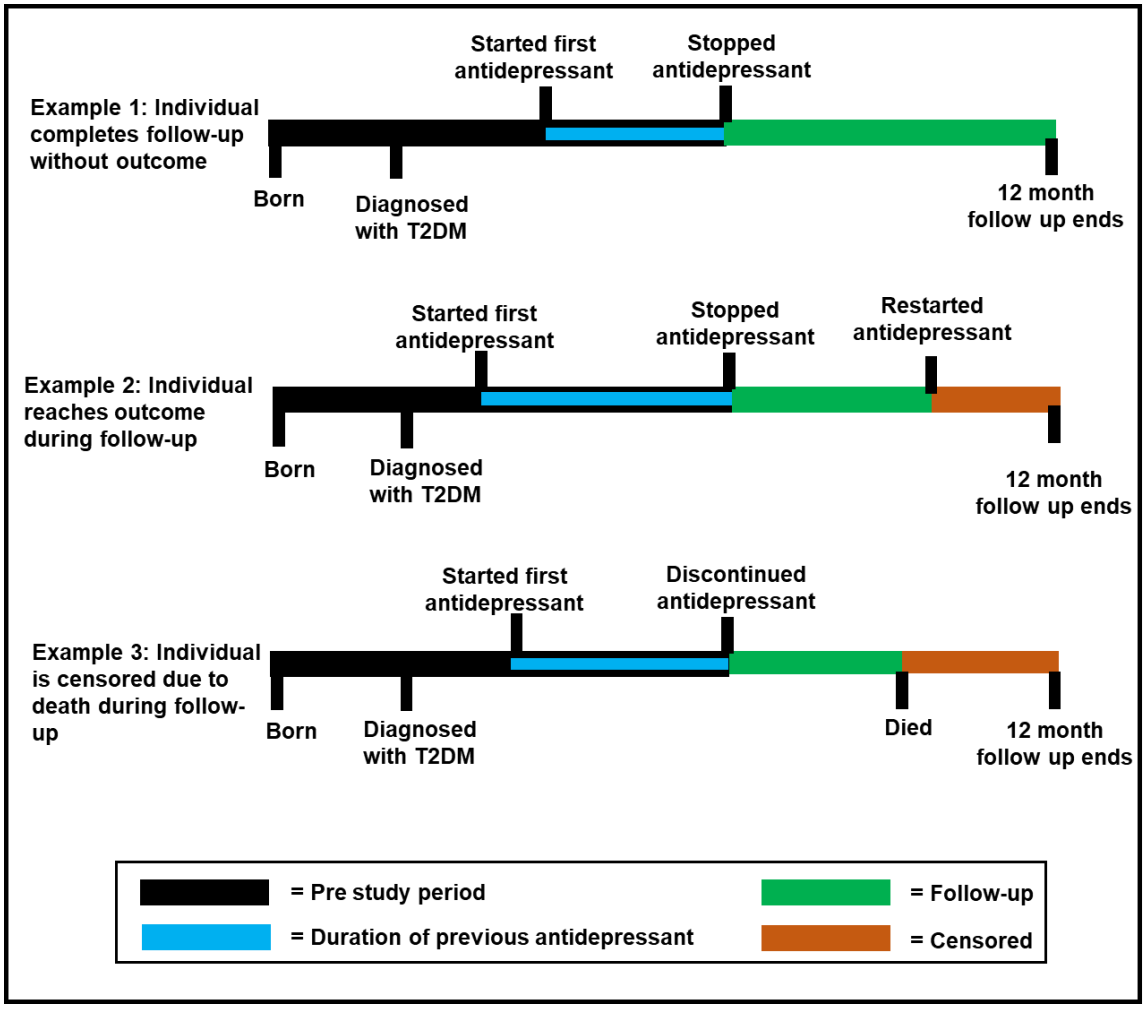
I started follow up on the expected end date of the last antidepressant prescription. I ended follow up after 365 days (12 months). I censored participants if they restarted antidepressant treatment (the outcome), at their date of death, end of registration with their primary care practice, end of the study period (31 December 2018), or after 365 days follow-up, whichever was first.

5.2.3 Outcome – restarting antidepressant treatment

I defined the outcome as restarting antidepressant treatment between 61 to 365 days after the stopping. This is in line with other studies investigating depression relapse after stopping antidepressants in a UK primary care population (400). The return of depression symptoms within 12 months may signify depression relapse (207). Whereas, the return of depression symptoms after more than 12 months would be considered as a new episode of depression (207). I did not consider individuals with an antidepressant prescription less than 61 days since the previous antidepressant prescription to have stopped treatment (as described above in **Section 5.2.2**).

I show a graphical representation of follow-up time in which the outcome may occur in **Figure 5.i**.

Figure 5.i Graphical representation of study design



5.2.4 Definition of exposures

5.2.4.1 Primary exposure – the number of concurrent medications

The primary exposure was the number of concurrent medications prescribed to a person on the date of the last antidepressant prescription before stopping or up to 90 days prior. I did not include the antidepressant itself in the count of medications prescribed. I specified 90 days to capture prescriptions which are issued for longer durations, which may be commonplace for long-term conditions. I excluded topical medications, supplements and vaccinations. I described the creation of the code list for all medications in my **Methods Chapter 3.5.3**.

Some people do not receive concurrent medications for T2DM, so the reference group was zero concurrent medications (not including the antidepressant).

5.2.4.2 Secondary exposure – the previous duration of antidepressant treatment

I defined the secondary exposure as the duration of antidepressant treatment before stopping. I measured this as the count in days between the first antidepressant prescription and the date that their final antidepressant prescription would run out. I categorised this length of antidepressant treatment into 5 categories, based on different guideline recommendations:

Early discontinuation: 0-6 months

NICE recommendations (73): 7-10 months

WHO recommendations (401): 11-13 months

Medium-term: 14-24 months

NICE + WHO recommended maintenance for high risk of relapse individuals (73,401): 25+ months

I used the early discontinuation category as the reference category.

5.2.5 Confounders

I included calendar year, age, gender, ethnicity and GP practice (as a stratum term) as potential confounders, as demonstrated in **Figure 5.ii**. Age was measured on the date of the last antidepressant prescription before stopping. I did not include comorbidities or the stage of the diabetes as confounders because they were highly

collinear with the main exposure (number of concurrent medications). Where ethnicity was missing, I recoded this as “White”, consistent with the rationale and approach taken in the previous **Chapter 4.**

5.2.6 Sensitivity analyses

5.2.6.1 Sensitivity analysis: restricting the exposure to ongoing concurrent medication (repeat prescriptions)

One off prescriptions do not necessarily mean that an individual is taking a medication. To account for this, I performed a sensitivity analysis to distinguish ongoing treatment with concurrent medications (repeat prescriptions) from one-off prescriptions. To do this, I redefined the primary exposure variable (number of concurrent medications), by recalculating the total number of concurrent medications. I only included medications with at least two prescriptions up to 180 days prior to the index date, and at least one of the prescriptions within 90 days of the index date.

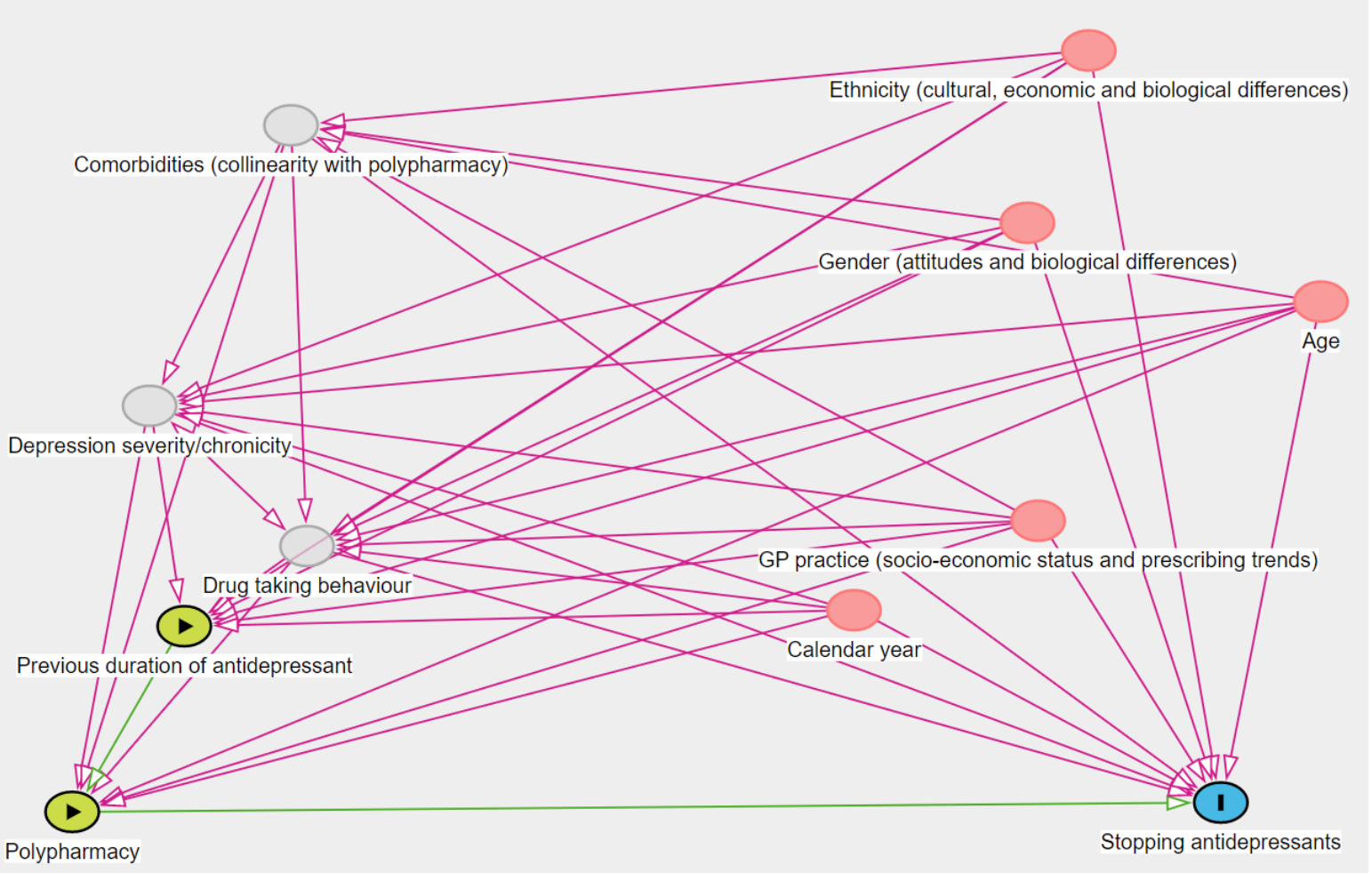
5.2.6.2 Sensitivity analysis: including only individuals with complete ethnicity data

I performed a second sensitivity analysis to investigate the effect of coding individuals with missing ethnicity as “White”. To do so, I repeated the main analysis including only individuals with completed ethnicity.

5.2.6.3 Sensitivity analysis: restricting follow-up to 6 months

I performed a third sensitivity analysis to assess the role of timing for depression relapse (within 365 days of discontinuation). I limited the observed period to 182 days, since some studies define relapse as occurring within 6 months of discontinuation (402)

Figure 5.ii DAG showing the relationship between confounders, exposures and outcome



*Green circle = exposure; blue circle = outcome; red circle = potential confounder; grey circle = unmeasured; direction of arrow shows potential causal effect – red arrow = confounding relationship, green arrow = causal pathway; relationships with the previous duration of antidepressant treatment was informed by the study in **Chapter 4**

5.2.7 Statistical analyses

I used a similar analysis approach in this study, to the study described in **Chapter 4** (investigating the association between the number of concurrent medications and stopping antidepressants). I used Cox regression to separately estimate hazard ratios for the association between the two exposures (1 – the number of concurrent medications, and 2 – the duration of previous antidepressant treatment) and the outcome of restarting antidepressant treatment. As the relationship between the number of concurrent medications and restarting antidepressants was not linear, I used a penalised B-splines term to transform the exposure variable (number of concurrent medications). I used the same spline-function approach to the exposure of concurrent medications in the previous Chapter 4 and I described this method in detail in my **Methods Chapter 3.6.1**.

I first performed two univariable analyses to determine the association between restarting antidepressant treatment and each of the exposures separately (1 – the number of concurrent medications, and 2 – the previous duration of antidepressant treatment). I then performed two multivariable analyses. The first was to determine the association between the number of concurrent medications at the time stopping antidepressants and subsequently restarting antidepressant treatment, adjusted for the previous duration of antidepressant treatment, and demographic confounders. The second was to determine the association between the previous duration of antidepressant treatment and subsequently restarting antidepressant treatment, adjusted for demographic confounders. In both adjusted models, I included the primary care practice as a stratum term, whereby separate baseline hazard functions were fitted for each stratum, to account for the clustering effect of each primary care practice.

I also tested for an interaction between the two exposures (1 – the number of concurrent medications, and 2 – the previous duration of antidepressant treatment), with regards to restarting antidepressants.

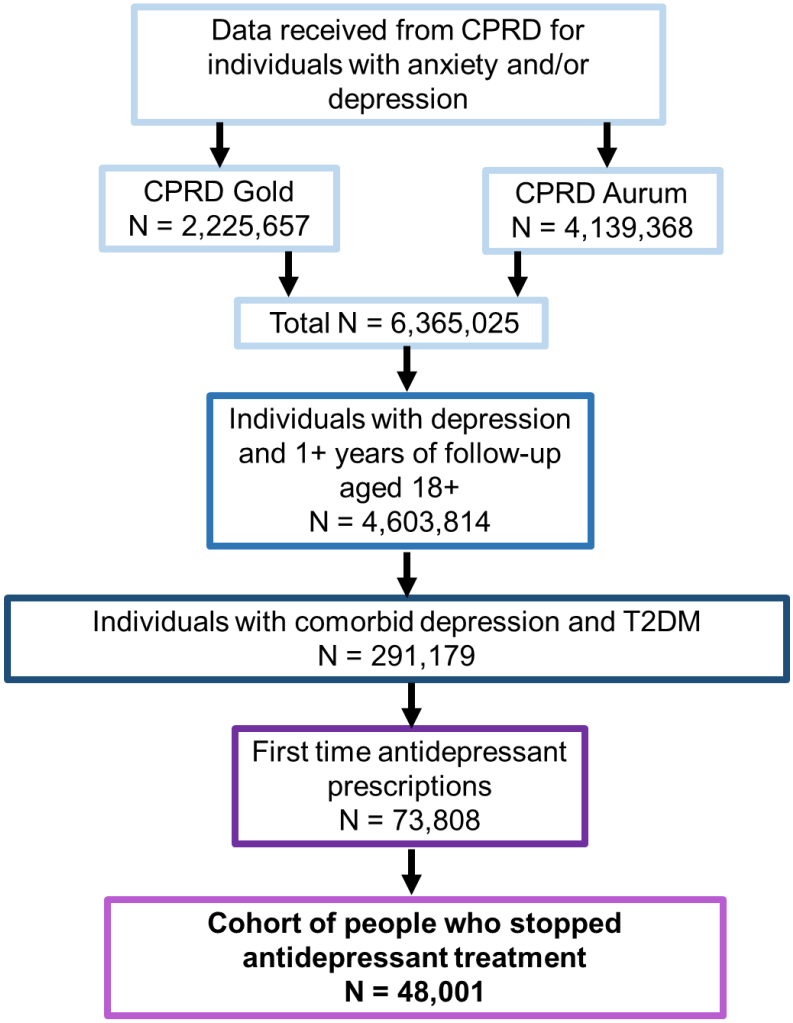
I repeated the first multivariable analysis for each sensitivity analysis described in **Section 5.2.6**.

5.3 Results

5.3.1 Characteristics of individuals included in this study

I demonstrate the number of individuals included or excluded in a flow diagram, **Figure 5.iii**.

Figure 5.iii Flow diagram of inclusion and exclusion



I describe the characteristics of individuals included in the study in **Table 5.i**.

From the cohort of adults with comorbid depression and T2DM starting antidepressant treatment for the first time, I identified 48,001 individuals who subsequently discontinued antidepressant treatment during the study period. The median age of included individuals was 62 (IQR 52-71) and 53% were female.

In terms of diabetes severity, 11.42% were at an early stage and were receiving no concurrent anti-diabetic treatments, 27.81% were receiving the first-line treatment metformin alone, 45.04% were receiving second-line oral antidiabetic treatments and 15.48% were at the later stage of diabetes where they were receiving insulin therapy.

The median number of concurrent prescriptions at the time of starting antidepressant treatment (including anti-diabetic medication but excluding the antidepressant itself) was 9 (IQR 6-12). When I restricted to longer-term prescriptions, the median was 6 (IQR 4-9).

The majority of individuals discontinued antidepressant treatment early, with a median treatment duration of the first antidepressant prescribed of 2.79 months. Within the first year following discontinuation 35.29% of individuals restarted antidepressant treatment.

5.3.2 Main analysis results

5.3.2.1 Association between polypharmacy and restarting antidepressants

In both the adjusted and unadjusted models, I found that the more medications people were receiving at the time of antidepressant discontinuation, the more likely they were to subsequently restart antidepressant treatment within one year (**Figure 5.ii**). Evidence of an association began at 2 concurrent medications, where there was an 8% increase in the rate of restarting antidepressant treatment, compared to individuals prescribed no medication other than their antidepressant (HR 1.08, 95% CI 1.01-1.15). The rate of restarting antidepressant treatment then increased for each additional medication prescribed, until 18 concurrent medications (HR 2.15, 95% CI 1.32-3.51). The median number of 9 concurrent medications was associated with a 64% increase in the rate of restarting antidepressant treatment altogether (HR 1.64, 95% CIs 1.44-1.86) compared to individuals in receipt of no medication other than their antidepressant. Adjustment for confounders had a minimal effect on the model (for example, changing from HR 1.52 to HR 1.64 for 9 concurrent medications). I report the hazard ratios in point estimates and 95% CIs in **Table 5.ii.**

Table 5.i – Characteristics of included individuals and descriptive analysis

	Whole sample (n = 48,001)
Median age (years)	62 (IQR 54-71)
Female, n (%)	25,437 (52.99)
Ethnicity group, n (%):	
Asian	4 3,322 (6.92)
Black	1,388 (2.89)
Mixed	262 (0.55)
Missing (imputed as White)	17,826 (37.14)
Other	357 (0.74)
White	24,846 (51.76)
Diabetes treatment stage:	
Early stage (no pharmacological treatment)	5,481 (11.42)
Metformin only	13,349 (27.81)
Second-line oral-antidiabetics	21,619 (45.04)
Insulin	7,480 (15.48)
Median number of concurrent prescriptions*	9 (IQR 6-12)
Median number of concurrent repeat prescriptions*	6 (IQR 4-9)
Previous antidepressant duration recommendations category:	
Early discontinuation (< 7 months)	33,039 (68.83)
NICE (7-10 months*)	3,167 (6.60)
WHO (11-13 months*)	2,204 (4.59)
Medium term (14-24 months*)	4,370 (9.10)
Maintenance (25+ months)	5,221 (10.88)
Restarted antidepressant treatment (%)	16,986 (35.29)
Censored (%)	1,560 (3.25)
Number of primary care practices included	1482

* Concurrent prescriptions were measured at/prior to the first recorded antidepressant medication; these include anti-diabetic medications but exclude the antidepressant itself

Figure 5.ii – Hazard ratios for the changing rate of restarting antidepressant treatment, by the number of concurrent medications prescribed at date of the previous antidepressant prescription before discontinuation (adjusted for confounders)

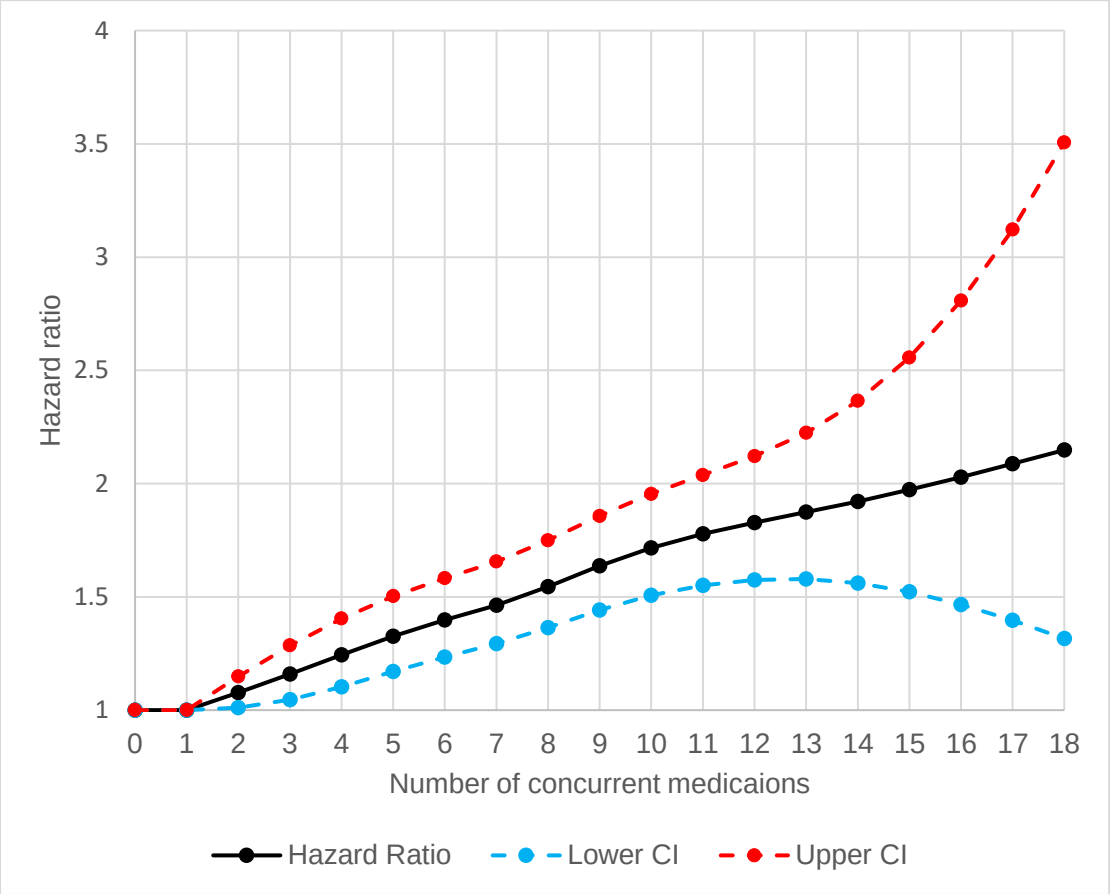


Table 5.ii Main analysis results for the association between the number of concurrent medications and restarting antidepressant treatment

	Unadjusted HRs (95% CIs)	Adjusted* HRs (95% CIs)
Number of medications:**		
0	Reference	Reference
2	1.08 (1.01-1.14)	1.08 (1.01-1.15)
3	1.15 (1.04-1.27)	1.16 (1.05-1.29)
4	1.22 (1.09-1.37)	1.24 (1.10-1.40)
5	1.29 (1.14-1.45)	1.33 (1.17-1.50)
6	1.34 (1.20-1.51)	1.40 (1.23-1.58)
7	1.39 (1.24-1.57)	1.46 (1.29-1.66)
8	1.45 (1.29-1.63)	1.54 (1.36-1.75)
9	1.52 (1.35-1.71)	1.64 (1.44-1.86)
10	1.60 (1.40-1.79)	1.72 (1.51-1.95)
11	1.63 (1.44-1.86)	1.78 (1.55-2.04)
12	1.68 (1.46-1.94)	1.83 (1.58-2.12)
13	1.74 (1.47-2.05)	1.87 (1.58-2.22)
14	1.79 (1.46-2.19)	1.92 (1.56-2.36)
15	1.85 (1.44-2.38)	1.97 (1.52-2.56)
16	1.90 (1.39-2.62)	2.03 (1.47-2.81)
17	1.97 (1.33-2.93)	2.09 (1.40-3.12)
18	2.04 (1.26-3.31)	2.15 (1.32-3.51)

* Adjusted for duration of previous antidepressant treatment, age, gender, ethnicity, GP practice and calendar year

**Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment altogether; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

5.3.2.2 Association between the previous duration of antidepressant treatment and subsequently restarting antidepressants

I report the association between the previous duration of antidepressant treatment and subsequently restarting antidepressants in **Table 5.iii**. In both the adjusted and unadjusted models, people who had been taking antidepressants for longer durations prior to discontinuation, were more likely to subsequently restart antidepressant treatment within one year. In the adjusted model, individuals with previous durations of 7-9 months were 60% more likely to restart antidepressant treatment compared to individuals who with previous durations of 1-6 months (HR 1.60, 95% CIs 1.51-1.70); at 9-12 months this increased to 79% (HR 1.79, 95% CIs 1.68-1.92); at 12-23 months to 113% (HR 2.13, 2.03-2.23); and at 24+ months to 136% (HR 2.36, 2.25-2.48).

I tested for an interaction between the duration of previous antidepressant treatment and the number of concurrent medications prescribed with regards to restarting antidepressant treatment. However, I found no evidence of an interaction (p-value > 0.1).

Table 5.iii Main analysis results for the association between the duration of previous antidepressant treatment and subsequently restarting antidepressant treatment

	Unadjusted HRs (95% CIs)	**Adjusted* HRs (95% CIs)**
Duration of previous antidepressant:		
<7 months	Reference category	Reference category
7-10 months	1.56 (1.48-1.66)	1.60 (1.51-1.70)
11-13 months	1.73 (1.62-1.84)	1.79 (1.68-1.92)
14-24 months	2.02 (1.93-2.12)	2.13 (2.03-2.23)
25+ months	2.14 (2.04-2.24)	2.36 (2.25-2.48)

* Adjusted for age, gender, ethnicity, GP practice and calendar year

5.3.3 Sensitivity analyses results

I performed three sensitivity analyses, described below. Results of all sensitivity analyses are shown in **Table 5.iv**

5.3.3.1 Restricting the exposure to include only repeat prescriptions.

I restricted the primary exposure (number of concurrent medications) to include repeat prescriptions only. The rate of restarting antidepressants was elevated in individuals receiving 5 or more repeat prescriptions compared to those receiving no repeat prescriptions. This association was maintained up to receipt of 10 repeat prescriptions. The median number of 6 repeat concurrent medications was associated with a 54% increase in the rate of restarting antidepressants (HR 1.52, 95% CIs 1.12-2.11) compared to individuals taking no medications other than their antidepressant.

5.3.3.2 Including individuals with completed ethnicity only

In the third sensitivity analysis I included only individuals with a completed value for ethnicity. There was no evidence of a change in the effect estimates between the main analysis and this sensitivity analysis, for either of the two exposures (1 – the number of concurrent medications, 2 – the duration of previous antidepressant treatment) .

5.3.3.3 Limiting the follow-up period to 6 months

In the second sensitivity analysis I limited the observed follow-up period to 6 months. There was no evidence of a change in the effect estimates between the main analysis and this sensitivity analysis, for either of the two exposures (1 – the number of concurrent medications, 2 – the duration of previous antidepressant treatment).

Table 5.iv Sensitivity analysis results for the association between the number of concurrent medications and restarting antidepressants, adjusted for the previous duration of antidepressant treatment and demographic confounders

	Sensitivity 1A**	Sensitivity 2A**	Sensitivity 3A**
Number of medications*:			
0	Reference	Reference	Reference
2	1.12 (0.84-1.50)	1.10 (1.03-1.18)	1.08 (1.01-1.15)
3	1.25 (0.90-1.75)	1.22 (1.09-1.36)	1.16 (1.04-1.30)
4	1.31 (0.96-1.79)	1.33 (1.17-1.52)	1.25 (1.09-1.42
5	1.41 (1.03-1.93)	1.45 (1.26-1.66)	1.33 (1.16-1.54)
6	1.54 (1.12-2.11)	1.55 (1.35-1.77)	1.40 (1.22-1.62)
7	1.52 (1.11-2.08)	1.63 (1.42-1.87)	1.46 (1.27-1.69)
8	1.66 (1.21-2.27)	1.73 (1.50-1.98)	1.54 (1.33-1.77)
9	1.81 (1.31-2.49)	1.82 (1.59-2.10)	1.62 (1.34-1.87)
10	1.98 (1.43-2.74)	1.91 (1.65-2.20)	1.70 (1.46-1.97)
11	1.95 (1.40-2.72)	1.97 (1.70-2.29)	1.76 (1.51-2.06)
12	1.76 (1.24-2.49)	2.02 (1.72-2.39)	1.83 (1.55-2.17)
13	1.60 (1.10-2.34)	2.07 (1.72-2.50)	1.90 (1.57-2.31)
14	1.49 (0.97-2.30)	2.13 (1.69-2.67)	1.98 (1.57-2.50)
15	1.44 (0.83-2.51)	2.19 (1.65-2.90)	2.06 (1.55-2.74)
16	1.43 (0.66-3.11)	2.25 (1.59-3.19)	2.15 (1.51-3.05)
17	1.43 (0.46-4.42)	2.32 (1.51-3.56)	2.24 (1.46-3.44)
18	1.44 (0.30-7.02)	2.39 (1.43-4.00)	2.34 (1.39-3.92)

*Each value for the number of concurrent medications represents a spline point optimally fitted to the shape of the relationship between the number of concurrent medications and discontinuing antidepressant treatment altogether; the number of splines was set automatically by the model to balance flexibility against overfitting; each spline point estimate provides a distinct hazard ratio

** Sensitivity model 1A = restricting primary exposure to include repeat prescriptions only; Sensitivity model 2A = limiting observed follow-up to 6 months; Sensitivity model 3A = including individuals with completed ethnicity only

Table 5.iv Sensitivity analysis results for the association between the previous duration of antidepressant treatment and restarting antidepressants, adjusted for demographic confounders

	Sensitivity 2B*	Sensitivity 3B*
Duration of previous antidepressant:		
<7 months	Reference	Reference
7-10 months	1.79 (1.67-1.92)	1.72 (1.50-1.85)
11-13 months	2.14 (1.98-2.30)	1.86 (1.71-2.03)
14-24 months	2.46 (2.33-2.59)	2.14 (2.01-2.28)
25+ months	2.75 (2.61-2.90)	2.44 (2.30-.2.50)

* Sensitivity model 2B = limiting observed follow-up to 6 months; Sensitivity model 3B = including individuals with completed ethnicity only

5.4 Discussion

5.4.1 Main findings

In this study, I examined whether people with comorbid depression and T2DM were more likely to restart antidepressant treatment if they were prescribed more concurrent medications at the time of previously stopping antidepressant treatment or if they had previously been prescribed antidepressants for longer durations.

I found that just over one third of people with comorbid depression and T2DM (35%) restarted antidepressant treatment within the first year of stopping. The more medications that people were taking at the time of stopping antidepressant treatment, the more likely they were to restart antidepressants within one year. The longer people had been taking antidepressants for prior to stopping, the more likely they were to restart antidepressant treatment within one year. There was no interaction between the number of concurrent medications prescribed and the duration of previous antidepressant treatment, with regards to subsequently restarting antidepressants.

5.4.2 Comparison to existing literature and my previous findings in this thesis

In a large meta-analysis of RCTs investigating depression relapse in the general population, by Geddes et al, 41% of people who stopped antidepressant treatment subsequently experienced depression relapse (210). This is only slightly higher than

the proportion of people in this study with comorbid depression and T2DM who restarted antidepressant treatment within 12 months of stopping (35%). The trials included in the review by Geddes et al had a broader range of follow-up times, however, the vast majority of participants were from trials that identified depression relapse over a period of 12 months, as I did in this study. Depression relapse may be easier to detect in clinical trials, where it is purposefully monitored as an outcome, than in primary care, which relies on people returning to seek help. In addition, even in clinically identified depression relapse, people may not necessarily restart antidepressant treatment. As such, the rate of restarting antidepressants that I found in people with comorbid depression and T2DM, is likely to be an underestimate of depression relapse in this population.

There are no studies, that I am aware, of investigating the association between the number of concurrent medications prescribed at the time of stopping antidepressants and subsequent depression relapse. However, a 2021 meta-analysis by Palapinyo et al, reported that people who were prescribed more medications were more likely to experience depression symptoms (197). This is in line with my findings in people with comorbid depression and T2DM, where the more concurrent medications an individual was prescribed, the more likely they were to restart antidepressant treatment, which is a marker of clinically identified depression relapse.

There are a number of studies which report that people with T2DM were more likely to be adherent to medications, the more medications they were prescribed (390–393). In my previous **Study Chapter 4**, I also found that the more concurrent medications people with comorbid depression and T2DM were prescribed, the more likely they were to continue to be issued repeat antidepressant prescriptions. As such, it may also be the case that people with comorbid depression and T2DM who were prescribed more concurrent medications, were more willing to restart antidepressant treatment when they experienced depression relapse, than those who were prescribed fewer concurrent medications. On the other hand, in other populations, the treatment burden from taking more medication is reported to make people less willing to take medication (186,192,193,203). My findings in this study, and the previous study described in **Chapter 4**, suggest that this is not the case for antidepressants in people with comorbid depression and T2DM.

In a meta-analysis by Williams et al, people who took antidepressant treatment for longer durations were more likely to experience depression relapse than those who took antidepressants for shorter durations (212). This is in line with my findings in people with comorbid depression and T2DM, where those who had previously been taking antidepressants for longer durations, had the highest rates of restarting antidepressant treatment, which is a marker of clinically identified depression relapse.

5.4.3 Potential explanations for these findings

Higher numbers of concurrent medications prescribed to an individual with comorbid depression and T2DM may represent worse overall health. Individuals with worse overall health may consequently have more severe depression (325). This may render such individuals at higher risk of depression relapse. This is supported by the meta-analysis described above, where individuals in other populations who take more medications were more likely to experience depression (197).

On the other hand, I found the rates of restarting antidepressant treatment in individuals with comorbid depression and T2DM to be lower than the rates of depression relapse following antidepressant discontinuation in the general population (207). While restarting antidepressant treatment may be a marker of clinically identified depression relapse, it is not a systematic measurement of depression relapse. There may be a number of individuals with comorbid depression and T2DM who experience depression relapse and either do not seek help, or do not wish to restart antidepressant treatment. Therefore, the association between the number of concurrent medications prescribed and restarting antidepressants, may alternatively be attributed to a willingness to seek help and accept pharmacological treatment for depression. This is supported by the studies described above, where individuals with T2DM who take more medications, are more likely to be adherent (186,192,193,203).

In **Chapter 4**, I suggested that individuals with T2DM who had more severe depression may be more likely to continue antidepressants for longer durations, due to an increased need for treatment in more severe compared to mild depression. If this is the case, longer previous durations of antidepressant treatment, prior to antidepressant discontinuation, may represent more severe depression. Therefore, the association between longer previous durations of antidepressant treatment and

subsequently restarting antidepressants, may be attributed to more severe depression.

Alternatively, similarly to individuals who are prescribed more concurrent medications, those who have been taking antidepressants for longer durations, may represent people who are more willing to take medication generally. This could also be the reason that they are more likely to restart treatment. Individuals with shorter durations of previous antidepressant treatment may also not have tolerated the antidepressant, and so may be less keen to restart similar treatments. Antidepressants may also have been inappropriately prescribed in these individuals, leading to shorter overall durations and decreased willingness to restart.

Another potential explanation may be the misidentification of restarting antidepressant treatment. Individuals with longer previous durations of antidepressant treatment may have accumulated a back supply of medication. This could allow them to have a longer gap between prescriptions without discontinuing. This would mean that these individuals had never really stopped antidepressant treatment (and so were continuing treatment, rather than restarting).

In the first sensitivity analysis, I restricted the polypharmacy exposure to include only repeat prescriptions. The effect estimates for the association between the number of repeat concurrent medications were lower than for the same number of medications in the main analysis (including both repeat and one-off prescriptions). Repeat prescriptions are likely to represent ongoing comorbidities. While acute health problems, are likely to be represented by one-off prescriptions. Therefore, the lower effect estimates for repeat prescriptions could suggest that individuals experiencing acute health problems at the time of antidepressant discontinuation are more likely to subsequently restart antidepressant treatment. In **Chapter 4**, I suggested that the psychological distress experienced from acute health events (395,396) may increase the need for antidepressant treatment. This could support the interpretation that polypharmacy is associated with more severe depression, leading to an increased risk of depression relapse requiring the individual to restart antidepressant treatment.

Alternatively, one-off prescriptions may represent a situation where an individual has trialled a medication and decided not to continue. This could be due to ineffectiveness (that the medication did not have a beneficial therapeutic action for the individual

patient) or intolerable side effects. Failed treatment of comorbid conditions, may indicate worse overall health which may lead to more severe depression (325). This alternative explanation, also supports the theory that more concurrent medications is associated with more severe depression, resulting in increased risk of depression relapse requiring the restarting of antidepressant treatment.

5.4.2 Strengths and limitations

This is the first study to investigate depression relapse or restarting antidepressant treatment after stopping in people with comorbid depression and T2DM. It is also the first study in any population to compare differences in depression relapse or restarting antidepressant treatment, according to the number of concurrent medications prescribed.

With a sample size of 48,001, this study is over 140 times larger than all studies combined in the 2012 Cochrane meta-analysis of antidepressant treatment outcomes in people with comorbid depression and T2DM (155). All RCTs included in the Cochrane review excluded individuals with severe depression, and the majority excluded individuals with comorbidities common in T2DM, or prescribed medications common in T2DM. In this study, I included people with comorbid depression and T2DM who had started antidepressant treatment for the first time and subsequently stopped, regardless of depression severity, comorbidities or concurrent medication use. The findings of this study provide a representative view of real world antidepressant treatment trajectories in people with comorbid depression and T2DM in the UK.

I intended the outcome of restarting antidepressant treatment to be a marker of depression relapse. Almost all prescribing in UK primary care is electronic, and the vast majority of prescriptions are entered accurately on a patient's EHR. Thus, I have high confidence in the completeness and accuracy of restarting antidepressant treatment as the outcome variable. On the contrary, I showed in my **Methods Chapter 3.4.1.2** that depression diagnoses, episodes or symptoms are not recorded consistently in the time periods before, during and after antidepressant prescribing. Therefore, these variables would not be suitable to identify depression relapse in EHR data. Restarting antidepressant treatment represents clinically identified depression, whereby the clinician and patient have agreed a need to restart treatment. I measured restarting antidepressant treatment within 61-365 days of stopping treatment – this

was within the timeframe to be considered depression relapse (207,400) and long enough not to count people who may restart antidepressant treatment due to withdrawal rather than relapse. However, it does not represent a systematic assessment for depression as an outcome. Individuals experiencing depression relapse may or may not present to health care services, or still may choose not to restart antidepressants. Furthermore, participants who discontinued antidepressant treatment might have never stopped being depressed. The period of time without an antidepressant may in these individuals represent a time where they had untreated depression, rather than being depression free. Individuals with longer previous durations of antidepressant treatment may also have accumulated a back supply of medication. This could allow them to have a longer gap between prescriptions without discontinuing. This would mean that these individuals were misclassified as having discontinued. Thus, restarting antidepressant treatment is not a perfect representation of depression relapse. This is reflected in the lower rates of restarting antidepressants in this study (35%) compared to the expected rate from RCTs in the general population (41%) (210).

As described above, all prescriptions issued in primary care are done so electronically, and so, are automatically recorded. Therefore, I have high confidence in the completeness and accuracy of my primary exposure variable – which was the count of concurrent medications prescribed at the time of antidepressant discontinuation. As discussed in the previous **Chapter 4**, other studies investigating polypharmacy have typically done so as a binary or categorised outcome (162,192,194,197,393,398). With the large sample size of this study, I was able to more precisely model the relationship between restarting antidepressant treatment and polypharmacy as a continuous count of concurrent prescriptions using spline functions. This means that I was able to identify the minimum number of concurrent medications that an individual needed to be more likely to restart antidepressant treatment. I was also able to observe the increasing effect size of each additional medication prescribed, compared to the reference value of zero.

I used the reference value of zero concurrent medications (other than the antidepressant itself) as the comparison group to which all other values for the count of concurrent medications were compared. While individuals taking 1 or more medications may be more representative of individuals with T2DM (as I discussed in

Chapter 4), the model did not fit a spline point at the value of 1 concurrent medication, showing that there was no evidence of a difference between 1 and 0 concurrent medications. Thus, I made comparisons to the group of individuals who were not prescribed any concurrent medications.

The definition of concurrent medication only required one prescription of any exposure medication in the 90 days prior to the index date. This could mean that they include one-off prescriptions that the patient did not take, or failed trials of multiple medications to treat the same issue. However, I addressed this with my sensitivity analysis, by including only ongoing repeat prescriptions only. The association between the number of concurrent medications prescribed at the time of stopping antidepressant treatment and subsequently restarting remained.

My secondary exposure was the previous duration of antidepressant treatment. Again, this exposure was based on prescription data, which is reliably complete and accurate in the CPRD. However, the duration of each individual prescription was estimated based on the number of tablets issued, recorded frequency and/or duration, length of previous prescriptions, or the median value for prescription duration from individuals with completed data when no other measures were available. Therefore, as this was a calculated estimate, rather than a directly recorded variable, it may not be 100% accurate. However, this was unlikely to make a large difference to the overall calculated duration.

I was unable to directly account for the severity of people's depression. Depression severity may be associated with polypharmacy, longer previous durations of antidepressant treatment, and depression relapse. However, there was no suitable variable in the dataset to account for this directly. Therefore, as discussed above in Section 5.4.3, I suspect that the findings of this study were confounded by the indication of depression severity. This would mean that the association between more concurrent medications and restarting antidepressants, as well as the association between longer previous durations of antidepressant treatment and restarting antidepressants, can be attributed to these people being more severely or more chronically depressed. However, with no direct way to account for depression severity, these hypotheses can only be speculative.

I adjusted for the following demographic variables: age, gender, ethnicity, calendar year and GP practice. There was very little difference in any of the results after confounder adjustment. There was a large amount of missing data for ethnicity, however, the findings did not differ when I only included individuals with completed ethnicity. It was not possible to account for patient-level deprivation, as this was not available for most individuals. However, deprivation was accounted for at GP practice level, by the inclusion of the GP practice ID as a stratum term in the model. The inclusion of GP practice as a stratum term accounted for clustering at practice level by fitting baseline hazard functions for each GP practice. In this way, I was able to account for geographical differences, and practice-level prescribing trends. Thus, my findings were robust in that they were not confounded by sociodemographic factors.

5.4.3 Implications

Restarting antidepressant treatment is common in adults with comorbid depression and T2DM. Individuals in this patient group who are prescribed more concurrent medications at the time of antidepressant discontinuation are at considerably higher risk of restarting antidepressants. Individuals in this patient group who had previously been taking antidepressants for a longer periods before stopping, are also at considerably higher risk of subsequently restarting antidepressants. Restarting antidepressants may represent clinically identified depression relapse (although it does not capture all individuals who have relapsed). As such, I found no evidence that longer durations of antidepressant treatment are of benefit for preventing the need to restart antidepressants in individuals with comorbid depression and T2DM, who are prescribed more concurrent medications, compared to those who are prescribed less concurrent medications. Enhanced support and monitoring when discontinuing antidepressants may be of benefit for individuals with comorbid depression and T2DM. This is particularly the case for individuals who are prescribed higher numbers of concurrent medications – and by implication individuals with worse physical health. This is also the case for individuals who have been taking antidepressants for longer durations previously. Both groups of individuals may be at higher risk of depression relapse.

Despite NICE guidelines recommending longer antidepressant durations for people at higher risk of relapse (82), there is no evidence from existing research to support this

in individuals with comorbid depression and T2DM. I also found no evidence that longer previous durations of treatment attenuated the risk of restarting antidepressants after stopping. However, this may be obscured by the possibility that people who took antidepressants for longer durations were more severely depressed.

People with comorbid depression and T2DM who are prescribed lower numbers of concurrent medications, or who had been taking antidepressants for a shorter period of time prior to discontinuation, may represent individuals who are less willing to take medication, including antidepressants. These individuals may still suffer from depression, but may not have sought help, or may have refused treatment. The identification and monitoring of these individuals may be of benefit, so that enhanced or alternative support can be offered, where required.

In **Chapter 4**, I suggested that individuals with comorbid depression and T2DM who are prescribed higher numbers of concurrent medications represent individuals with worse overall health, and, consequently, more severe depression. I suggested that these individuals may be more likely to continue antidepressant treatment for longer durations, because of an increased need for treatment. In this study, it seems that the same individuals are then more likely to restart treatment after stopping.

At any rate, individuals with comorbid depression and T2DM who are prescribed higher numbers of concurrent medications (by implication representing individuals who have worse overall health) are more likely to take antidepressants for longer durations. This includes the both the initial treatment period (as shown in **Chapter 4**) and restarting for multiple treatment periods (as shown in this study). Further research is required to understand the long-term safety of antidepressant treatment in individuals with comorbid depression and T2DM who are prescribed multiple other medications. In **Chapters 6-7**, I investigate the association between antidepressant treatment and the long-term physical health outcomes of T2DM progressing to need insulin (**Chapter 6**) and cause-specific mortality (**Chapter 7**).

Chapter 6: The Association between Antidepressant Prescribing and Starting Insulin in Individuals with Comorbid Depression and Type 2 Diabetes

At the time of writing, an abridged version of this study is undergoing peer review.

6.1 Introduction

In the previous **Chapters 4-5**, I demonstrated that people with comorbid depression and T2DM who take more medications at the same time, and so (by implication) have worse overall health, have increased exposure to antidepressant treatment. However, little is known regarding the long-term effects of antidepressant treatment on physical health outcomes in this patient group. In **Chapter 2**, I systematically searched the literature for studies investigating long-term physical health outcomes of antidepressant prescribing in people with comorbid depression and T2DM. I found no studies suitable for inclusion in a systematic review. In the next two chapters, I will explore the association between antidepressant prescribing and long-term physical health outcomes in individuals with comorbid depression and T2DM. In this current chapter, I focus on the outcome of starting insulin treatment. In my **Methods Chapter 3.5.1.3**, I explained why starting insulin is a good proxy, that is well recorded in EHR data, for the long-term decline of glycaemic control.

The long-term decline of glycaemic control leads to the development of diabetic complications and the deterioration of physical health. Therefore, understanding factors that may predict or prevent this is important. It is well established that depression negatively impacts glycaemic control (221) and increases the risk of developing diabetic complications in the long-term (220). Antidepressants have been shown to have a small effect on improving glycaemic control in the short term (155). However, the effect of antidepressant treatment on long-term glycaemic control is unknown.

There are no studies, that I am aware of, that investigate the association between antidepressant treatment and starting insulin, or long-term glycaemic control, in people

with comorbid depression and T2DM. There is one cross-sectional study, by Noordam et al, which found that people with T2DM were more likely to be prescribed insulin if they were also prescribed SSRIs, compared to if they were not prescribed SSRIs (215). However, this study was cross-sectional, and so it could not determine whether being prescribed an SSRI increases the risk of starting insulin, or vice versa. Also, Noordam et al did not measure whether or not people had depression. People who are prescribed SSRIs are more likely to be depressed than people who are not prescribed SSRIs. Therefore, the association seen in this study between SSRIs and insulin prescriptions may have been attributable to depression, whereby people who are depressed are more likely to have worse diabetic health and be prescribed insulin.

There is another nested case-control study by Derijks et al, which was able to establish that longer-term antidepressant use (>1 year) increased the risk of subsequently developing both hyperglycaemia and hypoglycaemia, compared to no antidepressant use (216). However, Derijks et al also did not measure whether or not people had either depression or T2DM. Therefore, again, the association in this study between antidepressants and adverse outcomes, may have been attributable to depression rather than the antidepressants themselves; and the increased rates of hyperglycaemia and hypoglycaemia would naturally be expected, compared to a population without T2DM.

There was one study, by Lee et al, which included only people with both depression and diabetes (type unspecified) (214). Lee et al performed a large cohort study of 26,746 people in Taiwanese EHR data and found that long-term antidepressant use prior to baseline was associated with a reduction in hyperglycaemic crisis episodes over time, compared to people with no antidepressant use prior to baseline. However, the antidepressant treatment may have been up to 12 years prior to the hyperglycaemic crisis, and antidepressant exposure in between baseline and the event was unknown. Antidepressant treatment is highly time-varying, due to the episodic and time-varying nature of depression itself. This makes it difficult to be confident in the validity of the association which Lee et al found.

Thus, there is need for a study investigating the association between antidepressant treatment and starting insulin, which meets the following criteria:

i) Is specific to people with comorbid depression and T2DM;

ii) Is longitudinal;

iii) Is able to account for the time-varying nature of antidepressant treatment.

In this chapter, I aimed to examine whether people with comorbid depression and T2DM were more or less likely to start insulin treatment if they were prescribed antidepressants, compared to if they were not prescribed antidepressants. I hypothesised that people with comorbid depression and T2DM would be less likely to start insulin if they were prescribed antidepressants compared to if they were not. This was based on the hypothesis that treating depression would have a positive impact on an individual's diabetic health and self-care, by improving their mental health.

I also performed four additional analyses (described in the following paragraphs) to explore why people with comorbid depression and T2DM who were prescribed antidepressants might be more or less likely to start insulin than those who were not.

In the first additional analysis, I aimed to look at whether the timing of antidepressant prescribing (in relation to starting insulin) made a difference to whether or not people with comorbid depression and T2DM start insulin therapy. I explored whether there were differences between those who were recently treated with antidepressants (in the last 6 months), and those who received antidepressants more than 6 months in the past. I hypothesised that there would be no difference in the likelihood of starting insulin according to the timing of the antidepressant prescriptions, as I did not expect antidepressant treatment to have an immediate impact on an individual's glycaemic control.

Secondly, I aimed to look at whether people with comorbid depression and T2DM who had been taking antidepressants for longer durations would be more or less likely to start insulin treatment. I hypothesised that people with comorbid depression and T2DM who were prescribed antidepressants for longer cumulative durations would be no more likely to start insulin than those who were prescribed antidepressants for shorter cumulative durations. This was based on the assumption that antidepressants would not directly cause an adverse effect on an individual's glycaemic control.

Thirdly, I aimed to look at whether people with comorbid depression and T2DM who had been prescribed larger numbers of different antidepressant agents, would be more likely to start insulin. The prescription of 3 or more different antidepressant agents suggests that the depression has been more "complex-to-treat". I hypothesised that

individuals with comorbid depression and T2DM whose depression is more “complex-to-treat” would also be more likely to start insulin than those who were only prescribed a single antidepressant agent. This was based on the assumption that “complex-to-treat” depression may continue to negatively impact an individual’s diabetic health and self-care, leading to worse glycaemic control.

Finally I aimed to determine whether starting insulin was more common in people taking particular classes of antidepressants. I hypothesised that individuals who were prescribed SSRIs would be the least likely to start insulin. This was based on evidence from Baumeister et al’s Cochrane review showing that SSRIs were most effective antidepressant agent in improving both depression symptoms and glycaemic control in the short-term (403). Additionally, mirtazapine, which is commonly prescribed to treat depression in the UK, has been linked to increased appetite and weight gain (153,311). Therefore, I also hypothesised that individuals who were prescribed mirtazapine would be the most likely to start insulin.

I aimed to look at all outcomes after accounting for potential confounding from demographic variables, comorbidities, other medication prescribing and health behaviours.

6.2 Methods

6.2.1 Study design and setting

I completed a nested case-control study using EHR data from the UK CPRD. I explained in detail the benefits of the nested-case control study design in my **Methods Chapter 3.3.3**. Nested-case control studies compare people with and without an outcome during a retrospective follow-up period during which an exposure can occur at any time (364–366). Therefore, they may have advantages over cohort studies when investigating time varying exposures, such as antidepressant treatment. In addition, case-control studies allow for the investigation of more than one exposure, which allowed me to investigate several different patterns of antidepressant prescribing, as described in the aims above.

I show a graphical representation of the study design in **Figure 6.i,** after describing the patient inclusion criteria and study exposures.

The study period ran from 1 January 2000 to 31 December 2018. However, I used data from earlier years (pre-2000) to select the cohort and to identify some of the confounders required in my study.

6.2.2 Patient inclusion criteria

I nested this case-control study within a cohort of adults (age 18+) with comorbid depression and T2DM, who had started oral antidiabetic medication during their EHR follow-up. I described how I identified people with comorbid depression and T2DM within the CPRD in detail in my **Methods Chapter 3.4.2-3**. I chose to include individuals who were being treated with oral antidiabetic medication for the first time, as this provided a standardised baseline in terms of T2DM illness progression from which individuals could be observed. To do this, individuals had to have at least one oral antidiabetic medication prescription during their EHR follow-up period. To ensure I was capturing the start of oral antidiabetic treatment, I only included individuals whose first oral antidiabetic prescription was prescribed at least 6 months after the individual's date of registration.

I defined the date that individuals entered the cohort in which this case-control study was nested (study entry date) as the date of their first oral antidiabetic prescription. I defined the date that individuals left the cohort in which this case-control study was nested (censored date) as the date of their first insulin prescription (the outcome), date of death, end of registration with their primary care practice, or end of the study period (31 December 2018), whichever was first.

6.2.2.1 Selection of cases: individuals who started insulin therapy

I defined cases as individuals who received a first prescription for insulin recorded after their study entry date and before or on their censored date. I defined the outcome date as the date of the first insulin prescription. I calculated the observation period for cases as the number of days between starting oral antidiabetic medication (study entry date) and the date of the first insulin prescription (outcome date).

To ensure individuals had experienced depression at some point during the observation period, I excluded any cases who did not have a code for depression between entering the study (the date of starting oral antidiabetic medication) and the

outcome date (the date of the first insulin prescription). I also excluded cases who could not be matched to one or more suitable controls.

6.2.2.2 Selection of controls: individuals who had not yet started insulin treatment

I included all individuals from the cohort in which this case-control study was nested in the risk-set from which potential controls were selected, regardless of whether or not they later became a case.

I matched all cases to up to 4 randomly selected eligible controls. Eligible controls were participants who were included in the base cohort for at least as many days as the case, with a code for depression but no insulin prescription recorded during this time. Eligible controls were potential matches for a case based on the age at study entry (within 5 years), gender and GP practice.

I defined the outcome date for controls to be after the same number of days as their matched case, with respect to the number of days observation period from study entry to the date of their first insulin prescription. This ensured cases and controls had the same duration of observation period in days.

6.2.3 Definition of antidepressant prescribing exposures

6.2.3.1 Primary exposure of any antidepressant prescribing during the follow-up period

I defined the primary exposure as being prescribed one or more antidepressant between the study entry and the outcome date. I included the following antidepressant medications which were licensed for use in treating depression in the UK during the follow-up period:

SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;

SNRIs: Duloxetine, venlafaxine;

TCAs: Amitriptyline >= 50mg per day*, amoxapine, clomipramine, dosulepin, oral doxepin, imipramine, lofepramine, maprotiline, nortriptyline >=50mg per day*, trimipramine;

MAOIs: Isocarboxazid, phenelzine, tranylcypromine;

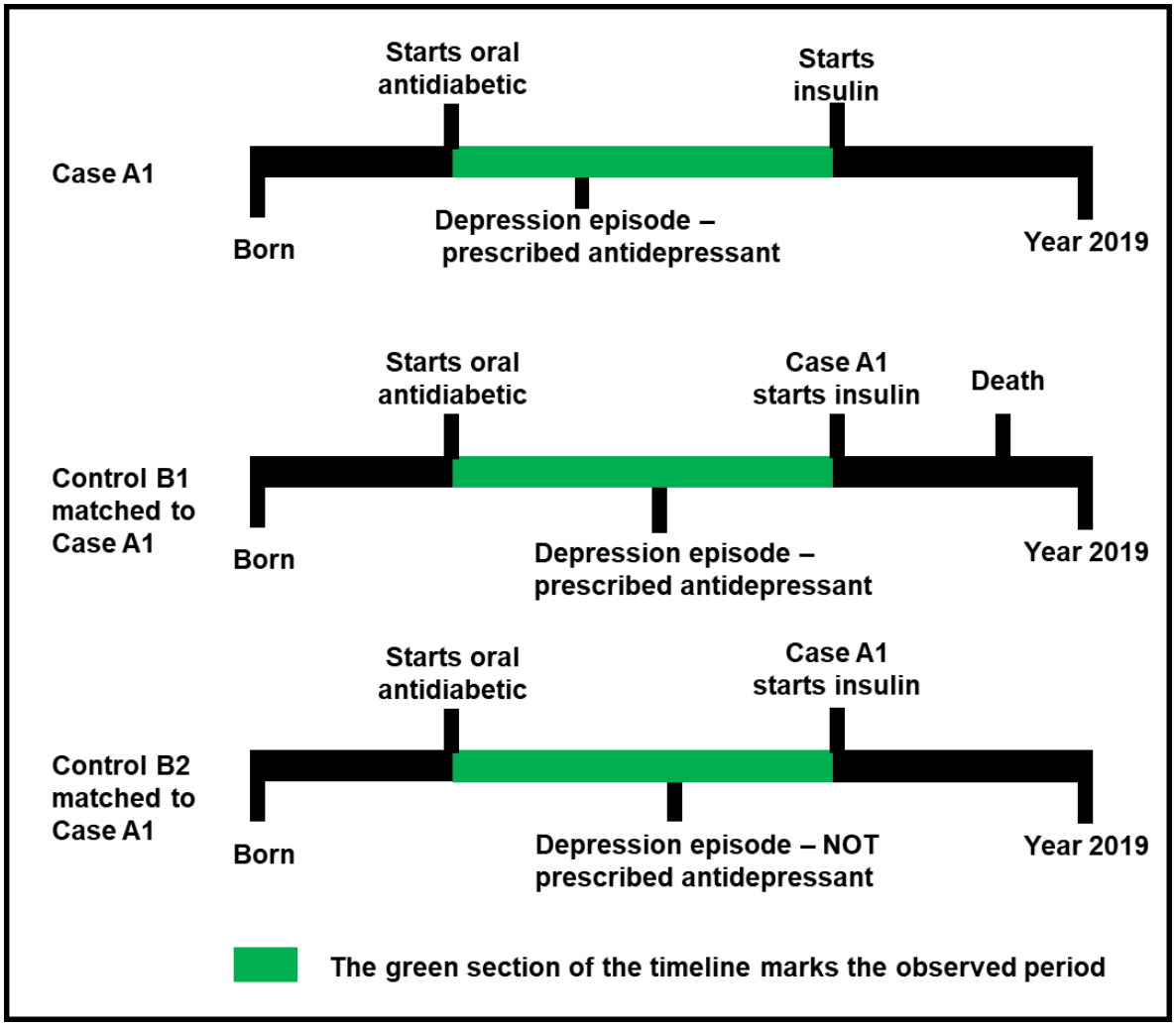
Atypical: Agomelatine, mianserin, mirtazapine, moclobemide, nefazodone, reboxetine, trazodone, tryptophan, vortioxetine.

*Amitriptyline and nortriptyline were included only at the anti-depressant dose of >= 50mg per day, rather than lower hypnotic or neuralgia doses.

I described the creation of the code list for antidepressants in the my **Methods Chapter 3.5.3**.

The follow-up period within which the exposure to antidepressant prescribing could be observed is demonstrated in **Figure 6.i**.

Figure 6.i Examples of participant timelines during which exposure to antidepressant treatment was evaluated for both cases (who started insulin) and controls (who did not start insulin)



6.2.3.2 Additional analyses with antidepressant exposure subcategories

As described above in my aims, I performed additional analyses on three subcategories of the primary exposure:

i) Recent or past antidepressant use: I defined recent antidepressant use as any antidepressant prescription within 182 days (6 months) of the outcome date. I defined individuals who only had a previous antidepressant prescription more than 182 days (6 months) before the outcome date as past antidepressant users. I defined the reference category as having no antidepressant prescription during the observation period.

ii) Cumulative duration of antidepressant treatment: I calculated an individual's cumulative duration of antidepressant treatment as the sum of the duration of each antidepressant treatment episode. To do this, I calculated the duration of each antidepressant treatment episode as the number of days between the first and last prescription of any antidepressant, plus the duration of that last prescription. If a participant had a gap of more than 60 days after the expected end date of the previous prescription without any subsequent antidepressant prescription recorded, that was considered to be the last prescription in that treatment episode (this is in line with my definition of antidepressant discontinuation in **Chapters 4-5**). I counted any subsequent prescriptions as new treatment episodes, and included them in the cumulative total duration of treatment. I categorised the cumulative duration of antidepressant treatment into four groups, namely <6 months, 6-12 months, 13-24 months and >24 months. I defined the reference category as no antidepressant prescription during the observation period.

iii) Number of different antidepressant agents prescribed during the observation period: I counted the number of different antidepressant agents, as defined for the primary exposure. I categorised these into four groups: 0 (reference category), 1, 2 and 3+.

6.2.3.3 Subgroup analysis comparing different antidepressant agents

I performed a subgroup analysis to compare exposure to different antidepressant agents. For this analysis, I excluded individuals who were not prescribed an antidepressant during the observation period, or who were prescribed more than one different antidepressant agent during the observation period (since I wanted to compare single antidepressants head to head). I defined the exposure as the individual antidepressant agent prescribed. I used citalopram as the reference category as this is the most commonly prescribed antidepressant in England (404). I

applied a Bonferroni correction of the p-values, whereby the p-value is multiplied by the number of exposures (with a maximum limit of 1), to account for the increased risk of type 1 error when making multiple statistical tests.

6.2.4 Confounders

I included the following potential confounders measured at or before the study entry date. I demonstrate the potential causal relationships and pathways between the confounders, exposure and outcome in **Figure 6.i**.

Demographic characteristics: In addition to the variables used for matching, I also included ethnicity. Where ethnicity was missing, I recoded this as "White", as discussed in **Chapter 4.2.5**.

Health characteristics: I included a range of health characteristics that may be confounders through an association with antidepressant use (either directly or indirectly through an association with depression) and insulin initiation (either directly or indirectly through an association with poor overall physical health, or health behaviours):

- The following comorbidities (as individual comorbidities rather than a count) based on codes from the Elixhauser comorbidity code list (405) (the Elixhauser code lists is a well established and validated list of comorbidities based on ICD-9 codes, widely used for research using electronic health record data (406)): alcohol abuse, blood loss anaemia, cardiac arrythmia, chronic pulmonary disease, coagulopathy, deficiency anaemia (iron/B12), drug abuse, fluid and electrolyte disorders, hypertension (uncomplicated), hypertension with end organ damage, hypothyroidism, liver disease, lymphoma (history), metastatic cancer, other neurological disorders, paralysis, peptic ulcer disease, peripheral vascular disease, psychoses, pulmonary circulation disorders, renal disease, rheumatoid arthritis and collagen diseases, solid tumor or leukaemia, valvular disease – I coded the presence of each individual condition for participants who had a relevant code recorded prior to the study entry date;
- The most recent recorded body mass index (BMI) value categorised into "normal" (<25 kg/m^2), "overweight" (25 to <30 kg/m^2), and "obese" (30+ kg/m^2); where no value for BMI was available, I estimated the value using multiple imputation – the method I used for multiple imputation was multiple imputation

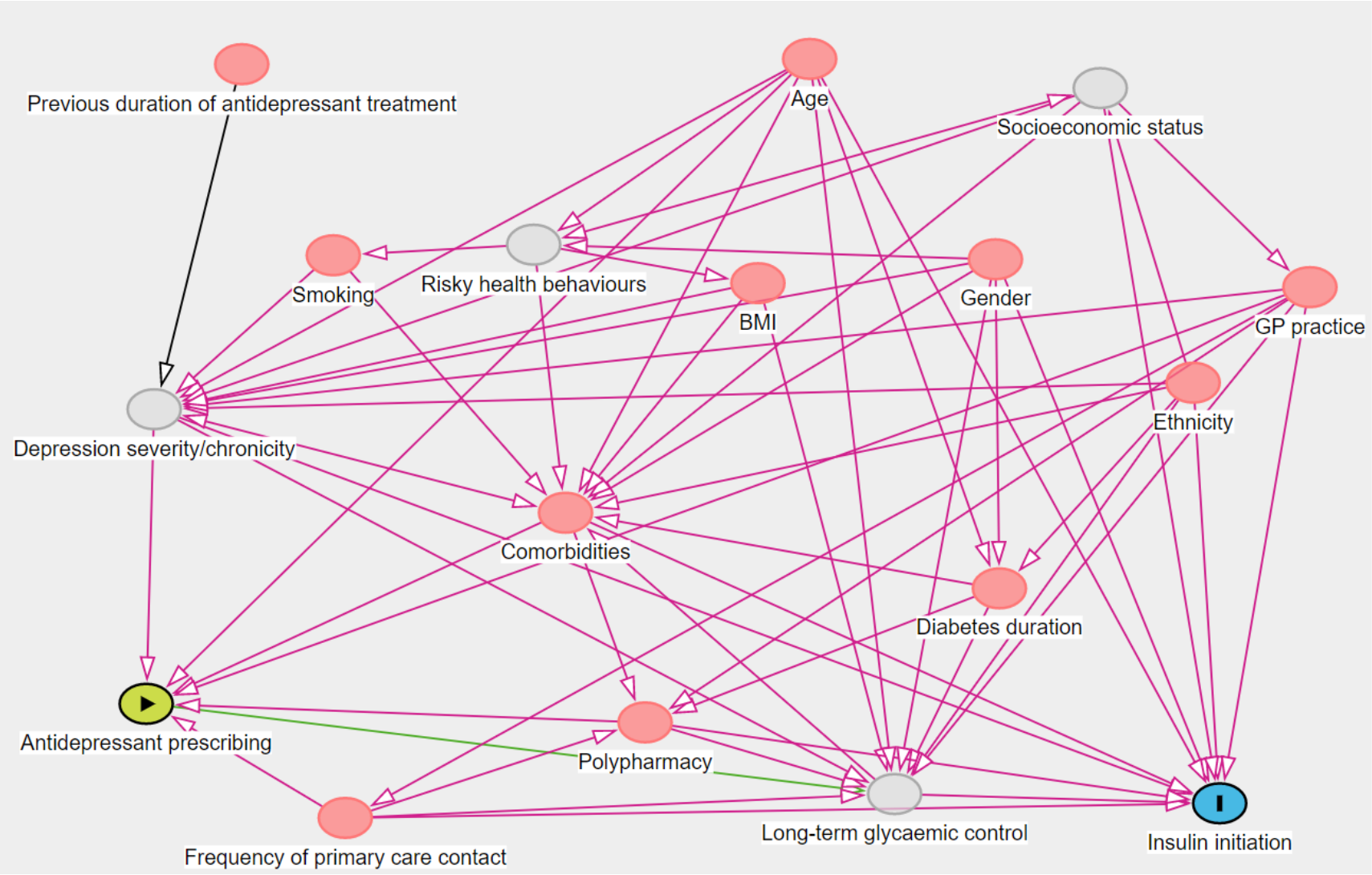
by chained equations using five iterations of logistic regression to impute missing values based on all other variables included in the study;

- Smoking status categorised into “current smoker” (most recent smoking code related to current smoking within 12 months before study entry), “ex-smoker” (most recent smoking code related to historic smoking, or most recent code related to current smoking more than 12 months before study entry, or most recent code related to non-smoking with prior codes related to current or historic smoking), “non-smoker” (no codes related to smoking, or non-smoking codes only);
- T2DM duration, defined as the number of months between the first diabetes related code (this could include diagnosis, symptom, process of care, or medication) and the date of the first oral antidiabetic medication prescription;
- Number of primary care contacts recorded in the 12 months prior to the study entry date. This included any face-to-face contacts and phone calls.

I did not include glycaemic control as a potential confounder, given the study inclusion criteria of starting oral antidiabetic medication (study entry) meant that all participants would be expected to have uncontrolled blood sugar levels at the time of study entry.

Medication history: I included the number of different pharmacological medications prescribed (excluding vaccinations, topical medications and supplements) in the 90 days before the study entry. It was not possible to account for markers of depression and depression severity at study entry. Therefore, to indicate previous depression at a severity requiring pharmacological treatment, I included any previous antidepressant prescription in the 12 months prior to study entry.

Figure 6.ii DAG showing the relationship between confounders, exposure and outcome



*Green = exposure; blue = outcome; red = potential confounder; grey = unmeasured; direction of arrow shows potential causal effect

6.2.5 Sensitivity analyses to investigate the effect of imputing missing data

I performed two sensitivity analyses to investigate the effect of imputing missing data. In the first, I included only individuals with complete data for ethnicity. In the second, I included only individuals with complete data for BMI.

6.2.6 Statistical analysis

I used conditional logistic regression to estimate adjusted incident rate ratios (IRR) and corresponding 95% confidence intervals (CI) for the association between each of the antidepressant prescribing exposures and starting insulin. I explained in **Chapter 3.7.2** how conditional logistic regression estimates incident rate ratios in case control studies where incident sampling and individual matching is used. I initially performed univariable analyses, and then multivariable analyses adjusting for all aforementioned confounders. I combined all confounders in one multivariable model due to the potential interaction between demographic variables, health characteristics, medication history and behavioural characteristics. This is demonstrated in the DAG in **Figure 6.ii**.

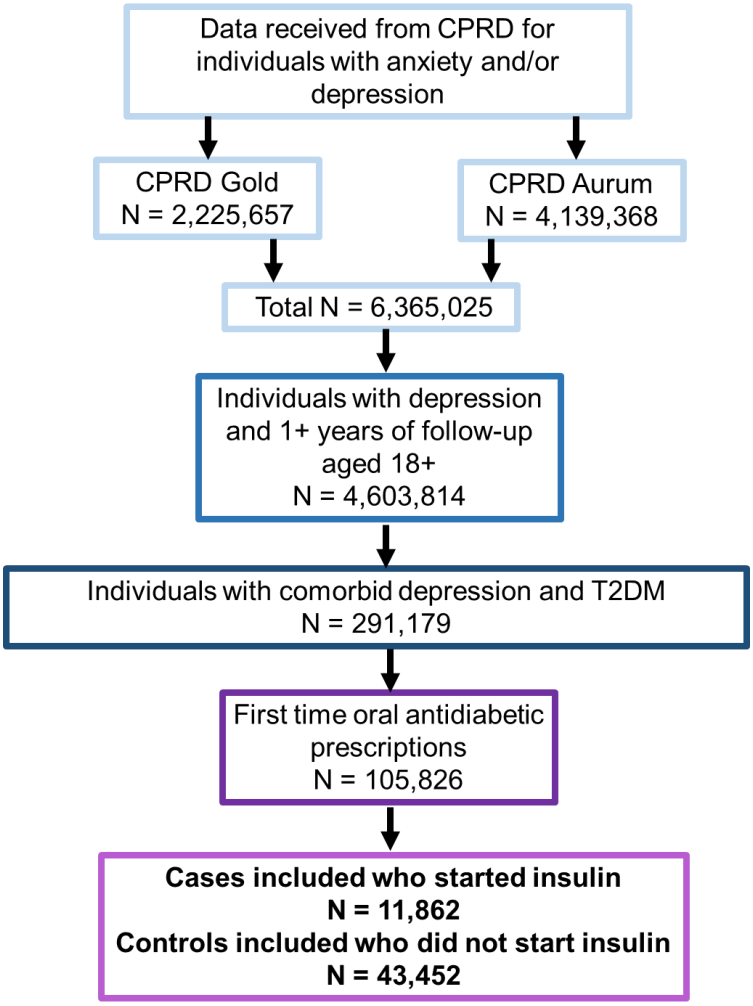
I repeated the multivariable analysis for the primary exposure (any antidepressant prescribing) for each sensitivity analysis described in **Section 6.2.5**.

6.3 Results

6.3.1 Characteristics of individuals included in this study

I demonstrate the number of individuals included or excluded in a flow diagram, **Figure 6.iii**.

Figure 6.iii Flow diagram of inclusion and exclusion



The base cohort in which this study was nested consisted of 105,826 individuals with comorbid depression and T2DM, who started oral antidiabetic medication during the study period. From this, I identified 11,862 cases who started insulin treatment, and matched these with 43,452 controls who did not start insulin.

In **Table 6.i** I report baseline characteristics of individuals included in the study, combined, and categorised as cases or controls. People included in the study were 53.84% female and 57.29% of White ethnicity. At study entry (on the date of the first oral antidiabetic prescription) the median age was 53 (IQR 46-61); the median diabetes duration was 2 months (IQR 0-23); and the median number of medications prescribed was 6 (IQR 3-9). The median number of primary care contacts in the previous 12 months was 23 (IQR 13-36). The proportion of individuals with a history of previous antidepressant prescribing was 40.84%. The two groups were balanced in

terms of demographic characteristics with the exception of a higher proportion of Asian and Mixed ethnicities in the control group.

In **Table 6.ii** I report the baseline comorbidities of included individuals, combined, and categorised as cases and controls. Cases had a higher prevalence of each comorbidity at baseline, with the exception of blood loss anaemia. The most common comorbidities in all participants were uncomplicated hypertension (41.33%), COPD (23.47%), renal disease (13.48%), other neurological disorders* (11.82%) and deficiency anaemia (iron/B12) (10.43%). The most common BMI category was obese (61.59%), and 29.15% were current smokers. *Other neurological disorders included brain trauma, cerebrovascular diseases, dementia, epilepsy, encephalitis, hydrocephalus, movement disorders, neurodegenerative diseases, other cerebral degeneration, spine injuries and disorders.

6.3.2 Comparison of characteristics at study entry between individuals who are subsequently prescribed antidepressants and those who are not

In **Table 6.iii** I report baseline characteristics and in **Table 6.iv** I report comorbidities of individuals included in the study, categorised by whether or not they received an antidepressant during the observational period. People with comorbid depression and T2DM who were prescribed antidepressants were more likely to be female (57.59% vs 49.46%) compared to those who were not prescribed antidepressants. People who were prescribed antidepressants had slightly higher proportions of most comorbidities at baseline compared to those who were not prescribed antidepressants.

Table 6.i Characteristics of cases and controls, at the time of study entry

	All N (%)	Cases N (%)	Controls N (%)
Sample size	55,314	11,862	43,452
Female (%)	29,782 (53.84)	6,378 (53.77)	23,404 (53.86)
Median age (IQR) (years)	53 (46-61)	53 (45-62)	53 (46-61)
Ethnicity:			
Asian (%)	2,781(5.03)	433 (3.65)	2,298 (5.29)
Black (%)	1,326 (2.40)	249 (2.10)	1,077 (2.48)
Missing* (%)	19,013 (34.37)	4,247 (35.80)	14,766 (33.98)
Mixed (%)	288 (5.21)	49 (0.09)	239 (0.55)
Other (%)	265 (0.50)	36 (0.41)	229 (0.53)
White (%)	31,691 (57.29)	6,848 (57.73)	24,843 (57.17)
Median diabetes duration in months (IQR)	2 (0-23)	2 (0-23)	2 (0-23)
Median (IQR) medication count (last 3 months)	6 (3-9)	6 (3-9)	6 (3-9)
Prescribed antidepressants in last 12 months, n (%)	22,590 (40.84)	4,703 (39.65)	17,887 (41.16)
Number of primary care contacts in last 12 months	22 (13-36)	25 (11-35)	23 (13-36)
Median follow-up time in years (IQR)	8.13 (4.83-11.70)	8.13 (4.83-11.70)	8.13 (4.83-11.70)

*Missing data imputed for ethnicity as “White”

Table 6.ii Comorbidities of cases and controls at time of study entry

	All N (%)	Cases N (%)	Controls N (%)
Comorbidity:			
Alcohol abuse	2,923 (5.28)	616 (5.19)	2,307 (5.31)
Blood loss anaemia	233 (0.42)	43 (0.36)	190 (0.44)
Cardiac arrhythmia	4,691 (8.48)	1,316 (11.09)	3,375 (7.77)
Chronic heart failure	3,002 (5.43)	1,103 (9.30)	1,899 (4.37)
Coagulopathy	612 (1.11)	172 (1.45)	440 (1.01)
COPD	12,983 (23.47)	3,107 (26.19)	9,876 (22.73)
Deficiency anaemia (iron/B12)	5,772 (10.43)	1,523 (12.84)	4,249 (9.78)
Drug abuse	1,318 (2.38)	293 (2.47)	1,025 (2.36)
Fluid and electrolyte disorders	2,622 (4.74)	805 (6.79)	1,817 (4.18)
Hypertension (uncomplicated)	22,862 (41.33)	5,157 (43.47)	17,705 (40.75)
Hypertension (late stage)	113 (0.20)	33 (0.28)	80 (0.18)
Hypothyroidism	4,395 (7.95)	1,026 (8.65)	3,369 (7.75)
Liver disease	1,526 (2.76)	454 (3.83)	1,072 (2.47)
Lymphoma	319 (0.58)	87 (7.33)	232 (0.53)
Metastatic cancer	538 (0.97)	199 (1.68)	339 (0.78)
Other neurological disorders	6,537 (11.82)	1,742 (14.69)	4,795 (11.04)
Paralysis	346 (0.63)	87 (7.33)	259 (0.60)
Peptic ulcer disease	1,499 (2.71)	415 (3.50)	1,084 (2.49)
Peripheral vascular disease	2,451 (4.43)	765 (6.45)	1,686 (3.88)
Psychosis	1,580 (2.86)	359 (3.03)	1,221 (2.81)
Pulmonary circulation disorders	1,112 (2.01)	333 (2.81)	779 (1.79)
Collagen vascular diseases	2,330 (4.21)	590 (4.97)	1,740 (4.00)
Renal disease	7,458 (13.48)	2,212 (18.65)	5,246 (12.07)
Solid tumour or leukaemia	5,225 (9.45)	1,408 (11.87)	3,817 (8.78)
Valvular disease	1,416 (2.56)	402 (3.39)	1,014 (2.33)
Smoking Status:			
Non-smoker	27,578 (49.86)	6,148 (51.83)	21,430 (49.32)
Current smoker	16,125 (29.15)	3,559 (30.00)	12,566 (28.92)
Ex-smoker	11,611 (20.99)	2,155 (18.17)	9,456 (21.76)
BMI category:			
Missing*	7,637 (13.81)	1,701 (14.34)	5,936 (13.66)
Normal	3,143 (5.68)	752 (6.34)	2,391 (5.50)
Overweight	10,467 (18.92)	2,386 (20.11)	8,081 (18.60)
Obese	34,067 (61.59)	7,023 (59.21)	27,044 (62.24)

*Missing data imputed for BMI using multiple imputation

Table 6.iii Sample characteristics at the time of study entry, by exposure group

	People prescribed antidepressants N (%)	People not prescribed antidepressants N (%)
Sample size	29,097	26,217
Female (%)	16,814 (57.79%)	12,968 (49.46%)
Median age (IQR) (years)	52 (45-61)	54 (46-62)
Ethnicity:		
Asian (%)	1,082 (3.72)	1,924 (7.34)
Black (%)	485 (1.67)	998 (3.81)
Mixed (%)	93 (0.32)	164 (6.26)
Missing (%)	10,154 (34.90)	8,402 (32.05)
Other (%)	152 (5.22)	169 (6.45)
White (%)	17,131 (58.88)	14,560 (55.54)
Median diabetes duration in months (IQR)	3 (0-22)	2 (0-25)
Median (IQR) medication count (last 3 months)	6 (4-10)	5 (3-8)
Prescribed antidepressants in last 12 months, n (%)	15,286 (52.53)	7,304 (27.86)
Number of primary care contacts in last 12 months	24 (14-38)	21 (12-33)

Table 6.iv Comorbidities at time of study entry, by exposure group

	People prescribed antidepressants N (%)	People not prescribed antidepressants N (%)
Comorbidity:	29,097	26,217
Alcohol abuse	1,654 (5.68)	1,269 (4.84)
Blood loss anaemia	107 (0.37)	126 (0.48)
Cardiac arrhythmia	2,514 (8.64)	2,177 (8.30)
Chronic heart failure	1,719 (5.91)	1,283 (4.89)
Coagulopathy	351 (1.21)	261 (1.00)
COPD	7,144 (24.55)	5,839 (22.27)
Deficiency anaemia (iron/B12)	3,364 (11.56)	2,409 (9.19)
Drug abuse	772 (2.65)	546 (2.08)
Fluid and electrolyte disorders	1,472 (5.06)	1,150 (4.39)
Hypertension (uncomplicated)	11,768 (40.44)	11,094 (42.32)
Hypertension (late stage)	62 (0.21)	51 (0.19)
Hypothyroidism	2,495 (8.57)	1,900 (7.25)
Liver disease	879 (3.02)	647 (2.47)
Lymphoma (history)	185 (0.64)	134 (0.51)
Metastatic cancer	289 (0.99)	249 (0.95)
Other neurological disorders	3,769 (12.95)	2,768 (10.56)
Paralysis	187 (0.64)	159 (0.61)
Peptic ulcer disease	813 (2.79)	686 (2.62)
Peripheral vascular disease	1,375 (4.73)	1,076 (4.10)
Psychosis	968 (3.33)	612 (2.33)
Pulmonary circulation disorders	708 (2.43)	404 (1.54)
Collagen vascular diseases	1,324 (4.55)	1,006 (3.84)
Renal disease	4,182 (14.37)	3,276 (12.50)
Solid tumour or leukaemia	2,807 (9.65)	2,418 (9.22)
Valvular disease	759 (2.61)	657 (2.51)
Smoking Status:		
Non-smoker	14,443 (49.64)	13,135 (50.10)
Current smoker	8,817 (30.30)	7,308 (27.88)
Ex-smoker	5,837 (20.06)	5,774 (22.02)
BMI category:		
Missing	3,918 (13.47)	3,716 (14.17)
Normal	1,577 (5.42)	1,566 (5.97)
Overweight	5,358 (18.41)	5,109 (19.49)
Obese	18,241 (62.69)	15,826 (60.37)

6.3.3 Main analysis results for the association between antidepressant prescribing and starting insulin

I report the main results for the association between antidepressant prescribing and starting insulin in individuals with comorbid depression and T2DM in **Table 6.iii**. All the results that I describe below are after adjustment for demographic characteristics, comorbidities and prescription history at baseline.

Individuals with comorbid depression and T2DM who were prescribed at least one antidepressant during the follow-up period were 3.78 times (95% CI 3.53-4.04) more likely to start insulin compared to those who were not prescribed an antidepressant during the follow-up period.

I found no evidence of a difference in the rate of starting insulin between individuals who had recent antidepressant prescriptions (in the 6 months before the index date/date of insulin initiation or not) and those who only had past (more than 6 months prior to the outcome date) antidepressant prescriptions.

The longer the cumulative duration of antidepressant treatment, the more likely an individual was to start insulin. The adjusted IRR for the shortest duration of treatment (<6 months) compared to no antidepressant prescription was 3.94 (95% CI 3.64-4.27), while in the longest duration of treatment (>24 months) the adjusted IRR compared to no antidepressant treatment was 5.61 (95% CI 5.23-6.03). However, there did not appear to be a dose response relationship between each increasing category of cumulative duration.

Individuals receiving larger numbers of different antidepressant agents were more likely to start insulin than those with fewer numbers of antidepressant agents. The adjusted RR for only one antidepressant agent compared to none was 3.93 (95% CI 3.69-4.19), while the adjusted RR for 3+ antidepressant agents compared to none was 5.72 (95% CI 5.25-6.24).

Table 6.v Univariable and Multivariable Analysis Results for the Association Between Antidepressant Prescribing and Insulin Initiation

Antidepressant prescription:	Cases n (%)	Controls n (%)	Univariable RR (95% CI)	Multivariable RR (95% CI)
None	2,636 (22.18)	23,581 (54.27)	Reference	Reference
Any	9,226 (77.78)	19,871 (45.73)	4.79 (4.55-5.05)	3.78 (3.53-4.04)
None	2,636 (22.18)	23,581 (54.27)	Reference	Reference
Recent	6,426 (54.17)	13,925 (32.05)	4.80 (4.54-5.06)	4.04 (3.74-4.37)
Non-recent only	2,800 (23.60)	5,946 (13.68)	4.79 (4.49-5.10)	3.47(3.19-3.77)
Duration:				
None	2,636 (22.18)	23,581 (54.27)	Reference	Reference
<6 months	1,984 (21.50)	4,515 (10.39)	4.35 (4.05-4.66)	3.94 (3.64-4.27)
6-12 months	964 (10.45)	2,178 (5.01)	4.39 (4.01-4.80)	4.35 (3.92-4.82)
13-24 months	1,292 (14.00)	2,821 (6.49)	4.68 (4.31-5.07)	4.93 (4.49-5.42)
>24 months	4,984 (54.02)	10,354 (23.83)	5.16 (4.87-5.46)	5.61 (5.23-6.03)
N antidepressant agents:				
0	2,636 (22.18)	23,581 (54.27)	Reference	Reference
1	4,874 (41.09)	11,748 (27.04)	4.23 (4.00-4.47)	3.93 (3.69-4.19)
2	2,486 (20.96)	4,878 (11.23)	5.40 (5.05-5.78)	5.03 (4.66-5.44)
3+	1,871 (15.77)	3,272 (7.53)	6.20 (5.75-6.68)	5.72 (5.25-6.24)

6.3.3 Sensitivity analysis results assessing the impact of imputing missing data

When I included only individuals with a completed value for ethnicity, there was no evidence of a change in the effect estimates from the main analysis (IRR 4.21, 95% CI 3.91-4.54).

When I included only individuals with a completed value for BMI, I found a slightly stronger association (compared to the main analysis) between any antidepressant prescribing and starting insulin (IRR 4.44, 95% CI 4.19-4.71).

6.3.4 Subgroup analysis results comparing different antidepressant agents

I report the subgroup analysis results comparing rates of starting insulin between individual antidepressant agents in **Table 6.iv**. I included 16,169 individuals who only received only one antidepressant agent during the study follow-up period in this subgroup analysis. When rates of starting insulin were compared to individuals who were prescribed citalopram, the Bonferroni corrected p-value for each individual antidepressant agent was 1. This showed that there was no statistically significant evidence of a difference between the rates of starting insulin for people who were prescribed different antidepressant agents compared to citalopram.

Table 6.vi Univariable and Multivariable Analysis Results for the Association Between Antidepressant Agent and Insulin Initiation

Antidepressant prescription:	Cases n (%)	Controls n (%)	Univariable RR (95% CI)	Multivariable RR (95% CI)
Total	4,797 (100.00)	11,732 (100.00)		
Citalopram	1,656 (34.52)	3,985 (33.97)	Reference	Reference
Amitriptyline	116 (2.42)	305 (2.60)	0.75 (0.55-1.03)	0.80 (0.54-1.12)
Clomipramine	30 (0.63)	74 (0.63)	1.07(0.57-1.99)	1.24 (0.61-2.54)
Dosulepin	191 (3.98)	372 (3.7)	1.4 (1.08-1.82)	1.38 (1.02-1.86)
Doxepin	8 (0.17)	13 (0.11)	1.33 (0.26-6.80)	2.14 (0.34-13.51)
Duloxetine	123 (2.56)	319 (2.72)	1.04 (0.77-1.40)	0.98 (0.69-1.39)
Escitalopram	55 (1.15)	249 (2.12)	1.19 (0.84-1.67)	1.11 (0.74-1.68)
Fluoxetine	1,173 (24.45)	2,602 (22.18)	1.05 (0.92-1.19)	1.00 (0.86-1.17)
Fluvoxamine	2 (0.04)	10 (0.09)	0.89 (0.15-5.49)	0.51 (0.05-5.24)
Imipramine	17 (0.35)	44 (0.38)	0.77 (0.32-1.85)	0.77 (0.28-2.09)
Lofepramine	55 (1.15)	105 (0.89)	0.72 (0.43- 1.20)	0.78 (0.44-1.38)
Mirtazapine	290 (6.05)	793 (6.76)	1.03 (0.84-1.27)	1.05 (0.82-1.33)
Moclobemide	3 (0.06)	8 (0.07)	0.77 (0.14-4.28)	0.27 (0.03-2.58)
Nortriptyline	4 (0.08)	21 (0.18)	0.34 (0.07-1.64)	0.44 (0.08-2.41)
Paroxetine	213 (4.44)	492 (4.19)	0.98 (0.77-1.25)	1.09 (0.82-1.44)
Phenelzine	7 (0.15)	4 (0.03)	10.34 (1.26-85.02)	11.30 (1.34-95.68)
Sertraline	546 (11.38)	1,650 (14.06)	0.83 (0.71-0.97)	0.84 (0.70-1.01)
Trazadone	46 (0.96)	100 (0.85)	1.00 (0.61-1.62)	0.90 (0.50-1.62)
Trimipramine	5 (0.10)	19 (0.16)	0.53 (0.14-2.03)	0.34 (0.08-1.47)
Venlafaxine	257 (5.36)	567 (4.83)	1.12 (0.90-1.39)	1.24 (0.95-1.61)

I have not reported results for the following antidepressants due to insufficient numbers: maprotiline, mianserin, reboxetine, tranylcypromine.

The Bonferroni corrected p-value for all antidepressant agents was 1. Bonferroni correction multiplies the original p-value by the number of different tests performed, with a maximum limit of 1.

6.4 Discussion

6.4.1 Main findings

I examined whether people with comorbid depression and T2DM were more likely to start insulin if they were prescribed antidepressants, compared to those who were not prescribed antidepressants.

When people with comorbid depression and T2DM received at least one prescription for any antidepressant after starting oral antidiabetic treatment, they were 3.78 times more likely to start insulin therapy compared to those who were not prescribed an antidepressant.

The longer the duration that people with comorbid depression and T2DM received antidepressant treatment for, and the more different individual antidepressant agents they had been prescribed, the more likely they were to start insulin therapy.

The rates of starting insulin in individuals with comorbid depression and T2DM did not change depending on the timing of the antidepressant prescribing (recent versus past) or on the specific antidepressant agent prescribed.

6.4.2 Comparison to existing literature and my previous findings in this thesis

In the introduction to this chapter, I noted three other studies with conflicting evidence concerning the long-term association between antidepressant prescribing and either insulin treatment or glycaemic control.

One of these studies, by Noordam et al, found that people with T2DM who were prescribed SSRIs were more likely to be prescribed insulin than those who were not prescribed SSRIs (215). This is inline with my findings that people with comorbid depression and T2DM were more likely to start insulin if they were prescribed an antidepressant than if they were not. The study by Noordam et al was cross-sectional. Therefore, it was not possible to determine whether being prescribed an SSRI increased the risk of starting insulin, or whether being treated with insulin increased the risk of starting SSRIs. My study, on the other hand, measured antidepressant prescribing before starting insulin. As such, I was able to show the direction of the association – that when people with comorbid depression and T2DM are prescribed

an antidepressant, this increases their risk of subsequently starting insulin treatment. In addition, Noordam et al did not measure whether or not people in their study had depression. Therefore, rather than SSRIs causing people to require insulin therapy, it may be that people who were prescribed SSRIs were more likely to be depressed, and that the association with insulin could be attributed to people who were depressed being more likely to have worse diabetic health and be prescribed insulin. In my study, I required that everyone included had depression at some point during the observed period. Therefore, I was able to show that it was not simply depression that was associated with insulin treatment, but specifically being prescribed an antidepressant.

Another nested-case control study by Derijks et al found that antidepressant prescribing for durations of >1 year were associated with increased risk of hyperglycaemia (216). This too is in line with my findings in this study. However, Derijks et al did not measure whether or not people in the study had depression. Therefore, people who were prescribed antidepressants would be more likely to have depression than those who were not. And so, the association between antidepressant prescribing and adverse outcomes may have been attributable to depression.

The only other study, as described in my introduction, that required the people to have both depression and diabetes (type unspecified) was the study by Lee et al (214). However, the findings of Lee et al were the opposite to my findings in this study. Lee et al found that of people with comorbid depression and diabetes (type unspecified) who were prescribed antidepressants at baseline were less likely to subsequently experience hyperglycaemic crises than those who were not prescribed antidepressants. Lee et al included only people with depression that was confirmed by a psychiatrist with at least two outpatient diagnoses or one hospitalisation. These are likely to represent people with more severe depression. Therefore, depression severity was better accounted for by Lee et al, than in my study. This may mean that the association between antidepressant prescribing and starting insulin found in my study, was attributable to more severe depression in people who were prescribed antidepressants. On the other hand, Lee et al only measured antidepressant prescribing at baseline, which may have been 12 years before the hyperglycaemic crises. While I measured antidepressant prescribing throughout a longitudinally observed period right up until the person with comorbid depression and T2DM started (or did not start) insulin. However, I found no evidence of a difference in the association

between antidepressant prescribing and starting insulin, according to the timing of the antidepressant prescription.

6.4.3 Potential explanations for these findings

Individuals with comorbid depression and T2DM were considerably more likely to start insulin if they received any antidepressant prescription at any time after starting oral antidiabetic treatment, compared to those who did not receive any antidepressant prescriptions during this time. This is contrary to my hypothesis, where I suggested that individuals with comorbid depression and T2DM would be less likely to start insulin if they were prescribed antidepressants, due to the positive effect of treating depression actively with antidepressants in terms of diabetic health and self care.

If antidepressants had a direct effect on causing individuals with comorbid depression and T2DM to start insulin, I would have expected to see further elevated rates of starting insulin in those individuals who were recently prescribed an antidepressant compared to those who only had antidepressant prescriptions more than 6 months in the past. This was not the case.

Even if antidepressants had a delayed and irreversible effect on causing individuals with comorbid depression and T2DM to start insulin, I would expect to see differences according to the different individual antidepressant agents prescribed. These differences would be due to different mechanisms of action and side effect profiles for different types of antidepressant. However, this was not the case. Individuals with comorbid depression and T2DM had the same risk of starting insulin, whatever antidepressant agent they were prescribed.

When I adjusted for demographic characteristics, comorbidities and prescribing history at study entry, this had little effect on my findings. Therefore, my findings were not confounded by any of these factors.

I adjusted for a number of confounders at study entry that are associated with depression severity. This included history of previous antidepressant prescribing. However, none of these represented a systematic assessment of depression severity. On the other hand, individuals with comorbid depression and T2DM who had taken antidepressants for longer cumulative durations and who had trialled more different antidepressant agents are likely to represent those with more severe depression, more

chronic, and/or with treatment resistant depression. These individuals were also more likely to start insulin. This suggests that the association I found between antidepressant prescribing and starting insulin may be explained, to an extent, by depression severity, chronicity, and/or treatment resistance. Antidepressant prescribing does not equate to successfully treated depression. Antidepressants have been shown to be moderately effective at reducing depression symptoms in the short-term (77), but this does not necessarily mean that patients are depression-free, either in the short or long-term.

It should be noted, however, that even individuals with comorbid depression and T2DM who were prescribed only one antidepressant and for cumulative durations of less than 6 months were considerably more likely to start insulin. NICE guidelines for the use of antidepressants in individuals with comorbid physical long-term conditions, advise that these should only be prescribed to individuals with more severe depression (81). Thus, any antidepressant prescribing in general practice may be a marker of more severe depression in individuals with comorbid depression and T2DM. This would suggest that the increased rates of starting insulin may be attributable to more severe depression in these individuals.

6.4.4 Strengths and limitations

This was the first study to investigate differences in the rates of starting insulin in people with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not prescribed antidepressants.

With a sample size of 55,314, this study is over 150 times larger than all studies combined in the 2012 Cochrane meta-analysis of antidepressant treatment outcomes in people with comorbid depression and T2DM (155). All RCTs included in the Cochrane review excluded individuals with severe depression, and the majority excluded individuals with comorbidities common in T2DM, or prescribed medications common in T2DM. In this study, I included people with comorbid depression and T2DM, who had started oral antidiabetic medication for the first time, regardless of depression severity, comorbidities or concurrent medication use. The individuals included in this study are representative of people in the UK with comorbid depression and T2DM who have been prescribed an oral antidiabetic medication for the first time in middle age (~45-65), and in the approximately 5-12 years following that. The

findings of this study provide a representative view of antidepressant outcomes in individuals within the first ten years of starting oral antidiabetic medication.

I chose the outcome of insulin initiation to represent the long-term decline in glycaemic control and diabetic health. When oral antidiabetic medication is no longer able to maintain glycaemic control, treatment with insulin is recommended. Starting insulin is a definitive outcome which will be recorded in a patient's EHR as it is prescribed, unlike health events, which may not be known of in primary care and/or may not be recorded on the primary care EHR. However, starting insulin in a proxy for the decline in glycaemic control – it does not measure glycaemic control itself. It is possible that some individuals who did not start insulin also had uncontrolled diabetes, but refused insulin treatment. People may decide not to start insulin treatment for a number of reasons, including concerns about the medication, injections or worsening health (407). It is estimated that one in four people with T2DM are not willing to take insulin (407). Individuals with comorbid depression and T2DM who are prescribed antidepressants may represent those who are more accepting of intensive pharmacological treatment, such as insulin. Although I adjusted for prescribing history at study entry, which should, in part, account for attitudes towards pharmacological treatment, this was a median of 8 years before the outcome date. Attitudes towards pharmacological treatment could change during this time. However, it is unlikely that the majority of the 43,452 controls met the criteria for starting insulin and then refused it, and more likely that they did not need to start insulin. Furthermore, the effect size for the association between antidepressant prescribing and starting insulin was considerable (IRR 3.78).

As I described above, all prescriptions issued in primary care are done so electronically, and so, are automatically recorded in a patients EHR. Therefore, I have high confidence in the completeness and accuracy of my antidepressant prescribing exposure. However, the indication of the antidepressant prescribed may be ambiguous, particularly in individuals with comorbid depression and T2DM. The CPRD does not record prescription indications. The indication for a prescription may be worked out if a patient also has a clinical code for a relevant disease from the same consultation. However, as I demonstrated in my **Methods Chapter 3**, 38% of individuals with comorbid depression and T2DM do not have a clinical code relevant to the first antidepressant they are prescribed within 6 months either side of the

prescription. Therefore, I could not be certain that any antidepressant was prescribed to treat depression. This is particularly relevant for amitriptyline, nortriptyline and duloxetine, which are also indicated in the UK to treat diabetic neuropathic pain. For amitriptyline and nortriptyline, I included only prescriptions that were issued at a dosage ≥ 50mg, which is indicated for depression, while neuropathic pain dosages are typically lower (173,332). However, this is not always the case. I could also not do this for duloxetine, which uses the same therapeutic doses for both depression and neuropathic pain. Similarly some TCAs or trazodone, for example, may be used to treat sleeplessness. However, I included in the study only individuals who had a diagnosis, symptom or process of care code for depression recorded during the follow-up period for which antidepressant treatment was measured. Therefore, all participants had depression as an indication for potential antidepressant prescribing during this time.

6.4.4.1 Study design issues

RCTs are the gold standard method for evaluating causal effects of an intervention, such as antidepressant treatment, on an outcome. This is due to the fact that randomisation of participants to an intervention or control group is an effective tool for minimizing bias, by balancing both measured and unmeasured confounders between groups. In real-world data, patients are not randomised to either an intervention or control group, but receive an intervention based on an indication of requiring treatment (e.g. depression at a level of severity requiring treatment), clinician prescribing habits, or local pressures in access to treatment (e.g. local waiting times for talking therapies). These factors may introduce bias, if they also offer alternative explanations for increased rates of mortality. I initially attempted to balance confounders by matching individuals based on gender, age and GP practice. Including GP practice level matching allowed me to account practice level differences in health care delivery and socioeconomic status. I then further attempted to balance confounders by adjusting for a large number of confounders that were associated with both antidepressant prescribing and starting insulin. These included comorbidities, polypharmacy, history of antidepressant prescribing, primary care contacts, smoking, drinking, drug use, BMI, and T2DM duration. However, while I was able to adjust for a large number of confounders that may be associated with depression severity, I could not adjust for depression severity itself. There is no routinely recorded variable for depression

severity in the CPRD dataset. Neither are there recorded specific symptoms and characteristics of depression that may be associated with both antidepressant prescribing and insulin initiation. Therefore, my findings may have been confounded by the indication of depression severity or subtype. I was also only able to adjust for confounders at study entry which may be subject to change over the median 7 year observation period, during which time both physical and mental health is subject to change. Furthermore, the higher rates of starting insulin that I observed may also be due to unmeasured confounding from a wide range of potential socio-economic, lifestyle, life event and environmental factors which are not recorded in data sources such as EHRs. However, due to my case-control study design, I was able to examine different patterns of antidepressant exposure. This allowed me to strengthen my causal understanding of the association between antidepressant prescribing and different causes of mortality in individuals with comorbid depression and T2DM.

6.4.5 Implications

Individuals with comorbid depression and T2DM in UK primary care are considerably more likely to start insulin treatment if they are prescribed any antidepressant, for any duration, at any time after starting oral antidiabetic treatment. This may represent a long-term decline in glycaemic control. I found no evidence to suggest that antidepressants were directly causing a decline in diabetic health or hyperglycaemia. On the other hand, individuals with comorbid depression and T2DM who were the most likely to start insulin were those who displayed antidepressant prescribing patterns typical of individuals with more severe, chronic and treatment-resistant depression. Furthermore, as antidepressants are recommended only for individuals with physical comorbidities who have more severe depression (81), antidepressant prescribing itself is likely to be a marker of depression severity. This interpretation is in line with my conclusions from the studies described in **Chapters 4-5**, where I suggested that polypharmacy, representing ill-health, is associated with worse depression severity.

Regardless of the reasons why people with comorbid depression and T2DM are more likely to be prescribed insulin, I have identified a sub-population of people with depression and T2DM who may be at very high risk of worse diabetic health. Although these individuals are being treated with antidepressant medication, this does not

appear to sufficiently improve depression symptoms such that the negative effects of depression on physical health are negated. These individuals could be targeted earlier for more intensive holistic interventions to improve their mental well-being and glycaemic control to reduce the chance of progressing to a point where they need to start insulin therapy. These are discussed in my Discussion **Chapter 8.4.1.2**.

As insulin therapy is a treatment outcome, and not a systematic assessment of physical health, further research is required to understand whether antidepressant prescribing is associated with worse physical health outcomes in individuals with comorbid depression and T2DM. In addition, further research is required in this patient group to understand whether antidepressant prescribing is associated specifically with the progression of T2DM, or with worse physical health overall. In **Chapter 7**, I will address this by investigating the association between antidepressant prescribing all-cause and cause-specific mortality (including deaths from cancer, cardiovascular, endocrine, respiratory, suicide and unnatural causes). In **Chapter 7**, I will also further explore my theory that the association between antidepressant prescribing can be attributed to worse depression severity, by comparing suicide and mortality from unnatural causes, to mortality from natural causes related to physical health conditions.

Chapter 7: The Association between Antidepressant Prescribing and Mortality in Adults with Comorbid Depression and Type 2 Diabetes

At the time of writing, an abridged version of this study was being prepared for submission to a peer-reviewed journal.

7.1 Introduction

In the previous **Chapter 6**, I investigated the long-term decline in diabetic health marked by the initiation of insulin therapy in people with comorbid depression and T2DM. I found that individuals in this patient group were considerably more likely to start insulin, if they were prescribed antidepressants. I suggested that this may be due to confounding by the indication of more severe depression. In this chapter, I describe a study exploring mortality rates in individuals with comorbid depression and T2DM who are prescribed antidepressants, compared to those who are not prescribed antidepressants. I originally hypothesised that treating depression would improve physical health outcomes, including mortality. I have kept my original hypotheses in place in my introduction to this study below. However, following the findings of the previous chapter, I suspected that my findings in this study too would be subject to bias from confounding by the indication of depression severity. I discuss this further in the **Discussion Section 7.4** of this chapter, and in detail in my **Discussion Chapter 8**.

Ultimately, the deterioration of diabetic health and development of diabetic complications may lead to premature mortality. Reducing preventable mortality in individuals with comorbid depression and T2DM is an important unmet need. Diabetes directly causes over 1.5 million deaths each year and is the eighth leading cause of death globally (217). Cardiovascular disease, which is the leading cause of death in people with T2DM, causes almost 20 million deaths each year and is the leading cause of death globally (217). Suicide, the risk of which is increased by depression, is the fifteenth leading cause of death globally, affecting over 750,000 individuals each year (217). Furthermore, a meta-analysis of longitudinal studies in people with T2DM

reported 1.5 times higher rates of mortality in people with T2DM who had depression compared to those who did not have depression (408).

If depression increases the risk of mortality in people with comorbid depression and T2DM, we might expect the successful treatment of depression to mitigate this risk. In **Chapter 2**, I described how I systematically searched the literature for studies investigating the association between antidepressant treatment and long-term outcomes (including mortality) in people with comorbid depression and T2DM, and found none suitable for inclusion in a systematic review. However, in my **Introduction Chapter 1.6.2.3**, I described how I found one large population-based study from Taiwan that did not meet did not meet my inclusion criteria for the systematic review, but did investigate the association between antidepressants and mortality in people with diabetes (type unspecified) (219). This study found a 35% decrease in the rates of all-cause mortality in individuals who were prescribed antidepressants compared to those who were not prescribed antidepressants (HR 0.65, 95% CI, 0.59 to 0.71).

There are no studies that investigate the association between antidepressants and cause-specific mortality. Failure to discern between mortality causes may obscure differential effects of antidepressants on cause specific mortality. For example, successfully treating depression may lead to a reduction in deaths from suicide (222), while the cardiovascular (409) or weight-gain (153) side effects associated with some antidepressants may contribute to an increase in mortality rates from cardiovascular causes. Differentiating between causes of death may enable hypotheses concerning any association found between antidepressant prescribing and mortality.

In this chapter, I aimed to examine whether individuals with comorbid depression and T2DM have higher rates of mortality from different causes if they were prescribed an antidepressant, compared to those who were not prescribed an antidepressant. I examined the following causes of mortality: all-cause, endocrine, cardiovascular, cancer, infectious disease, respiratory, suicide, and any unnatural (including suicide).

I originally hypothesised that individuals with comorbid depression and T2DM who are prescribed antidepressants would have lower rates of all-cause mortality compared to those who were not prescribed antidepressants. This was based on previous evidence that has shown increased mortality rates in T2DM for individuals who have depression compared to those who do not (408); and on the theory that treating depression would

mitigate this increased risk of mortality. I hypothesised that suicide would be the cause of death with the least elevated effect estimate in individuals with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not. This was based on the theory that successfully treating depression would have a direct effect on decreasing suicide rates, and on evidence of this in the general population (222). I also hypothesised that the natural causes of death with the least elevated effect estimate for mortality, in individuals with comorbid depression and T2DM prescribed antidepressants compared to those who were not, would be cardiovascular and endocrine causes. This was based on evidence that depression in individuals with T2DM is associated with worse diabetic outcomes (221) and the development of (220) and mortality from (408) cardiovascular complications; and that treating depression would mitigate the risk of mortality from these causes. This was also based on evidence from the 2012 Cochrane review of antidepressant treatment in people with T2DM, that showed a short-term effect of antidepressants on improving glycaemic control (155).

I also performed three additional analyses (described in the following paragraphs) to explore why people with comorbid depression and T2DM who were prescribed antidepressants might have higher or lower rates of mortality (all cause and cause specific) compared to those who were not prescribed antidepressants.

Firstly, I aimed to look at whether the timing of antidepressant prescribing (in relation to the outcome date) made a difference to mortality rates in people with comorbid depression and T2DM. I explored whether there were differences between those who were recently treated with antidepressants (in the last 6 months), and those who received antidepressants more than 6 months ago, compared to individuals who had not received any antidepressant treatment. I hypothesised that there would be no difference between rates of mortality in people recently vs not recently prescribed antidepressants, as there is no evidence for an immediate effect of antidepressants on causing death in this patient group.

Secondly, I aimed to examine whether individuals with comorbid depression and T2DM who had been taking antidepressants for longer cumulative durations had higher mortality rates than those who had been taking antidepressants for shorter durations. I hypothesised that there would be no difference between rates of mortality according to the cumulative duration of antidepressant treatment. This was based on

the theory that there would be no dose-response effect, if antidepressants were not causing mortality.

Finally, I aimed to examine whether individuals with comorbid depression and T2DM who were prescribed multiple different antidepressant agents during their follow-up time had higher rates of mortality than those who were only prescribed one single antidepressant agent. I hypothesised that individuals in this patient group who were prescribed higher numbers of different antidepressant agents would have higher rates of mortality than those prescribed only one antidepressant agent. This was based on the theory that higher numbers of different antidepressant agents represents complex-to-treat depression (386,410). Depression may not be effectively treated in these individuals, and so may continue to negatively impact an individual's risk of mortality.

I aimed to look at all outcomes after accounting for potential confounding from demographic variables, comorbidities, other medication prescribing and health behaviours.

7.2 Methods

7.2.1 Study design and setting

I completed a nested case-control study using EHR data from the UK CPRD. I used the same nested-case control study design as in the previous **Study Chapter 6**. I explained in detail the benefits of the nested-case control study design in my **Methods Chapter 3.3.3**. Nested-case control studies compare people with and without an outcome during a retrospective follow-up period during which multiple time-varying exposures can be observed (364–366).

I show a graphical representation of the study design in **Figure 7.i,** after describing the patient inclusion criteria and study exposures.

The study period ran from 1 January 2000 to 31 December 2018. However, I used data from earlier years (pre-2000) to select the cohort and to identify some of the confounders required in my study.

7.2.2 Patient inclusion criteria

I nested this case-control study within a cohort of adults (age 18+) with comorbid depression and T2DM, who had started oral antidiabetic medication during their EHR

follow-up. I described how I identified people with comorbid depression and T2DM within the CPRD in detail in my **Methods Chapter 3.4.2-3**. I chose to include individuals who were being treated with oral antidiabetic medication for the first time, as this provided a standardised baseline in terms of T2DM illness progression from which individuals could be observed. To do this, individuals had to have at least one oral antidiabetic medication prescription during their EHR follow-up period. To ensure I was capturing the start of oral antidiabetic treatment, I only included individuals whose first oral antidiabetic prescription was prescribed at least 6 months after the individual's date of registration.

I excluded individuals who were not eligible for linkage to ONS mortality data. Individuals who were eligible for linkage were those based in participating CPRD primary care practices in England.

I defined the date that individuals entered the cohort in which this case-control study was nested (study entry date) as the date of their first oral antidiabetic prescription. I defined the date that individuals left the cohort in which this case-control study was nested (censored date) as their date of death (the outcome), end of registration with their primary care practice, or end of the study period (31 December 2018), whichever was first.

7.2.2.1 Selection of cases: individuals with a recorded date of death

I defined cases as individuals with a date of death recorded after their study entry date and before or on their censored date. I defined the outcome date as the date of death. I calculated the observation period for cases as the number of days between starting oral antidiabetic medication (study entry date) and the date of death (outcome date).

To ensure individuals had experienced depression at some point during the observation period, I excluded any cases who did not have a code for depression between entering the study (the date of starting oral antidiabetic medication) and the outcome date (the date of death). I also excluded cases who could not be matched to one or more suitable controls.

7.2.2.2 Selection of controls: individuals who did not yet have a recorded date of death

I included all individuals from the cohort in which this case-control study was nested in the risk-set from which potential controls were selected, regardless of whether or not they later became a case.

I matched all cases to up to 4 randomly selected eligible controls. Eligible controls were participants who were included in the base cohort for at least as many days as the case, with a code for depression but no record of death during this time. Eligible controls were potential matches for a case based on the age at study entry (within 5 years), gender and GP practice.

I defined the outcome date for controls to be after same number of days as their matched case, with respect to the number of days observation period from study entry to the date of death. This ensured cases and controls had the same duration of observation period in days.

7.2.2.3 Outcome subgroups for cause-specific mortality

I used linked ONS data to identify the cause of death and categorised cases into the following subgroups according to their primary recorded cause of death: endocrine, cancer, cardiovascular, infectious disease, respiratory, suicide, any unnatural cause (including suicide). I excluded cases that did not fit into one of these categories from the cause-specific mortality analysis. Controls followed their respective cases into the different cause-specific mortality subgroups for analysis.

7.2.3 Definition of antidepressant prescribing exposures

7.2.3.1 Primary exposure of any antidepressant prescribing during the follow-up period

I defined the primary exposure as being prescribed one or more antidepressant between the study entry and the outcome date. I included the following antidepressant medications which were licensed for use in treating depression in the UK during the follow-up period. These were the same medications included in the study described in **Chapter 6** (investigating the association between antidepressant prescribing and insulin initiation):

SSRIs: Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline;

SNRIs: Duloxetine, venlafaxine;

TCAs: Amitriptyline >= 50mg per day*, amoxapine, clomipramine, dosulepin, oral doxepin, imipramine, lofepramine, maprotiline, nortriptyline >=50mg per day*, trimipramine;

MAOIs: Isocarboxazid, phenelzine, tranylcypromine;

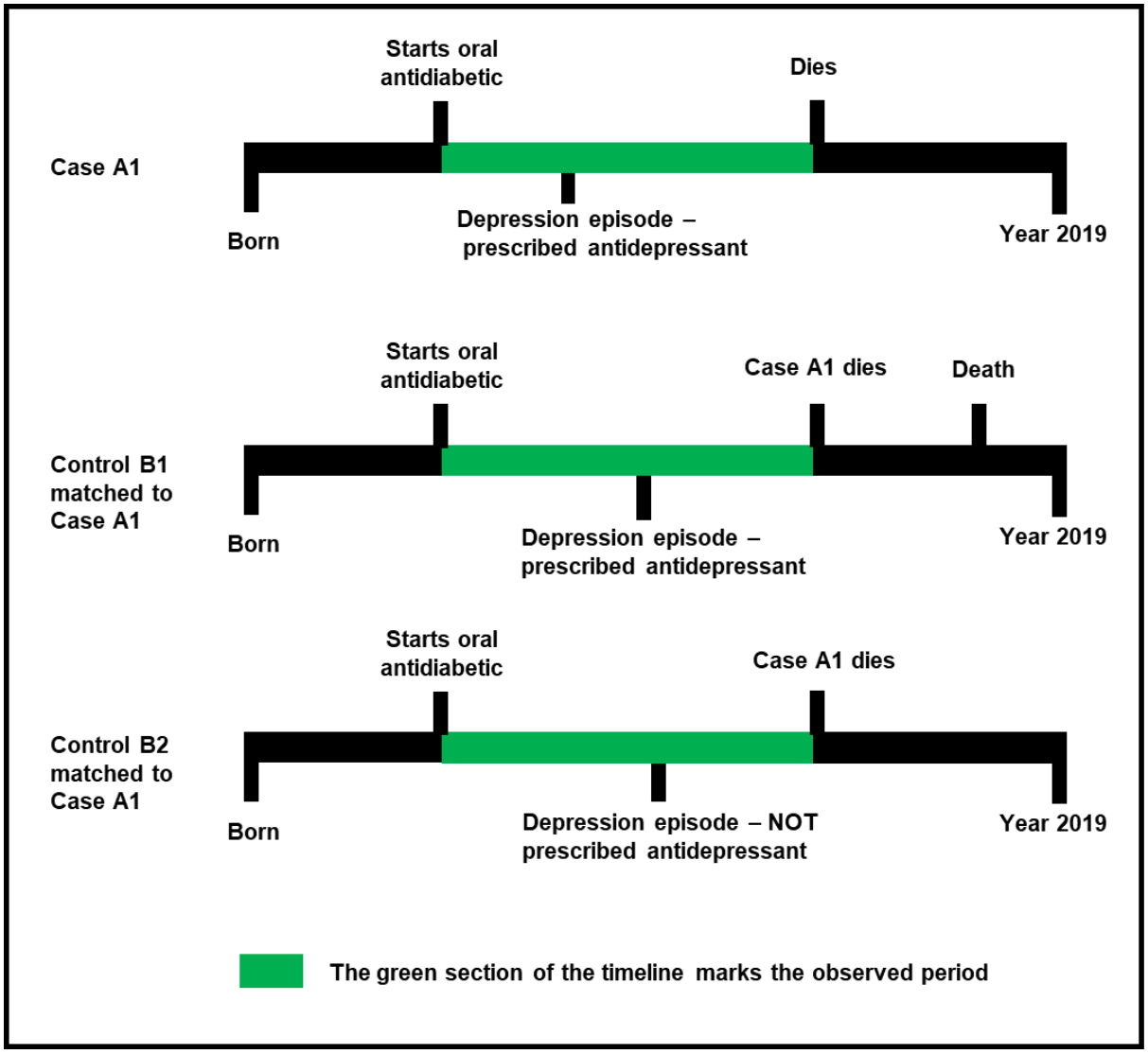
Atypical: Agomelatine, mianserin, mirtazapine, moclobemide, nefazodone, reboxetine, trazodone, tryptophan, vortioxetine.

*Amitriptyline and nortriptyline were included only at the anti-depressant dose of >= 50mg per day, rather than lower hypnotic or neuralgia doses.

I described the creation of the code list for antidepressants in the my **Methods Chapter 3.5.3**.

The follow-up period within which the exposure to antidepressant prescribing could be observed is demonstrated in **Figure 7.i**.

Figure 7.i Examples of participant timelines during which exposure to antidepressant treatment was evaluated for both cases (who started insulin) and controls (who did not start insulin)



7.2.3.2 Additional analyses with antidepressant exposure subcategories

As described above in my aims, I performed additional analyses on three subcategories of the primary exposure. These were the same antidepressant exposure subcategories as in **Chapter 6**:

i) Recent or past antidepressant use: I defined recent antidepressant use as any antidepressant prescription within 182 days (6 months) of the outcome date. I defined individuals who only had a previous antidepressant prescriptions more than 182 days before the outcome date as past antidepressant users. I defined the reference category as having no antidepressant prescription during the observation period.

ii) Cumulative duration of antidepressant treatment: I calculated an individual's cumulative duration of antidepressant treatment as the sum of the duration of each antidepressant treatment episode. To do this, I calculated the duration of each antidepressant treatment episode as the number of days between the first and last prescription of any antidepressant, plus the duration of that last prescription. If a participant had a gap of more than 60 days after the expected end date of the previous prescription without any subsequent antidepressant prescription recorded, that was considered to be the last prescription in that treatment episode (this is in line with my definition of antidepressant discontinuation in **Chapters 4-5**). I counted any subsequent prescriptions as new treatment episodes, and included them in the cumulative total duration of treatment. I categorised the cumulative duration of antidepressant treatment into four groups, namely <6 months, 6-12 months, 13-24 months and >24 months. I defined the reference category as no antidepressant prescription during the observation period.

iii) Number of different antidepressant agents prescribed during the observation period: I counted the number of different antidepressant agents, as defined for the primary exposure. I categorised these into four groups: 0 (reference category), 1, 2 and 3+.

7.2.4 Confounders

I included the same confounders in this study, as in the previous study described in **Chapter 6** (investigating the association between antidepressant prescribing and insulin initiation). I demonstrate the potential causal relationships between the confounders, exposure and outcome in **Figure 7.i**. These included:

Demographic characteristics: In addition to the variables used for matching, I also included ethnicity. Where ethnicity was missing, I recoded this as "White", as discussed in **Chapter 4.2.5**.

Health characteristics: I included a range of health characteristics that may be confounders through an association with antidepressant use (either directly or indirectly through an association with depression) and mortality (either directly or indirectly through an association with poor overall physical health, or health behaviours):

- The following comorbidities (as individual comorbidities rather than a count) based on codes from the Elixhauser comorbidity code list (as in **Chapter 6**) (405): alcohol abuse, blood loss anaemia, cardiac arrythmia, chronic pulmonary disease, coagulopathy, deficiency anaemia (iron/B12), drug abuse, fluid and electrolyte disorders, hypertension (uncomplicated), hypertension with end organ damage, hypothyroidism, liver disease, lymphoma (history), metastatic cancer, other neurological disorders, paralysis, peptic ulcer disease, peripheral vascular disease, psychoses, pulmonary circulation disorders, renal disease, rheumatoid arthritis and collagen diseases, solid tumor or leukaemia, valvular disease – I coded the presence of each individual condition for participants who had a relevant code recorded prior to the study entry date;
- The most recent recorded BMI value categorised into "normal" (<25 kg/m^2), "overweight" (25 to <30 kg/m^2), and "obese" (30+ kg/m^2); where no value for BMI was available, I estimated the value using multiple imputation – the method I used for multiple imputation was multiple imputation by chained equations using five iterations of logistic regression to impute missing values based on all other variables included in the study;
- Smoking status categorised into "current smoker" (most recent smoking code related to current smoking within 12 months before study entry), "ex-smoker" (most recent smoking code related to historic smoking, or most recent code related to current smoking more than 12 months before study entry, or most

recent code related to non-smoking with prior codes related to current or historic smoking), “non-smoker” (no codes related to smoking, or non-smoking codes only);

- T2DM duration, defined as the number of months between the first diabetes related code (this could include diagnosis, symptom, process of care, or medication) and the date of the first oral antidiabetic medication prescription;
- Number of primary care contacts recorded in the 12 months prior to the study entry date. This included any face-to-face contact or phone calls.

I did not include glycaemic control as a potential confounder, given the study inclusion criteria of starting oral antidiabetic medication (study entry) meant that all participants would be expected to have uncontrolled blood sugar levels at the time of study entry.

Medication history: I included the number of different pharmacological medications prescribed (excluding vaccinations, topical medications and supplements) in the 90 days before the study entry. It was not possible to account for markers of depression and depression severity at study entry. Therefore, to indicate previous depression at a severity requiring pharmacological treatment, I included any previous antidepressant prescription in the 12 months prior to study entry.

7.2.5 Sensitivity analyses to investigate the role of imputing missing data

I performed two sensitivity analyses to investigate the role of imputing missing data. In the first, I included only individuals with complete data for ethnicity. In the second, I included only individuals with complete data for BMI.

7.2.6 Statistical analysis

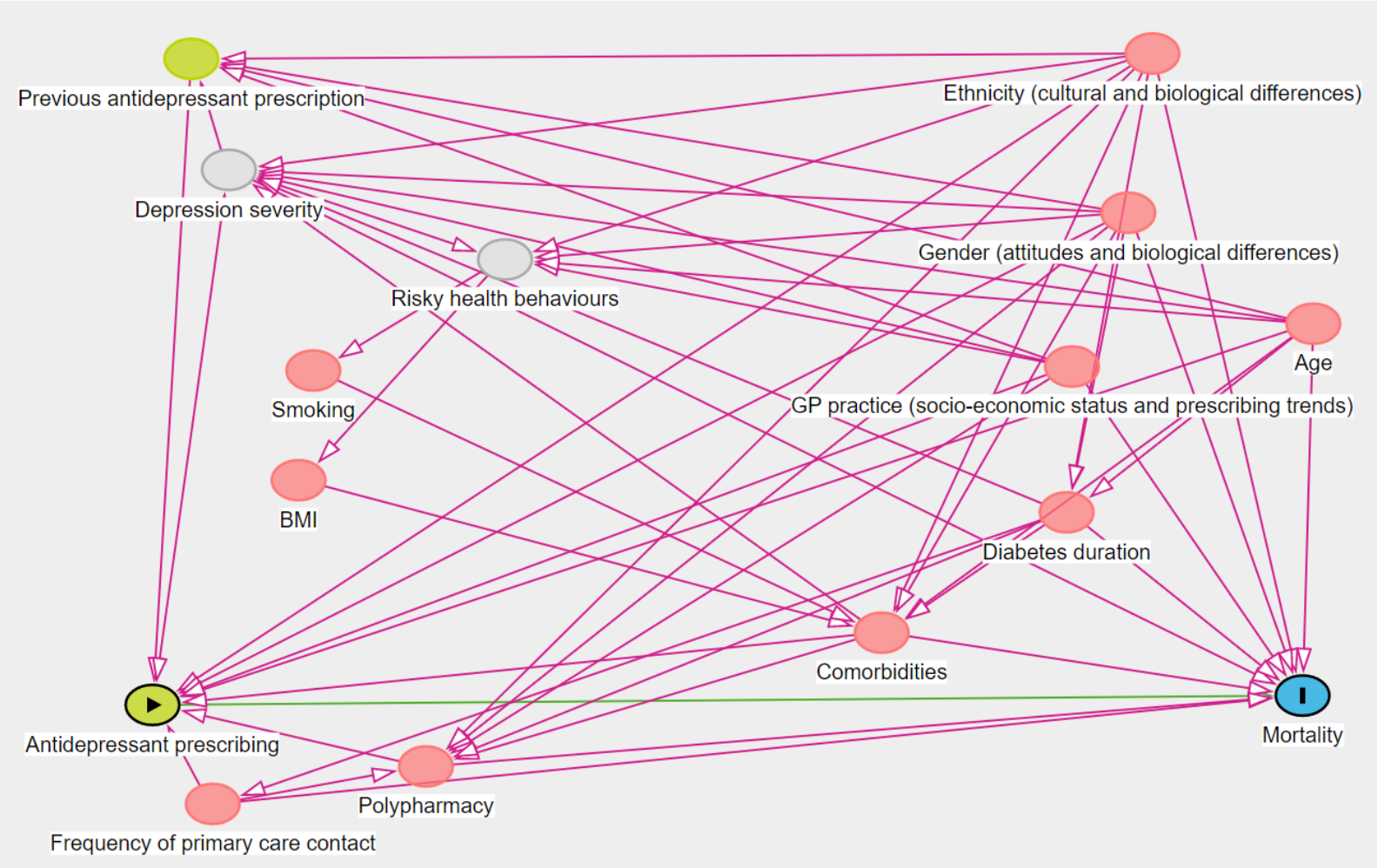
I used conditional logistic regression to estimate adjusted incident rate ratios (IRR) and corresponding 95% confidence intervals (CI) for the association between each of the antidepressant prescribing exposures and all cause mortality. I explained in **Chapter 3.7.2** how conditional logistic regression estimates incident rate ratios in case-control studies where incident sampling and individual matching is used. I initially performed univariable analyses, and then multivariable analyses adjusting for all aforementioned confounders. I combined all confounders in one multivariable model due to the potential interaction between demographic variables, health characteristics,

medication history and behavioural characteristics. This is demonstrated in the DAG in **Figure 7.ii**.

I repeated all analyses for each mortality cause subgroup described in **Section 7.2.2.3**.

I repeated the multivariable analysis for the primary exposure (any antidepressant prescribing) and outcome (all cause mortality) for each sensitivity analysis described in **Section 7.2.5**.

Figure 7.ii DAG showing the relationship between confounders, exposure and outcome



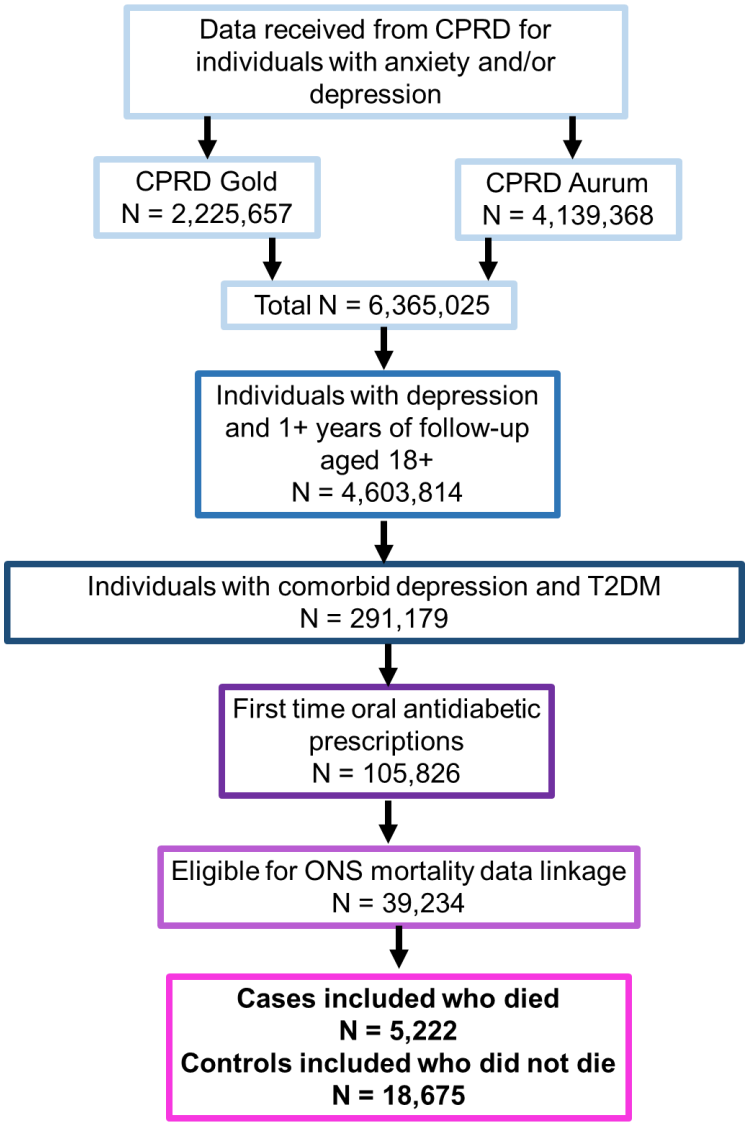
*Green = exposure; blue = outcome; red = potential confounder; grey = unmeasured; direction of arrow shows potential causal effect

7.3 Results

7.3.1 Characteristics of individuals included in this study

I demonstrate the number of individuals included or excluded in a flow diagram, **Figure 7.iii**.

Figure 7.iii Flow diagram of inclusion and exclusion



The cohort in which this study was nested consisted of 39,234 individuals with comorbid depression and T2DM, who started oral antidiabetic medication during the study period and were eligible for ONS mortality data linkage. From this, I identified 5,222 cases who had a recorded date of death, and 18,675 controls who were presumed still alive at the time of their respective case's date of death.

Out of 5,222 cases with comorbid depression and T2DM who died after starting oral antidiabetic medication, 207 died from endocrine causes, 1,635 died from cardiovascular causes, 1,474 died from cancer, 789 died from respiratory causes, 70 died by suicide, and 137 died from any unnatural cause (including suicide).

Individuals included in the study were followed up for a median of 7.05 years (IQR 4.25-10.20).

In **Table 7.i** I report baseline characteristics of all individuals included in the study, and categorised as cases or controls. The median age of at the time of study entry (date of the first oral antidiabetic prescription) was 69 (IQR 61-76). The majority of participants (56.42%) were of White ethnicity and 49.35% of individuals were female. The two groups were balanced in terms of demographic characteristics with the exception of ethnicity, where cases had a higher proportion with missing ethnicity (46.57% compared to 35.34% of controls). The median T2DM duration prior to the initiation of oral antidiabetic medication was longer in cases (6.78 months, IQR 0.23-35.73) compared to controls (5.91 months, IQR 0.13-35.91). Cases and controls were similar in terms of the number of concurrent medications prescribed at the time of study entry (median for all participants was 6, IQR 4-9) and the number of primary care contacts in the past 12 months (median for all participants was 26, IQR 15-40). The proportion of all included individuals with a history of antidepressant prescribing in the past 12 months was 27.79% - this was similar between cases and controls.

In **Table 7.ii** I report the baseline comorbidities of included individuals, combined, and categorised as cases and controls. Cases had a higher prevalence of each comorbidity at baseline, with the exception of uncomplicated hypertension (which was slightly higher in controls). The most common comorbidities in all participants were uncomplicated hypertension (75.13%), renal disease (38.85%), COPD (38.22%), other neurological disorders* (33.23%) and solid tumour/leukaemia (28.41%). The most common BMI category was obese (39.76%), and 22.65% were current smokers. *Other neurological disorders included brain trauma, cerebrovascular diseases, dementia, epilepsy, encephalitis, hydrocephalus, movement disorders, neurodegenerative diseases, other cerebral degeneration, spine injuries and disorders.

Table 7.i Characteristics of cases and controls, at the time of study entry

	All N (%)	Cases N (%)	Controls N (%)
Sample size	23,897	5,222	18,675
Female (%)	11,792 (49.35)	2,579 (49.39)	9,213 (49.33)
Median age (IQR) (years)	69 (61-76)	70 (62-77)	69 (60-75)
Ethnicity:			
Asian (%)	908 (3.80)	136 (2.60)	772 (4.13)
Black (%)	345 (1.44)	54 (1.03)	291 (1.56)
Missing* (%)	9,032 (37.80)	2,432 (46.57)	6,600 (35.34)
Mixed (%)	58 (0.24)	7 (0.13)	51 (0.27)
Other (%)	72 (0.30)	4 (0.08)	68 (0.36)
White (%)	13,482 (56.42)	2,589 (49.58)	10,893 (58.33)
Median T2DM duration in months (IQR)	6.11 (0.12-35.88)	6.78 (0.23-35.73)	5.91 (0.13-35.91)
Median (IQR) medication count (last 3 months)	6 (4-9)	6 (4-9)	6 (4-9)
Prescribed antidepressants in last 12 months, n (%)	6,640 (27.79)	1,343 (25.72)	5,297 (28.36)
Median number of primary care contacts in last 12 months	26 (15-40)	26 (15-40)	26 (16-40)
Median follow-up time in years (IQR)	7.05 (4.25-10.20)	7.05 (4.25-10.20)	7.05 (4.25-10.20)

*Missing data imputed for ethnicity as “White”

Table 7.ii Comorbidities of cases and controls at time of study entry

	All N (%)	Cases N (%)	Controls N (%)
Comorbidity:			
Alcohol abuse	1,399 (5.85)	382 (7.32)	1,017 (5.45)
Blood loss anemia	28 (0.12)	9 (0.17)	19 (0.10)
Cardiac arrhythmia	6,225 (26.05)	1,616 (30.95)	4,609 (24.68)
Chronic heart failure	4,031 (16.87)	1,276 (24.44)	2,755 (14.75)
Coagulopathy	496 (2.08)	144 (2.76)	352 (1.88)
COPD	9,133 (38.22)	2,208 (42.28)	6,925 (37.08)
Deficiency anaemia (iron/B12)	4,234 (17.72)	970 (18.58)	3,264 (14.48)
Drug abuse	391 (1.64)	92 (1.76)	299 (1.60)
Fluid and electrolyte disorders	2,883 (12.06)	771 (14.76)	2,122 (11.36)
Hypertension (uncomplicated)	17,955 (75.13)	3,794 (72.65)	14,161 (75.83)
Hypertension (late stage)	106 (0.44)	36 (0.69)	70 (0.37)
Hypothyroidism	3,264 (13.66)	764 (14.63)	2,500 (13.39)
Liver disease	900 (3.77)	281 (5.38)	619 (3.31)
Lymphoma (history)	338 (1.41)	110 (2.11)	228 (1.22)
Metastatic cancer	792 (3.31)	405 (7.76)	387 (2.07)
Other neurological disorders	7,942 (33.23)	2,072 (39.68)	5,870 (31.43)
Paralysis	294 (1.23)	99 (1.90)	195 (1.04)
Peptic ulcer disease	1,830 (7.66)	469 (8.98)	1,361 (7.29)
Peripheral vascular disease	2,995 (12.53)	880 (16.85)	2,115 (11.33)
Psychosis	920 (3.85)	252 (4.83)	668 (3.58)
Pulmonary circulation disorders	1,172 (4.90)	374 (7.16)	798 (4.27)
Collagen vascular diseases	2,403 (10.06)	550 (10.53)	1,853 (9.92)
Renal disease	9,285 (38.85)	2,311 (44.26)	6,974 (37.34)
Solid tumour or leukaemia	6,788 (28.41)	1,963 (37.59)	4,825 (25.84)
Valvular disease	1,841 (7.70)	456 (8.73)	1,385 (7.42)
Smoking Status:			
Non-smoker	12,091 (50.60)	2,702 (51.74)	9,389 (50.28)
Current smoker	5,413 (22.65)	1,350 (25.85)	4,063 (21.76)
Ex-smoker	6,393 (26.75)	1,170 (22.41)	5,223 (27.97)
BMI category:			
Missing*	8,180 (34.23)	1,960 (37.53)	6,221 (33.31)
Normal	1,633 (6.83)	418 (8.00)	1,215 (6.51)
Overweight	4,583 (39.76)	1,862 (35.66)	7,639 (40.90)
Obese	9,501 (19.18)	983 (18.82)	3,600 (19.28)

*Missing data imputed for BMI using multiple imputation

7.3.2 Comparison of characteristics at study entry between individuals who are subsequently prescribed antidepressants and those who are not

In **Table 7.iii** I report baseline characteristics and in **Table 7.iv** I report comorbidities of individuals included in the study, categorised by whether or not they received an antidepressant during the observational period. People with comorbid depression and T2DM who were prescribed antidepressants were more likely to be female (55.03% vs 45.27%) and of missing ethnicity (39.42 vs 35.99) compared to those who were not prescribed antidepressants. People who were prescribed antidepressants had slightly higher proportions of most comorbidities at baseline compared to those who were not prescribed antidepressants.

Table 7.iii Sample characteristics at the time of study entry, by exposure group

	People prescribed antidepressants N (%)	**People not prescribed antidepressants N (%)**
Sample size	12,553	11,344
Female (%)	6,657 (53.03)	5,135 (45.27)
Median age (IQR) (years)	69 (60-75)	69 (61-76)
Ethnicity:		
Asian (%)	339 (2.70)	569 (5.02)
Black (%)	92 (0.73)	253 (2.23)
Missing (%)	4,949 (39.42)	4,083 (35.99)
Mixed (%)	26 (0.21)	32 (0.28)
Other (%)	29 (0.23)	43 (0.38)
White (%)	7,118 (56.70)	6,364 (56.10)
Median diabetes duration in months (IQR)	5.88 (0.23-33.61)	6.41 (0.10-38.41)
Median (IQR) medication count (last 3 months)	7 (4-9)	6 (4-8)
Prescribed antidepressants in last 12 months, n (%)	4,996 (39.80)	1,644 (14.49)
Number of primary care contacts in last 12 months	28 (17-42)	24 (14-38)

Table 7.iv Comorbidities at time of study entry, by exposure group

	People prescribed antidepressants N (%)	People not prescribed antidepressants N (%)
Comorbidity:		
Alcohol abuse	816 (6.50)	583 (5.14)
Blood loss anaemia	15 (0.12)	13 (0.11)
Cardiac arrhythmia	3,434 (27.36)	2,791 (24.60)
Chronic heart failure	2,391 (19.05)	1,640 (14.46)
Coagulopathy	289 (2.30)	207 (1.82)
COPD	5,160 (41.11)	3,973 (35.02)
Deficiency anaemia (iron/B12)	2,459 (19.59)	1,775 (15.65)
Drug abuse	260 (2.07)	131 (1.15)
Fluid and electrolyte disorders	1,654 (13.18)	1,229 (10.83)
Hypertension (uncomplicated)	9,574 (76.27)	8,381 (73.88)
Hypertension (late stage)	67 (0.53)	39 (0.34)
Hypothyroidism	1,892 (15.07)	1,372 (12.09)
Liver disease	523 (4.17)	377 (3.32)
Lymphoma (history)	210 (1.67)	128 (1.13)
Metastatic cancer	512 (4.08)	280 (2.47)
Other neurological disorders	4,614 (36.76)	3,328 (29.34)
Paralysis	186 (1.48)	108 (0.95)
Peptic ulcer disease	1,042 (8.30)	788 (6.95)
Peripheral vascular disease	1,706 (13.59)	1,289 (11.36)
Psychosis	570 (4.54)	350 (3.09)
Pulmonary circulation disorders	691 (5.50)	481 (4.24)
Collagen vascular diseases	1,399 (11.14)	1,004 (8.85)
Renal disease	5,331 (42.47)	3,954 (34.86)
Solid tumour or leukaemia	3,783 (30.14)	3,005 (26.49)
Valvular disease	983 (7.83)	858 (7.56)
Smoking Status:		
Non-smoker	6,367 (50.72)	5,724 (50.46)
Current smoker	3,003 (23.92)	2,410 (21.24)
Ex-smoker	3,183 (25.36)	3,210 (28.30)
BMI category:		
Missing	5,522 (43.99)	3,658 (32.25)
Normal	727 (5.79)	906 (7.99)
Overweight	1,234 (9.83)	2,349 (20.71)
Obese	5,070 (40.39)	4,431 (39.06)

7.3.3 Results for the association between any antidepressant prescribing and mortality in individuals with comorbid depression and T2DM

I report the main results for the association between antidepressant prescribing and mortality in **Table 7.iii**.

Individuals with comorbid depression and T2DM who were prescribed any antidepressant after starting oral antidiabetic medication, had considerably higher rates of all-cause mortality than those who were not prescribed an antidepressant. After adjusting for demographic characteristics, comorbidities and prescription history at baseline, the incident rate ratio (IRR) for the rate of all-cause mortality in individuals who were prescribed at least one antidepressant prescription during the follow-up period compared to those without any antidepressant prescription was 2.77 (95% CI 2.48-3.10).

I observed considerably elevated rates of mortality in individuals who were prescribed an antidepressant compared to those who were not across each of the specific causes of death that I investigated. I observed the highest IRR in suicide (IRR 61.48, 95% CI 1.47-2567.00), followed by any unnatural causes of death (IRR 9.27, 95% CI 3.02-28.47), followed by endocrine causes (IRR 3.65, 95% CI 1.83-7.29), cancer (IRR 2.94, 95% CI 2.27-3.83), respiratory (IRR 2.94, 95% CI 2.13-4.04), and cardiovascular (IRR 2.27, 95% CI 1.86-2.77). The confidence intervals for suicide and all unnatural causes of death were wide due to small numbers of individuals experiencing these outcomes.

7.4.4 Sensitivity analysis to investigate the role of imputing missing data

In a first sensitivity analysis I included only individuals with a completed value for ethnicity. There was no evidence of a change in the effect estimates between the main analysis and this sensitivity analysis (IRR 2.72, 95% CI 2.36-3.14).

In a second sensitivity analysis I included only individuals with a completed value for BMI. There was no evidence of a change in the effect estimates between the main analysis and this sensitivity analysis (IRR 2.77, 95% CI 2.48-3.09).

Table 7.v – IRRs and 95% CIs for the association between antidepressant prescribing and mortality

Mortality cause	Exposure	Cases	Controls	Univariable	Multivariable
All-cause	**No antidepressant**	1,460 (27.96)	9,884 (52.93)	Reference	Reference
	Any antidepressant	3,762 (72.04)	8,791 (47.07)	3.24 (3.02-3.49)	2.77 (2.48-3.10)
Endocrine	**No antidepressant**	52 (25.12)	387 (52.02)	Reference	Reference
	Any antidepressant	155 (74.88)	357 (47.98)	3.51 (2.42-5.09)	3.65 (1.83-7.29)
Cardiovascular	**No antidepressant**	483 (29.56)	3,083 (53.03)	Reference	Reference
	Any antidepressant	1,152 (70.46)	2,791 (46.97)	2.93 (2.58-3.33)	2.27 (1.86-2.77)
Cancer	**No antidepressant**	445 (30.19)	2,878 (53.11)	Reference	Reference
	Any antidepressant	1,030 (69.88)	2,546 (46.98)	2.98 (2.60-3.40)	2.94 (2.27-3.83)
Respiratory	**No antidepressant**	201 (25.48)	1,515 (54.79)	Reference	Reference
	Any antidepressant	588 (74.52)	1,293 (46.76)	3.82 (3.15-4.64)	2.94 (2.13-4.04)
Suicide	**No antidepressant**	[Censored due	69 (47.92)	Reference	Reference
	Any antidepressant	to small	75 (52.08)	11.05 (3.19-38.27)	61.48 (1.47-2567.00)
		numbers]*			
All unnatural	**No antidepressant**	23 (16.79)	261 (52.41)	Reference	Reference
	Any antidepressant	114 (83.21)	237 (47.59)	7.28 (4.24-12.53)	9.27 (3.02-28.47)

*CPRD data protection does not allow reporting of data for less than 5 people – therefore when this is the case, the values have been censored

I report the breakdown of unnatural causes of death in **Table 7.iv**.

Aside from suicide, a number of other unnatural causes of death in individuals with comorbid depression and T2DM had considerably higher proportions of individuals who were prescribed antidepressants than who were not. These were: falls (8.88% vs 2.47%), accidental poisoning (4.87% vs <1.77%), unspecified accidents (3.44% vs <1.77 %) and transport accidents (1.43% vs 0.00%).

Table 7.vi Breakdown of unnatural causes of death, and associated antidepressant prescribing

	Prescribed an antidepressant N(%)	Not prescribed an antidepressant N(%)
Controls	237 (67.91)	261 (92.23)
Transport accidents	5 (1.43)	0 (0.00)
Falls	31 (8.88)	7 (2.47)
Exposure to fire/smoke	<5 (<1.43)*	<5 (<1.77)*
Accidental poisoning	17 (4.87)	<5 (<1.77)*
Unspecified accident	12 (3.44)	<5 (<1.77)*
Suicide	35 (10.03)	<5 (<1.77)*
Complications of medical care	6 (1.72)	5 (1.77)
Unspecified external causes	5 (1.43)	<5 (<1.77)*

*Values <5 have been censored due to data protection

7.3.5 Results for the association between antidepressant prescribing and mortality, according to the timing of the antidepressant prescription, in individuals with comorbid depression and T2DM

I report results for the association between antidepressant prescribing and mortality, according to the timing of the antidepressant prescription, in **Table 7.vii.**

I observed the most elevated rates of all-cause mortality in individuals with comorbid depression and T2DM when they were recently prescribed an antidepressant (within 6 months of the outcome date) compared to those who were prescribed no antidepressant (IRR 3.19, 95% CI 2.82-3.61). Individuals with comorbid depression and T2DM who were only prescribed antidepressants in the past (more than 6 months before the outcome date) still had higher rates of mortality compared to those who were not prescribed antidepressants, but the difference in mortality rates was smaller than in those with recent antidepressant prescriptions (IRR 2.14, 95% CI 1.84-2.48).

This pattern of higher mortality rates for individuals with comorbid depression and T2DM who were recently prescribed antidepressants was seen across all cause-specific mortalities. In mortality caused by suicide, any unnatural cause (including suicide) and endocrine causes, there was no evidence of a difference in mortality rates between individuals with comorbid depression and T2DM who had been prescribed antidepressants more than 6 months in the past and those who had never been prescribed antidepressants.

7.3.6 Results for the association between antidepressant prescribing and mortality, according to the cumulative duration of antidepressant treatment, in individuals with comorbid depression and T2DM

I report results for the association between antidepressant prescribing and mortality, according to the cumulative duration of antidepressant treatment, in **Table 7.vi.**

Although individuals with comorbid depression and T2DM who were prescribed antidepressants had considerably higher rates of all-cause and cause specific mortality (from all investigated causes) compared to those who were not prescribed antidepressants, this did not vary according to the cumulative duration of antidepressant treatment. This was the case regardless of mortality cause.

Table 7.vii – IRRs and 95% CIs for the association between antidepressants and mortality, according to timing of prescription

Mortality cause	Exposure	Cases	Controls	Univariable	Multivariable
All-cause	**No antidepressant**	1,460 (27.96)	1,460 (27.96)	Reference	Reference
	Recent antidepressant	2,742 (52.51)	6,080 (32.56)	3.41 (3.16-3.68)	3.19 (2.82-3.61)
	Past antidepressant	1,020 (27.11)	2,711 (14.52)	2.85 (2.59-3.14)	2.14 (1.84-2.48)
Endocrine	**No antidepressant**	52 (25.12)	387 (52.02)	Reference	Reference
	Recent antidepressant	820 (50.18)	245 (32.93)	3.78 (2.56-5.57)	4.45 (2.10-9.43)
	Past antidepressant	332 (20.32)	112 (15.05)	2.84 (1.69-4.66)	2.08 (0.80-5.37)
Cardiovascular	**No antidepressant**	483 (29.56)	3,083 (53.03)	Reference	Reference
	Recent antidepressant	820 (50.18)	1,860 (31.99)	3.06 (2.68-3.51)	2.48 (1.98-3.12)
	Past antidepressant	332 (20.32)	872 (15.00)	2.65 (2.25-3.13)	1.96 (1.51-2.55)
Cancer	**No antidepressant**	445 (30.19)	2,878 (53.11)	Reference	Reference
	Recent antidepressant	755 (51.22)	1,791 (33.05)	3.11 (2.70-3.58)	3.25 (2.43-4.34)
	Past antidepressant	275 (18.66)	755 (13.93)	2.66 (2.23-3.19)	2.43 (1.70-3.48)
Respiratory	**No antidepressant**	201 (25.48)	1,515 (54.79)	Reference	Reference
	Recent antidepressant	451 (57.16)	900 (32.55)	4.28 (3.49-5.25)	3.88 (2.72-5.54)
	Past antidepressant	137 (17.36)	393 (14.21)	2.82 (2.17-3.67)	1.76 (1.13-2.73)
Suicide	**No antidepressant**	[Censored due	69 (47.92)	Reference	Reference
	Recent antidepressant	to small	48 (33.33)	12.15 (3.489-42.30)	239.50 (2.03-28260.00)
	Past antidepressant	numbers]	27 (18.75)	7.513 (1.77-31.86)	31.53 (0.41-2435.00)
All unnatural	**No antidepressant**	23 (16.79)	261 (52.41)	Reference	Reference
	Recent antidepressant	95 (69.34)	165 (33.13)	8.21 (4.73-14.24)	28.86 (6.60-126.15)
	Past antidepressant	19 (13.87)	72 (14.46)	4.11 (1.97-8.59)	0.98 (0.16-6.17)

Table 7.viii – IRRs and 95% CIs for the association between antidepressants and mortality, according to the cumulative duration of treatment, page 1 of 2

Mortality cause	Cumulative duration of antidepressant treatment	Cases	Controls	Univariable	Multivariable
All-cause	**No antidepressant**	1,460 (27.96)	1,460 (27.96)	Reference	Reference
	1-6 months	1,088 (20.83)	2,378 (12.73)	3.39 (3.08-3.73)	3.10 (2.71-3.55)
	7-12 months	429 (8.22)	942 (5.04)	3.37 (2.95-3.85)	3.45 (2.86-4.16)
	13-23 months	514 (9.84)	1,202 (6.44)	3.15 (2.79-3.55)	3.53 (2.97-4.19)
	24+ months	1,729 (33.11)	4,260 (22.81)	3.15 (2.86-3.43)	3.40 (3.00-3.87)
Endocrine	**No antidepressant**	52 (25.12)	387 (52.02)	Reference	Reference
	1-6 months	42 (20.29)	85 (11.42)	3.98 (2.39-6.64)	3.10 (2.71-3.55)
	7-12 months	13 (6.28)	41 (5.51)	2.44 (1.21-4.94)	3.49 (2.87-4.17)
	13-23 months	14 (6.76)	55 (7.39)	2.16 (1.10-4.23)	3.53 (3.53-4.20)
	24+ months	86 (41.55)	176 (23.66)	4.10 (2.68-6.27)	3.40 (3.00-3.87)
Cardiovascular	**No antidepressant**	483 (29.56)	3,083 (53.03)	Reference	Reference
	1-6 months	315 (19.28)	792 (13.62)	2.72 (2.30-3.22)	2.59 (2.04-3.29)
	7-12 months	140 (8.57)	295 (5.07)	3.11 (2.47-3.92)	2.94 (2.07-4.16)
	13-23 months	161 (9.85)	353 (6.07)	2.96 (2.38-3.68)	3.15 (2.89-4.35)
	24+ months	535 (32.74)	1,291 (22.21)	3.01 (2.59-3.49)	2.87 (2.27-3.34)

Table 7.viii continued page 2 of 2

Mortality cause	Duration of antidepressant treatment	Cases	Controls	Univariable	Multivariable
Cancer	**No antidepressant**	445 (30.19)	2,878 (53.11)	Reference	Reference
	1-6 months	359 (24.36)	669 (12.35)	3.88 (3.26-4.60)	4.07 (2.96-5.61)
	7-12 months	132 (8.96)	259 (4.78)	3.81 (2.98-4.87)	3.86 (2.47-6.03)
	13-23 months	128 (8.68)	360 (6.64)	2.58 (2.05-3.26)	3.18 (2.10-4.81)
	24+ months	410 (27.82)	1,253 (23.12)	2.42 (2.07-2.84)	3.00 (2.21-4.07)
Respiratory	**No antidepressant**	201 (25.48)	1,515 (54.79)	Reference	Reference
	1-6 months	149 (18.88)	344 (12.44)	3.49 (2.70-4.51)	2.85 (1.95-4.16)
	7-12 months	69 (8.75)	138 (4.99)	2.47 (3.03-6.02)	4.53 (2.68-7.65)
	13-23 months	84 (10.65)	183 (6.62)	3.67 (2.70-5.00)	3.81 (2.38-6.11)
	24+ months	286 (36.25)	627 (22.67)	4.01 (3.01-5.01)	4.67 (3.23-6.76)
Suicide	**No antidepressant**	[Censored due	69 (47.92)	Reference	Reference
	1-6 months	to small	19 (13.19)	7.39 (1.70-32.19)	148.00 (2.48-8828.00)
	7-12 months	numbers]	9 (6.25)	16.82 (3.19-88.61)	299.00 (1.84-48690.00)
	13-23 months		8 (5.56)	18.24 (3.58-93.01)	859.70 (5.73-129100.00)
	24+ months		39 (27.08)	11.28 (2.95-43.10)	261.80 (4.87-14070.00)
All unnatural	**No antidepressant**	23 (16.79)	261 (52.41)	Reference	Reference
	1-6 months	22 (16.09)	47 (9.44)	6.61 (3.24-13.49)	7.71 (1.88-31.55)
	7-12 months	10 (7.30)	28 (5.62)	6.68 (2.71-16.51)	10.86 (2.48-47.63)
	13-23 months	20 (14.60)	31 (6.22)	11.28 (5.17-24.58)	23.73 (5.58-100.87)
	24+ months	62 (45.26)	131 (26.31)	7.01 (3.92-12.53)	10.75 (3.44-33.61)

7.4.7 Results for the association between antidepressant prescribing and mortality, according to the number of different antidepressant agents prescribed, in individuals with comorbid depression and T2DM

I report results for the association between antidepressant prescribing and mortality, according to the number of different individual antidepressant agents prescribed, in **Table 7.x**

Individuals with comorbid depression and T2DM had increasingly higher rates of all-cause mortality the more different individual antidepressant agents they were prescribed, compared to those who were not prescribed any antidepressants. The IRR for all-cause mortality in individuals with comorbid depression and T2DM who were prescribed one individual antidepressant agent compared to no antidepressant prescriptions was 3.64 (95% CIs 3.01-3.77), for two antidepressant agents the IRR was 3.71 (95% CIs 3.21-4.28) and for three or more antidepressant agents the IRR was 4.93 (95% CIs 4.16-5.83). This pattern remained across all cause-specific mortalities that I investigated.

Table 7.x – IRRs and 95% CIs for the association between antidepressants and mortality, according to the number of different individual antidepressant agents prescribed, page 1 of 2

Mortality cause	Number of antidepressant agents	Cases	Controls	Univariable	Multivariable
All-cause	**0**	1,460 (27.96)	1,460 (27.96)	Reference	Reference
	1	2,149 (41.15)	5,295 (28.35)	3.13 (2.89-3.39)	3.64 (3.01-3.77)
	2	940 (18.00)	1,990 (10.66)	3.73 (3.37-4.13)	3.71 (3.21-4.28)
	3+	673 (12.89)	1,228 (6.58)	4.52 (4.03-5.07)	4.93 (4.16-5.83)
Endocrine	**0**	52 (25.12)	387 (52.02)	Reference	Reference
	1	73 (35.27)	202 (27.15)	2.98 (1.97-4.53)	4.32 (2.15-8.65)
	2	46 (22.22)	88 (11.83)	4.62 (2.81-7.60)	3.79 (1.49-9.66)
	3+	36 (17.39)	51 (6.85)	6.54 (3.78-11.32)	7.77 (2.92-20.69)
Cardiovascular	**0**	483 (29.56)	3,083 (53.03)	Reference	Reference
	1	650 (39.78)	1,697 (29.02)	2.73 (2.38-3.14)	2.75 (2.24-3.37)
	2	286 (17.50)	563 (9.68)	3.64 (3.03-4.36)	3.38 (2.59-4.40)
	3+	216 (13.22)	383 (6.59)	4.23 (3.46-5.19)	4.30 (3.16-5.86)
Cancer	**0**	445 (30.19)	2,878 (53.11)	Reference	Reference
	1	621 (42.13)	1,536 (28.34)	3.05 (2.64-3.54)	3.88 (2.96-5.08)
	2	243 (16.49)	584 (10.78)	3.15 (2.60-3.81)	3.27 (2.30-4.63)
	3+	166 (11.26)	343 (6.33)	3.76 (3.02-4.68)	5.93 (3.87-9.10)

Table 7.xi continued – IRRs and 95% CIs for the association between antidepressants and mortality, according to the number of different individual antidepressant agents prescribed, page 2 of 2

Mortality cause	Duration of antidepressant treatment	Cases	Controls	Univariable	Multivariable
Respiratory	**0**	201 (25.48)	1,515 (54.79)	Reference	Reference
	1	342 (43.35)	773 (27.96)	3.78 (3.06-4.67)	3.83 (2.78-5.27)
	2	136 (17.24)	285 (10.31)	4.24 (3.23-5.56)	4.42 (2.92-6.68)
	3+	110 (13.94)	192 (6.94)	5.42 (4.02-7.32)	5.73 (3.64-9.01)
Suicide	**0**	[Censored due to	69 (47.92)	Reference	Reference
	1	small numbers]	47 (32.64)	7.84 (2.12-28.96)	6.28 (0.11-358.80)
	2		18 (12.50)	20.58 (4.85-87.32)	279.40 (2.50-31200.00)
	3+		10 (6.94)	25.35 (4.75-135.27)	799.10 (1.32-483800.00)
All unnatural	**0**	23 (16.79)	261 (52.41)	Reference	Reference
	1	58 (11.65)	140 (28.11)	6.21 (3.48-11.06)	10.08 (3.41-29.85)
	2	33 (6.63)	58 (11.65)	8.80 (4.53-17.08)	16.88 (4.30-66.23)
	3+	23 (16.79)	33 (6.63)	`11.68 (5.50-24.79)	45.37 (7.92-259.89)

7.4 Discussion

7.4.1 Main findings

In this study, I examined whether people with comorbid depression and T2DM had higher rates of mortality from different causes if they were prescribed antidepressants, compared to those who were not prescribed antidepressants.

When individuals with comorbid depression and T2DM received at least one prescription for any antidepressant after starting oral antidiabetic treatment, the rates of mortality from any cause were 2.77 times higher than those who were not prescribed any antidepressants. The rates of mortality were equally elevated in these individuals across all natural causes of death. Individuals with comorbid depression and T2DM who were prescribed antidepressants were 9.27 times more likely to die by unnatural causes of death compared to those who were not prescribed antidepressants. However, the confidence intervals were very wide (3.02-28.47) due to low numbers. Therefore, the exact estimated IRR for unnatural causes of death in individuals with comorbid depression and T2DM prescribed antidepressants compared to those not prescribed antidepressants may not be accurate.

I observed the highest difference in the rates mortality in individuals with comorbid depression and T2DM when they were recently prescribed an antidepressant (within 6 months of the outcome date) compared to those who were prescribed no antidepressant. In mortality caused by suicide, any unnatural cause (including suicide) and endocrine causes, there was no evidence of a difference in mortality rates between individuals with comorbid depression and T2DM who had been prescribed antidepressants more than 6 months in the past and those who had never been prescribed antidepressants. However, the number of deaths explicitly by suicide were extremely low, therefore these results do not represent reliable evidence and should be interpreted with caution.

Although individuals with comorbid depression and T2DM who were prescribed antidepressants had considerably higher mortality compared to those who were not prescribed antidepressants, this did not vary according to the cumulative duration of antidepressant treatment.

Individuals had increasingly higher rates of all-cause mortality if they had been prescribed greater numbers of different individual antidepressant agents, compared to those who were not prescribed any antidepressants. However, there was some overlap between confidence intervals, as these were wide for people prescribed greater numbers of individual antidepressant agents, due to small numbers of these individuals.

7.4.2 Comparison to existing literature and my previous findings in this thesis

There is only one other study that investigates whether individuals with comorbid depression and diabetes (type unspecified) have different rates of mortality according to whether or not they are prescribed antidepressants. A large population-based study in Taiwan by Chen et al found that individuals with comorbid depression and diabetes had lower mortality rates if they were prescribed antidepressants compared to those who were not prescribed antidepressants (219). This is opposite to the findings in my study. Chen et al did not adjust for comorbidities, while I adjusted for a wide range of comorbidities. However, this adjustment made little difference in my fully adjusted models, meaning that comorbidities do not fully explain this disparity. Chen et al included individuals with a new diagnosis of depression made by a psychiatrist after their diabetes diagnosis. On the other hand, I included individuals with depression from a primary care population where depression often does not receive a formal diagnosis, but may be based on the recording of symptoms. Therefore, individuals included by Chen et al are more likely to represent individuals with more severe depression but who are accessing specialist care. Whereas the individuals that I included in this study may represent a broader range of depression severity, and are unlikely to be accessing specialist care (74). Chen et al also did not included individuals with a history of depression prior to their diabetes diagnosis, whereas I did. Depression is often a chronic condition that may start in adolescence and persist throughout the life course (204,371). Depression that is new onset following a physical disease diagnosis, may have different characteristics caused by distress from the physical disease itself (411–413). For example, depression following diabetes onset may specifically be associated with difficulty in living with diabetes, disruption to daily life and poor sleep (139,414). Therefore, the depression characteristics of the individuals included by

Chen et al, may be different from ours; these individuals may have better access to specialist care and may respond better to antidepressant treatment.

There are no studies that investigate whether individuals with comorbid depression and T2DM have different rates of suicide depending on whether or not they are prescribed an antidepressant. In the general population, antidepressants have been shown in RCTs to reduce the risk of suicidal events in adults aged 25+, and considerably so in adults more similar in age to those in this study (in adults aged 65+, OR 0.06, 95% CI 0.01 to 0.58) (415). However, RCTs commonly exclude individuals who are considered to be at risk of suicide (222). Nevertheless, a systematic review of observational studies in the general population also reported reduced rates of suicide in individuals who were prescribed SSRIs (the most commonly prescribed antidepressant class) (416) compared to those who were not (417). This evidence is conflicting with my findings of increased rates of mortality from unnatural causes in individuals with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not (IRR 9.27, 95% CIs 3.02-28.47). However, the only study in this review that found a evidence of a reduction in completed suicide attempts in people prescribed SSRIs compared to those who were not prescribed SSRIs included only individuals who had recently been discharged from psychiatric inpatient wards and were already at increased risk of suicide (418). Thus, while RCTs include individuals with milder depression, and the one relevant observational study included individuals with more severe depression, both types of study accounted directly for depression severity, while I was unable to. Therefore, the difference in my findings may have been attributable to depression severity.

In addition, the timing of antidepressant treatment may also be relevant to an individual's risk of suicide. A large observational study using UK primary care data found that suicide rates in individuals in receipt of antidepressant prescriptions are highest in the first 28 days of treatment, and remained increased for 28 days following the discontinuation of treatment (419). This could be in line with my findings in individuals with comorbid depression and T2DM, where recent antidepressant prescribing was associated with increased risk of death from suicide, whereas past (more than 6 months previously) prescribing was not. However, as described above, the number of cases who died by suicide were very small in my study, therefore, this

does not represent reliable evidence and the findings should be interpreted with caution.

I am not aware of any studies investigating whether individuals who are prescribed an antidepressant are more likely to die of endocrine causes compared to those who are not prescribed an antidepressant. However, in an analysis of spontaneous reports listed in the WHO Adverse Drug Reaction Database, antidepressant treatment was found to increase the risk of hyperglycaemia by 52% (OR 1.52, 95% CI 1.20–1.93) and of hypoglycaemia by 84% (OR 1.84, 95% CI 1.40–2.42) (216). On the other hand, a 14-year long observational study found that individuals with comorbid depression and diabetes who were prescribed antidepressants were 64% less likely to experience hyperglycaemic crises (HR 0.44, 95% CI 0.35–0.55). Again, the timing of antidepressant treatment could be relevant to the risk of adverse effects – as the long-term study shows a protective association, whereas the short-term study shows a harmful association. This is in line with my findings in individuals with comorbid depression and T2DM, where recent antidepressant prescriptions increased the risk of endocrine mortality, whereas past (more than 6 months previously) antidepressant prescriptions did not.

I am not aware of any studies in any population that compare cause-specific mortality for different natural causes of death in individuals prescribed antidepressants compared to those not prescribed antidepressants. However, a Danish population-based study by Madsen et al found that individuals who were prescribed antidepressants to treat depression were no more likely to die from any natural cause if they had “treatment resistant depression”, compared to “treatment responsive depression” (420). There were no differences between the different natural causes of mortality. This is different to my findings in individuals with comorbid depression and T2DM, where there appeared to be a dose-response relationship between the number of different antidepressant agents prescribed (representing more complex to treat depression) and rates of mortality. This may be due to the fact that Madsen et al’s study included individuals in the general population who were younger (median age in Madsen et al’s study was 37, compared to 69 in my study). As such, the individuals included in Madsen et al’s study would generally be healthier than the individuals with comorbid depression and T2DM included in my study.

On the other hand Madsen et al found that individuals with “treatment resistant depression” were significantly more likely to die by suicide than those who had “treatment respondent depression”. This is in line with my findings, where the elevated rates of suicide in individuals with comorbid depression and T2DM were only present in those who were prescribed 2+ different antidepressant agents, compared to no antidepressants.

7.4.3 Potential explanations for these findings

Rates of mortality from all causes, and in all specific causes, were elevated in individuals with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not.

Mortality from suicide or any unnatural causes only had elevated rates in individuals with comorbid depression and T2DM who were recently (within six months of the outcome date) prescribed antidepressants compared to those who were not prescribed antidepressants at all during follow-up. This suggests an acute association, whereby individuals with comorbid depression and T2DM who are currently taking antidepressants are at increased risk of immediate death from suicide or any unnatural causes, compared to those who have not been prescribed an antidepressant since starting pharmacological treatment for diabetes. At the same time, it suggests that there is no long-term association between antidepressant prescribing and suicide or any unnatural-caused mortality.

Some common antidepressants may worsen suicidal ideation during the initial phases of treatment, as they are known to cause side effects of agitation and activation (421). Similarly, withdrawal symptoms from recently stopping antidepressants include agitation and suicidal ideation (333). The increased rates of suicide that I observed in individuals with comorbid depression and T2DM who were recently prescribed antidepressants, could have been from individuals who had recently started or stopped treatment. Both of these may be relevant to individuals with comorbid depression and T2DM who had recently been prescribed antidepressants.

Alternatively, current antidepressant treatment may simply indicate current depression or poor overall quality of life. While all individuals that I included during the study had a clinical code for depression at some point during the observed period, these codes could have been years before the date of death. Therefore, people who were not

prescribed antidepressants may not have been depressed at the exact same point in time as those who were prescribed antidepressants. The introduces bias due to confounding by the indication of depression. I discuss this in detail in my **Discussion Chapter 8**. The prescription of an antidepressant does not necessarily indicate successfully treated depression. An individual may not take the antidepressants prescribed, or, they may not respond to treatment. Indeed, elevated rates of suicide were only seen in individuals with comorbid depression and T2DM who were prescribed 2 or more antidepressants, suggesting more complex to treat depression.

Individuals with comorbid depression and T2DM who had recent prescriptions for antidepressants were also at higher risk of mortality from any unnatural cause compared to those who were not prescribed antidepressants, and compared to those who were only prescribed antidepressants more than 6 months previously. Within the most common of these (falls, accidental poisoning, road traffic accidents and unspecified accidents), the vast majority of individuals were prescribed antidepressants. There is evidence in the general population to suggest that falls, accidental poisoning and road traffic accidents could all in fact be misclassified suicide (422). On the other hand, falls (423), accidental poisoning (424,425), and road traffic accidents (426) may also all be caused by antidepressant side effects, or overdose. Therefore, it is plausible that the increased risk of mortality from unnatural causes observed in individuals with comorbid depression and T2MD who were recently prescribed antidepressants compared to those who were not, was in part directly attributable to the antidepressant medication.

Individuals with comorbid depression and T2DM who were recently (within 6 months of the outcome date) prescribed antidepressants also had elevated rates of mortality from endocrine causes. This suggests that current antidepressant use is associated with acute fatal endocrine events in individuals with comorbid depression and T2DM. These may include events related to hyperglycaemia, such as diabetic ketoacidosis (DKA) or hyperglycaemic hyperosmolar state (HHS), or severe hypoglycaemia. However, ICD-10 codes used to record causes of death in ONS data do not distinguish between these.

Hyperglycaemic crises can occur when an individual is unable to manage their blood glucose levels. The most common cause of this in Western countries is non-adherence to antidiabetic treatment (427). In T2DM, polypharmacy is associated with improved

adherence (391,393). However, the association between antidepressants and antidiabetic medication adherence is unknown. Depression, on the other hand, is known to increase the risk of non-adherence to antidiabetic medication (394,428). A study of 367 hospital admissions for DKA or HHS in the USA found that depression was a predictor of DKA or HHS readmissions (429). Also, depression is a risk factor for hypoglycaemia (430). While all participants had a depression-related code recorded during follow-up, this was not necessarily within 6 months of the outcome date (the death of the case). Therefore, recent antidepressant prescribing may simply be a marker of current depression. Although these individuals are receiving antidepressant treatment, as I described above, this does not necessarily represent the successful treatment of depression.

In **Chapter 6**, I described how antidepressant prescribing was associated with starting insulin in individuals with comorbid depression and T2DM. However, I found no difference in the rate of starting insulin in individuals in this patient group who were recently prescribed antidepressants, compared to those who were only prescribed antidepressants more than 6 months in the past. However, starting insulin would typically not be in response to an acute event, but is a long-term treatment strategy (83). I concluded in **Chapter 6**, that antidepressant prescribing was associated with a long-term decline in diabetic heath. I did not observe the same finding in this study, where antidepressant prescribing in individuals with comorbid depression and T2DM more than 6 months previously was not associated with an increased risk of endocrine mortality, compared to individuals who were not prescribed antidepressants. However, with a median follow-up time of 7.05 years, this may not have been long enough to see T2DM progress to the point of death. Furthermore, endocrine mortality is likely to be caused by an acute diabetic emergency. Whereas deaths caused by a longer-term decline in diabetic health, are more likely to be from complications such as cardiovascular disease.

In the long term, rates of mortality were similarly elevated across the three major causes of death – cardiovascular, cancer and respiratory – in individuals with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not. If antidepressant prescribing were associated specifically with a decline in diabetic health, I would have expected to see the most elevated rates of mortality in cardiovascular causes of mortality, as this is the leading cause of death for people with

T2DM. As this was not the case, antidepressant prescribing may be a marker for worse overall health generally, rather than specifically diabetic health. On the other hand, participants in this cohort are 16 years older, on average, than in the previous study described in **Chapter 6**. At a starting age of 69, these individuals may have competing risks of death, including from cancer and respiratory disease, which simply occur before T2DM has had a chance to directly cause death (431).

It is unlikely that the increased risk of mortality from these different causes (cardiovascular, respiratory or cancer) is directly caused by antidepressants for two main reasons. Firstly, the risk was equally increased across cardiovascular, cancer and respiratory causes, which are caused by different mechanisms – therefore, there is no theoretical explanation to support a direct effect of antidepressants. The exception to this is that all conditions are linked to smoking (432), however, I adjusted for smoking status in my analysis and this had very little effect. Secondly, there was no difference in the increased risk of mortality from these causes (cardiovascular, respiratory, cancer) according to the timing of the antidepressant prescribing or from increased levels of exposure to antidepressants from longer cumulative durations of treatment.

Antidepressant prescribing in individuals with comorbid depression and T2DM may indicate more severe depression. Indeed, NICE guidelines only recommend that antidepressants are prescribed for individuals with comorbid depression and T2DM who are moderately-to-severely depressed (81). I was unable to adjust directly for depression severity due to there being no routinely recorded variable for depression severity in the CPRD dataset. However, I did adjust for a large number of confounders that may be associated with depression severity – including history of antidepressant treatment, comorbidities, polypharmacy, gender, ethnicity, health behaviours (smoking and drinking) and contact with primary care services. Nevertheless, adjustment for these confounders did not have an impact on my findings. All confounders included in this study were measured at study entry while the median duration of follow-up was 7 years. Individuals who were prescribed antidepressants may have seen a decline in physical and mental health since study entry, due to factors that were not available from EHR data. This could include person-level socio-economic status, lifestyle, life events, social factors, cultural factors, or environmental

factors (41). I am not aware of previous studies that have included such confounders, or indeed other markers of physical or mental health beyond a baseline date.

In addition, the timing of antidepressant treatment, which, as discussed above, may indicate current depression, did not have an impact on my findings. Neither did the cumulative duration of antidepressant treatment, which may indicate more severe, chronic depression. On the other hand, there did seem to be a positive association between the number of different antidepressant agents prescribed, and the rate of mortality across all-causes and all specific-causes of mortality in individuals with comorbid depression and T2DM. Individuals with more complex to treat depression are more likely to be prescribed multiple antidepressant agents, compared to individuals with successfully treated depression. Therefore, the higher rates of mortality seen in individuals with comorbid depression and T2DM, may be attributable to the fact that depression is not being successfully treated in these individuals.

Finally, due to my study design, unless the onset of cancer, respiratory disease or cardiovascular disease occurred prior to the study entry date (when comorbidities were measured), it was not possible to see whether this occurred before or after antidepressant prescribing. Therefore, my findings may have been due to reverse causation, whereby the distress from each of these physical conditions may have caused episodes of depression requiring antidepressant treatment.

7.4.4 Strengths and limitations

This is the first study to investigate differences in cause-specific mortality rates in people with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not prescribed antidepressants. It is also the first study in any population to compare different mortality causes in people who were prescribed antidepressants compared to those who were not.

With a sample size of 23,897, this study is over 70 times larger than all studies combined in the 2012 Cochrane meta-analysis of antidepressant treatment outcomes in people with comorbid depression and T2DM. All RCTs included in the Cochrane review excluded individuals with severe depression, and the majority excluded individuals with comorbidities common in T2DM, or prescribed medications common in T2DM. In this study, I included people with comorbid depression and T2DM, who had started oral antidiabetic medication for the first time, regardless of depression

severity, comorbidities or concurrent medication use. However, as this was a case control study where cases were people who died and controls were matched to these based on age, the median age of people included in this study was elevated. For example, in the study reported in **Chapter 6**, where the outcome was insulin initiation, the median age was 16 years younger. Differences between individuals in this study and the younger individuals included in **Chapter 6** can be seen in the higher rates of comorbidities for individuals in this study that would naturally occur with age. In addition, as I classified deaths by cause, I required linkage to ONS mortality data. This is only available for individuals registered at participating CPRD practices in England. Otherwise, these practices are representative of all GP practices in England with regards to age, gender and ethnicity (242,243). As such, this study provides a representative view of mortality outcomes in adults in England aged 60+ with comorbid depression and T2DM who are starting oral antidiabetic medication for the first time and in the approximately 4-10 years following. The findings of this study may not be generalisable to younger populations with comorbid depression and T2DM.

Mortality is a definitive outcome for both physical and mental health. As it is mandatory by law to record death in the UK, this ensures full confidence in the reliability of mortality as an outcome variable. However, it is still possible that the cause of death may be misclassified. It is unlikely that a death recorded as suicide would be a misclassification. However, accidental poisoning or unspecified accidents may in fact be misclassified suicides (433). This does not impact my interpretation of the findings related to suicide. However, conclusions should not be drawn about any direct effect from antidepressant treatment on mortality from accidental medication poisoning, and I did not perform statistical analysis on unnatural causes of death at this granular a level.

The coding of endocrine causes of mortality are also vague. These codes most commonly state that the individuals died of diabetes with or without complications (434). Therefore, there is scope for these codes to mean different things. However, deaths directly caused by diabetes, such as from DKA, HHS or severe hypoglycaemia, are acute. Therefore, I assumed that mortality from endocrine causes represented acute diabetic crises.

All prescriptions issued in primary care are done so electronically, and so, are automatically recorded in a patients EHR. Therefore, I have high confidence in the

completeness and accuracy of my antidepressant prescribing exposure. However, the indication of the antidepressant prescribed may be ambiguous, particularly in individuals with comorbid depression and T2DM. The CPRD does not record prescription indications. The indication for a prescription may be worked out if a patient also has a clinical code for a relevant disease from the same consultation. However, as I demonstrated in my **Methods Chapter 3**, 38% of individuals with comorbid depression and T2DM do not have a clinical code relevant to the first antidepressant they are prescribed within 6 months either side of the prescription. Therefore, I could not be certain that any antidepressant was prescribed to treat depression. This is particularly relevant for amitriptyline, nortriptyline and duloxetine, which are also indicated in the UK to treat diabetic neuropathic pain. For amitriptyline and nortriptyline, I included only prescriptions that were issued at a dosage ≥ 50mg, which is indicated for depression, while neuropathic pain dosages are typically lower (173,332). However, this is not always the case. I could also not do this for duloxetine, which uses the same therapeutic doses for both depression and neuropathic pain. Similarly some TCAs or trazodone, for example, may be used to treat sleeplessness. However, I included in the study only individuals who had a diagnosis, symptom or process of care code for depression recorded during the follow-up period for which antidepressant treatment was measured. Therefore, all participants had depression as an indication for potential antidepressant prescribing during this time.

7.4.4.1 Study design issues

RCTs are the gold standard method for evaluating causal effects of an intervention, such as antidepressant treatment, on an outcome. This is due to the fact that randomisation of participants to an intervention or control group is an effective tool for minimizing bias, by balancing both measured and unmeasured confounders between groups. In real-world data, patients are not randomised to either an intervention or control group, but receive an intervention based on an indication of requiring treatment (e.g. depression at a level of severity requiring treatment), clinician prescribing habits, or local pressures in access to treatment (e.g. local waiting times for talking therapies). These factors may introduce bias, if they also offer alternative explanations for increased rates of mortality. I initially attempted to balance confounders by matching individuals based on gender, age and GP practice. Including GP practice level matching allowed me to account for practice level differences in health care delivery

and socioeconomic status. I then further attempted to balance confounders by adjusting for a large number of confounders that were associated with both antidepressant prescribing and mortality. These included comorbidities, polypharmacy, history of antidepressant prescribing, primary care contacts, smoking, drinking, drug use, BMI, and T2DM duration. However, while I was able to adjust for a large number of confounders that may be associated with depression severity, I could not adjust for depression severity itself. There is no routinely recorded variable for depression severity in the CPRD dataset. Neither are there recorded specific symptoms and characteristics of depression that may be associated with both antidepressant prescribing and mortality. Therefore, my findings may have been confounded by the indication of depression severity or subtype. I was also only able to adjust for confounders at study entry which may be subject to change over the median 7 year observation period, during which time both physical and mental health is subject to change. Furthermore, the higher rates of mortality that I observed may also be due to unmeasured confounding from a wide range of potential socio-economic, lifestyle, life event and environmental factors are not recorded in data sources such as EHRs. However, due to my case-control study design, I was able to examine different patterns of antidepressant exposure. This allowed me to strengthen my causal understanding of the association between antidepressant prescribing and different causes of mortality in individuals with comorbid depression and T2DM.

7.4.5 Conclusions and implications

Individuals with comorbid depression and T2DM have considerably higher rates of mortality if they are prescribed any antidepressant, for any duration, at any time after starting oral antidiabetic treatment. Thus, antidepressant prescribing is a marker for high risk of mortality in individuals with comorbid depression and T2DM. The elevated risk of mortality in individuals with comorbid depression and T2DM who are prescribed antidepressants is not specific to causes related to T2DM. Therefore, antidepressant prescribing in these individuals is likely to be a marker for worse physical health outcomes generally. Individuals with comorbid depression and T2DM who were recently prescribed antidepressants also had a considerably higher risk of suicide, death from unnatural causes (including falls, accidental poisoning and road traffic accidents), and fatal diabetic crises. Although these individuals are being treated with antidepressant medication, this does not appear to sufficiently improve depression

symptoms such that the negative effects of depression on physical health are negated. Alternatively, these individuals may have wider determinant of health characteristics that are causing worse physical health outcomes.

Individuals with comorbid depression and T2DM who are being treated with antidepressants should be closely monitored and offered enhanced holistic care to improve their physical and mental health. In my **Discussion Chapter 8**, I make recommendations for policy and practice improvements that could benefit these individuals. I also make recommendations for further research.

Chapter 8: Discussion

In this chapter, I will begin by recapping on the relevance and importance of the studies included in this thesis, as discussed in my **Introduction Chapter 1**. I will then summarise in brief the key findings of each study in relation to my overarching thesis aims. Following this I will describe the strengths and limitations of my data source and methods used. Finally, I will discuss in detail the clinical, policy and research implications of my findings and how I am disseminating these.

8.1 Relevance and importance of the studies included in this thesis

Depression and T2DM are serious and common long-term conditions which are leading contributors the global burden of disease (1). There is a bidirectional relationship between the two conditions where each condition increases the risk of (334) and potentially worsens (139,140,220,221) the other. Therefore, the successful treatment of both conditions is important to the management of the other.

Antidepressants are recommended as a treatment option for individuals with depression and physical long-term conditions (81). Existing evidence from RCTs report that antidepressants were effective in the short-term (3 weeks to 6 months) for improving depression symptoms and glycaemic control in individuals with comorbid depression and T2DM (155). However, these short-term studies included only a small number of individuals who were not representative of this patient group. There is a lack of evidence concerning the long-term outcomes of antidepressant treatment in individuals with T2DM, and concerning the use of antidepressants alongside other medications commonly prescribed to people with T2DM. The treatment burden of T2DM is already high. Individuals with T2DM are required to manage their diet, physical activity, monitoring of blood glucose levels, antidiabetic medication, other metabolic syndrome comorbidities, and the prevention or treatment of a range of serious diabetic complications (83). The concurrent use of multiple medications (polypharmacy) is, therefore, a common situation in people with T2DM. However, there are risks associated with polypharmacy. These include increased risk of drug side effects (184), drug-drug or drug-disease interactions (178–180,184,202), poor quality of life from higher treatment burden (184,194–196), and reduced adherence to treatment (186,192,193,203). The addition of one or more antidepressant

medications, with their associated side effects, may add to these risks. There are also potential risks directly associated with antidepressant treatment that may be relevant to the long-term health of people with T2DM, such as weight gain (153), hypoglycaemia, cardiac complications, gastrointestinal disturbances, and visual impairment (154). As such, the treatment of depression with antidepressant medication in individuals with comorbid depression and T2DM may be more complex than in otherwise healthy individuals. This can make it challenging for clinicians to make prescribing decisions.

Routinely collected EHR data enables the investigation of prescribing patterns and outcomes as they occur in the real world. They enable the investigation of real-world populations, including individuals across the entire spectrum of disease severity, with any range of comorbidities and concurrent medication use. I chose to focus my thesis on exploring outcomes of real-world antidepressant prescribing and polypharmacy in people with comorbid depression and T2DM. I did this by reviewing literature from observational studies and with original research studies using routinely collected EHR data from the UK CPRD.

My thesis included two overarching aims:

Aim 1: In people with comorbid depression and T2DM, to explore differences in antidepressant prescribing trajectories according to concurrent medication prescribing. I defined antidepressant prescribing trajectories as being prescribed an antidepressant, stopping or switching antidepressants (as markers of antidepressant acceptability) and restarting antidepressants (as a marker of depression relapse).

Aim 2: In people with comorbid depression and T2DM, to explore the association between antidepressant treatment and long-term physical health outcomes, specifically starting insulin (as a marker of the long-term decline in diabetic health) and mortality.

8.2 Key findings of my thesis

8.2.1 Summary of the key findings from my first aim: in people with comorbid depression and T2DM, to explore differences in antidepressant prescribing trajectories according to concurrent medication prescribing

In my first systematic review, I synthesised existing observational studies reporting the prevalence of antidepressant prescribing in people with comorbid depression and T2DM. I found considerable variation in the rates of antidepressant prescribing, from 18-87%. Three studies reported rates of insulin prescribing – when combined in meta-analysis there was no difference in the rate of antidepressant prescribing, according to whether or not someone was being treated with insulin. I found no studies reporting any other concurrent medication prescribing. I found no studies suitable for inclusion that were based in the UK. Thus, there was still an evidence gap regarding the prevalence of antidepressant prescribing in people with comorbid depression and T2DM in the UK, and the effect of concurrent medication prescribing on the likelihood of being prescribed an antidepressant.

My first EHR study looked at what happens to people with comorbid depression and T2DM after they start antidepressant treatment for the first time. The majority of people stopped the first antidepressant prescribed before the recommended duration of treatment (7 months), with 44.26% stopping antidepressant treatment completely. I had hypothesised that the burden from polypharmacy would negatively impact antidepressant acceptability in people with comorbid depression and T2DM; and that this would result in people who were prescribed more concurrent medications being more likely to stop antidepressants before the recommended duration. However, I found the opposite to what I had hypothesised. The more concurrent medications prescribed to an individual with comorbid depression and T2DM, the *less* likely they were to stop antidepressants before the recommended treatment duration. Although, the number of concurrent medications had no effect on the likelihood of switching antidepressant agents.

The reasons for starting and stopping medications are not included in CPRD data. An individual may switch antidepressant agents if they did not respond to or could not tolerate the first antidepressant tried, but still wish to continue treatment. On the other hand, stopping antidepressants completely (my primary outcome for this study – described above) represents an unwillingness to continue pharmacological treatment (or a lack of need to). Thus, I suggested that individuals with comorbid depression and T2DM who are prescribed more concurrent medications, may be more exposed to antidepressant medication, potentially as they may be more willing (or have an increased need) to adhere to the recommended duration antidepressant treatment.

However, as it was only possible to see prescriptions issued rather than taken, this can only be speculative.

My second EHR study looked at what happens to people with comorbid depression and T2DM who are prescribed multiple concurrent medications, after they stop antidepressant treatment. Within one year of stopping antidepressant treatment, 35.29% of individuals with comorbid depression and T2DM subsequently restarted. I considered restarting antidepressant treatment within one year to be a marker of clinically identified depression relapse. I had hypothesised that the more concurrent medications prescribed to an individual with comorbid depression and T2DM, the more likely they would be to restart antidepressant treatment. This was based on evidence that polypharmacy is associated with more severe depression (197). My findings were in line with what I had hypothesised. However, I found no evidence that longer durations of antidepressant treatment attenuated the risk of depression relapse.

People who take more concurrent medications, by implication, are likely to represent those who have worse overall health. Both polypharmacy (197) and worse overall health (325) have been shown in meta-analytical research to be associated with more severe depression. As such, it is possible that the individuals in my studies with comorbid depression and T2DM who were taking more concurrent medications represented individuals who were more severely depressed. Consequently, the patient or clinician may have been less likely to stop antidepressant treatment than in individuals with less severe depression. If this hypothesis is true, individuals who were taking fewer medications may have been less severely depressed, felt better sooner and therefore stopped taking antidepressants earlier. Similarly, when antidepressant treatment was stopped, if people taking more concurrent medications were more severely depressed, they may also have been more likely to experience depression relapse.

Alternatively, people who are prescribed more medications may reflect individuals who are more accepting of pharmacological treatment generally. Indeed, people with T2DM have been shown to be more adherent to somatic medications, the more medications they were prescribed (390–393). Therefore, people with comorbid depression and T2DM who are prescribed more concurrent medications may be more likely to adhere to antidepressant treatment. These individuals may also be more likely to restart antidepressant treatment when they experience depression relapse, compared to

people who are prescribed fewer concurrent medications (and are less accepting of pharmaceutical treatment).

8.2.2 Summary of the key findings from my second aim: investigating the association between antidepressant treatment and long-term physical health outcomes in individuals with comorbid depression and T2DM

In my second systematic review, I searched the literature for studies investigating long-term outcomes of antidepressant treatment in people with comorbid depression and T2DM. I found no studies suitable for inclusion. Therefore, the two EHR studies that I did looking at long-term outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM were the first of their kind.

My first EHR study within this aim looked at rates of starting insulin treatment in people with comorbid depression and T2DM after starting oral antidiabetic medication. I considered starting insulin to be a marker of the long-term decline in glycaemic control and the failure of oral antidiabetic medication. I had hypothesised that treating depression with antidepressant medication would reduce the risk of starting insulin in this patient group. This was based on the theory that depression treatment would have a positive impact on an individual's diabetic health and self-care, by improving their mental health. On the contrary, I found that individuals with comorbid depression and T2DM who were prescribed antidepressants after starting oral antidiabetic treatment were considerably more likely to subsequently start insulin than those who were not prescribed any antidepressant.

I explored different patterns of antidepressant prescribing to elucidate potential routes to starting insulin. If antidepressants were directly causing hyperglycaemia leading to a necessity for insulin, I would have expected to have observed different levels of risk between different antidepressant agents with different mechanisms of action. I found no evidence of this. I also would have expected to observe further increased rates of starting insulin in individuals who were recently prescribed antidepressants (within the last 6 months) compared to those with past (more than 6 months previously) antidepressant prescriptions only. I found no evidence of this either.

Antidepressant treatment is only recommended in individuals with physical comorbidity if they have moderate-to-severe depression (81). Therefore, I suggested that people who prescribed antidepressants may be more severely depressed than

those who were not prescribed antidepressants. In addition, I observed the highest rates of starting insulin in people who had antidepressant prescribing patterns representative of more chronic and “complex-to-treat” depression. Depression is known to be associated with worse diabetic outcomes in people with T2DM (220,221,435). Therefore, the higher rates of starting insulin in these individuals may be attributable to more severe, chronic and complex-to-treat depression, which can contribute to the deterioration of diabetic health.

My second EHR study within this aim looked at rates of all-cause and cause-specific mortality in people with comorbid depression and T2DM after starting oral antidiabetic medication. I had hypothesised that treating depression with antidepressant medication would reduce the risk of mortality by any cause in individuals with comorbid depression and T2DM. This was based on the theory that depression treatment would have a positive impact on an individual’s physical health and self-care, by improving their mental health. On the contrary, I found higher rates of mortality in people with comorbid depression and T2DM who received any prescription for antidepressants after starting oral antidiabetic treatment, compared to those who were not prescribed antidepressants.

I observed the highest rates of mortality in unnatural causes of death (including suicide). However, mortality rates were only elevated for unnatural causes of death when individuals were recently (in the previous 6 months) prescribed antidepressants. The prescription of an antidepressant does not necessarily indicate successfully treated depression. An individual may not take the antidepressants prescribed or they may not respond to treatment. Thus, the increased rates of unnatural deaths that I observed in people recently prescribed antidepressants may be attributable to current depression. Furthermore, I only observed elevated rates of suicide in individuals who were prescribed 2 or more different individual antidepressant agents, which may represent a failure to respond to antidepressant treatment. Alternatively, it is possible that the increased rates of mortality by unnatural causes were attributable to the antidepressants themselves. Some common antidepressants may worsen suicidal ideation and agitation during the initial phases of treatment and during immediate withdrawal from treatment (333,421). In addition, the other most common unnatural causes of death that I observed (falls (423), accidental poisoning (424,425) and road traffic accidents (426) may be related to the side-effects or overdose of

antidepressants. However, given that all my other findings suggest that the association between antidepressant prescribing and worse physical health outcomes is confounded by the indication of depression, this may be the more likely explanation.

For mortality directly caused by diabetes, people with comorbid depression and T2DM again only had higher rates of mortality when they were recently (in the previous 6 months) prescribed antidepressants compared to those who were not prescribed antidepressants. Deaths directly from diabetes are related to hyperglycaemia or hypoglycaemia (436,437). Depression is a known risk factor for both of these (258,429,430). In addition, depression is known to increase the risk of non-adherence to antidiabetic treatment (394,428), which is the most common cause of hyperglycaemic crisis in Western countries (427). There is no evidence that I am aware of to suggest that antidepressants directly cause diabetic deaths or any proposed mechanisms through which this would be possible.

In the long term, rates of mortality in people with comorbid depression and T2DM who were prescribed antidepressants were similarly elevated across the three major causes of death – cardiovascular, cancer and respiratory – compared to people who were not prescribed antidepressants. This suggests that antidepressant prescribing at any time is a marker for worse overall health generally. It is unlikely that the increased risk of mortality from these different causes (cardiovascular, respiratory or cancer) is directly caused by antidepressants for two main reasons. Firstly, the risk was equally increased across cardiovascular, cancer and respiratory causes, which are caused by different mechanisms. Therefore, there is no theoretical explanation to support a direct effect of antidepressants. Secondly, there was no difference in the increased risk of mortality from these causes (cardiovascular, respiratory, cancer) according to the timing of the antidepressant prescribing or from increased levels of exposure to antidepressants from longer cumulative durations of treatment. Instead, the higher rates of mortality that I observed in the long-term (from cancer, cardiovascular or respiratory causes) may, again, be attributable to people with comorbid depression and T2DM being more severely depressed when they are prescribed antidepressants, compared to those who were not prescribed antidepressants. As I explained above, more severe depression may lead to worse physical health outcomes. Additionally, the more different antidepressant agents prescribed the higher the rates of

cardiovascular, respiratory and cancer caused mortality. Again, this may represent unsuccessfully treated depression, which may lead to worse overall health

In summary, people with comorbid depression and T2DM were considerably more likely to start insulin and had considerably higher rates of mortality if they were prescribed antidepressants, compared to those who were not prescribed antidepressants. This may be attributable to current depression (in the case of unnatural causes of mortality or mortality caused by diabetic crises), more severe or chronic depression, and/or unsuccessfully treated depression.

8.3 Strengths and limitations of the studies included this thesis

The studies in this thesis are the first to explore the long-term outcomes of antidepressant treatment and polypharmacy in individuals with comorbid depression and T2DM. I have discussed study specific strengths and limitations in each chapter. In this section, I discuss the more fundamental strengths and limitations of the studies included in this thesis.

8.3.1 Sensitivity and specificity of reviewing existing literature

The two systematic reviews included in this thesis were the first to investigate antidepressant prescribing patterns and outcomes as they occur in the real-world. However, very few studies (none from the UK) were found that were suitable for inclusion in my first review (looking at the prevalence of antidepressant prescribing) and no studies were found that were suitable for inclusion in my second review (looking at the long-term outcomes of antidepressant prescribing).

The breadth of my search was wide: The search terms that I used were broad. I did not include terms for concurrent medication exposures or long-term outcomes. I included a wide range of terms to represent depression, T2DM and antidepressants. I also searched seven databases to provide a wide range of coverage. This resulted in a large number (14,389) of references being screened.

However, my inclusion/exclusion criteria were strict. This resulted in the exclusion of the vast majority of studies identified in the search. For both reviews, I required precise case definitions T2DM and depression. If I had not done this, studies would have been included that were not specific to my patient group of interest. For my second review investigating the long-term outcomes associated with antidepressant prescribing, I

required a minimum of 7 months antidepressant treatment duration, based on NICE treatment guidelines for antidepressants to be effective (82). I deemed this criteria to be essential, as my outcomes of interest were long-term, rather than focusing on initial response to treatment. However, no studies were excluded on this basis alone.

Thus, my reviews highlighted a considerable evidence gap which the observational studies in my thesis have begun to address. In addition, my reviews highlighted methodological issues with existing studies (such as lack of case definition or short follow-up times) that the observational studies in my thesis aimed to overcome.

While I excluded a number of studies that did not meet my inclusion criteria but may have been relevant. I included these studies in the *Comparison to existing literature* sections of each chapter, where relevant.

8.3.2 Use of electronic health records (EHRs)

The introduction of EHRs has made it easier to access large-scale, longitudinal clinical data for research. The use of EHR data provides insight to real-world clinical populations, practice and outcomes. In addition, EHR studies do not require expensive and time consuming participant recruitment and data collection. The data source that I used for each of the observational studies in my thesis was the CPRD – a UK-based database of electronic primary care records. Most depression (74) and T2DM (244) in the UK is treated in primary care, which includes the issuing of medication prescriptions. This made the CPRD an ideal data source for conducting representative and generalisable research exploring outcomes of antidepressant treatment and polypharmacy in individuals with comorbid depression and T2DM. At the time of data extraction, the CPRD contained health records for 60 million individuals. This meant that my largest study included 73,808 people, and even my smallest study included 23,897 people. These large sample sizes allowed me to investigate granular patterns of antidepressant and polypharmacy prescribing exposures (I explain the benefits of this below in **Section 8.3.6**), and rare outcomes such as cause-specific mortality (I explain the benefits of this in **Section 8.3.5**). The average follow-up time for people included in the CPRD dataset is 5-6 years (335,337). This was enough time for the long-term outcomes of starting insulin and mortality to occur. In my final study investigating the association between antidepressant prescribing and mortality, the median age at study entry was 69 years and the median follow-up time was 7.25 years.

People with T2DM are expected have a reduced life expectancy of up to 10 years compared to the UK average (83-85 years) (438). Therefore, 7.25 years covers the peak risk time for mortality in this group.

However, EHR systems are not designed for research but for clinical practice (439,440). The lack of randomisation results in confounding and missing data results in selection and measurement bias (439). The majority of my findings in the EHR studies I performed were unexpected. I had hypothesised that the risks associated with polypharmacy (increased drug interactions, increased side-effects, increased treatment burden, reduced adherence) would negatively affect antidepressant acceptability. However, I found the opposite – the more concurrent medications people were prescribed, the more likely they were to continue and restart antidepressant treatment. I had also hypothesised that antidepressant treatment would improve physical health outcomes through better self-care and health behaviours by improving their mental health. However, I found the opposite – antidepressant prescribing was associated with considerably worse physical health outcomes. In the following **Sections 8.3.3-9** I discuss the validity of my findings in relation to the methods and data source that I used.

8.3.3 Diagnostic validity of depression

The individuals included in this thesis are a primary care population with clinically identified depression.

It is estimated that 19.3% of people in England with T2DM have undiagnosed depression (441). Despite contact with primary care services, people may not always report depression symptoms to their primary care clinicians (442–444). As all the observational studies that I did as part of this thesis were based in primary care data, I will have missed individuals with comorbid depression and T2DM who did not report their depression in primary care. However, antidepressants are only prescribed to treat depression when it is clinically identified. As the purpose of my thesis was to explore patterns and outcomes of antidepressant prescribing, the inclusion only of people with clinically identified depression is appropriate. While it is important to understand the impact of undiagnosed depression in people with T2DM, it is outside the scope of this thesis.

To identify people in the CPRD dataset with depression, I used a list of clinical codes that included depression diagnoses, symptoms and processes of care. Primary care practitioners may avoid using diagnostic codes for depression, potentially due to the stigma associated with diagnosis (350), or following the introduction of performance indicators based on the number of individuals receiving diagnostic codes (351). Hence my inclusion also of symptoms and processes of care to identify people with depression. Indeed, only 65.14% of individuals starting antidepressant treatment ever had a diagnosis code for depression, and 4.35% of individuals starting antidepressant treatment for the first time only ever had process of care codes related to depression.

A number of UK-based EHR studies used antidepressant prescriptions to identify depression in addition to or instead of clinical codes (445). This would not have been appropriate for the two case-control studies in my thesis, where antidepressant prescribing was the exposure of interest. It has also been shown that only 1.1% of people in UK primary care EHRs have antidepressant prescriptions without any clinical code related to depression (446). Furthermore, a number of antidepressants are prescribed to treat non-depression conditions, such as diabetic neuropathic pain (particularly relevant to the individuals included in my study) (80,173), sleep disorders (79,173) or anxiety (154,409). Whereas, the use of clinical codes to identify depression has been shown to have a high validated specificity of 89.14% (446).

8.3.3.1 Identifying newly treated depression

The first two observational studies of my thesis were cohort studies that followed the prescribing trajectories of people with comorbid depression and T2DM who were newly treated for depression. As such, I aimed to include individuals who had started antidepressant treatment for the first time during their EHR follow-up. I did this by including only those whose first antidepressant prescription was with a single antidepressant agent that is commonly prescribed as a first-line option for people with depression in the UK. I also excluded individuals without 6 months of antidepressant-free data before their first antidepressant prescription, to ensure I captured incident prescribing. This is not a perfect assessment of newly treated depression, as individuals may have been treated elsewhere, without their prescriptions record being transferred. However, it is the best estimate of newly treated depression possible in CPRD data.

8.3.4 Diagnostic validity T2DM

To identify individuals with T2DM, I created an algorithm that used clinical codes, antidiabetic medication and confirmatory diagnostic testing to optimise my case definition specificity and sensitivity.

Studies on the validation of T2DM clinical codes in UK primary care data have shown that the use of clinical coding alone has limited sensitivity and specificity (352,353). These studies found that not all patients with T2DM were detectable using clinical coding (estimated 24% would be missed) and that there was significant misclassification and cross-over in coding between the different types of diabetes mellitus (estimated 27% of people with a code for T2DM also had a code for T1DM).

A number of recent studies involving individuals with T2DM and using CPRD data (100-103) identified people with T2DM based on antidiabetic prescriptions. These studies excluded individuals who were prescribed insulin less than six months after the date of starting oral antidiabetic medication, as potential T1DM cases. They also excluded people who had records of non-diabetes conditions for which oral antidiabetics such as metformin could be prescribed. However, I considered this approach to be too exclusive. It would exclude people with early stage T2DM who were not yet prescribed antidiabetic medication and controlled their diabetes through lifestyle management. On the other hand, it may include people being prescribed metformin for the prevention of T2DM or for non-diabetic conditions such as polycystic ovary syndrome which may be under-recorded (93).

I identified people with potential T2DM as having either a clinical code for T2DM or oral antidiabetic medication. I then confirmed that these individuals had some type of diabetes, by only including individuals who had two or more blood/serum glucose/HbA1c results above the diagnostic threshold for T2DM. The requirement for two or more tests is in line with T2DM diagnostic criteria (328). To rule out T1DM, I excluded any individuals who had insulin prescriptions without at 6 least months of oral antidiabetic prescriptions dated before the first insulin prescription. To rule out individuals who only had gestational diabetes, I excluded individuals who only had codes or medications related to T2DM during recorded periods of pregnancy. This is the most thorough identification of T2DM in EHR data that I am aware of.

My requirement of confirmatory diagnostic testing excluded 8.52% of individuals that were previously being considered for inclusion. This may have excluded people with T2DM whose diagnostic tests were performed prior to the existence of their EHR. However, I chose to take this approach rather than include people who may not have diabetes.

8.3.5 Validity of outcomes used in this thesis

I explained in my **Methods Chapter 3.4** that some aspects of both physical and mental health may not be well recorded in a patient's primary care EHR, which is designed for clinical management, rather than research. For this reason, I used prescriptions-based proxy measures to estimate the outcomes for my first three EHR studies:

i) Stopping antidepressant treatment before the recommended duration as a marker of antidepressant acceptability;
ii) Restarting antidepressant treatment within one year as a marker of clinically identified depression relapse;
iii) Starting insulin as a marker of the long term decline of glycaemic control.

Prescriptions data in EHRs are ideal proxies of the outcomes of interest as they are highly accurate and complete. Prescriptions are issued electronically and automatically recorded on a patient's record. Therefore, the EHR matches exactly the prescriptions issued. I go into detail on the specific validity of each outcome in the relevant **Chapters 4-6**. The general limitation of the proxy measures used is that they were not systematic assessments of the outcomes of interest. Therefore, the interpretation of any findings could only be speculative. For example, in my first cohort study, the more concurrent medications that were prescribed, the more likely people with comorbid depression and T2DM were to continue to be prescribed antidepressant treatment. However, it was not clear whether this was due to improved antidepressant acceptability (the outcome of interest) or a greater need for antidepressant treatment due to more severe depression (if indeed they were still taking the antidepressants that were prescribed). I attempted to distinguish between these potential explanations in two ways. Firstly, I performed a secondary analysis where the outcome of interest was switching antidepressant agents instead of stopping antidepressant treatment completely. Secondly, I performed a subgroup analysis comparing people who were prescribed different antidepressant drug classes with different side-effect profiles. If

my findings were attributable to the acceptability of the antidepressant agent itself, I would have expected to see differences in the rates of switching antidepressant agents and between people who were prescribed different antidepressant drug classes. However, I observed neither of these.

In my second cohort study, the more concurrent medications that were prescribed, the more likely people with comorbid depression and T2DM were to restart antidepressant treatment. It was not clear whether this was due to depression relapse (the outcome of interest) or simply an increased willingness to restart antidepressant treatment.

Regardless of the mechanisms behind the findings in my first two observational studies, understanding antidepressant prescribing trajectories in people with comorbid depression and T2DM is important information in itself. This has not been examined by any previous research, as far as I am aware. In these two studies, I found that antidepressant prescribing in people with comorbid depression and T2DM is suboptimal in terms of adherence and relapse prevention. However, while evidence from the general population suggests that polypharmacy may lead to suboptimal prescribing, my findings showed that this was not the case for antidepressant prescribing in people with comorbid depression and T2DM.

In my first case-control study, people with comorbid depression and T2DM who were prescribed antidepressants were considerably more likely to start insulin than those who were not prescribed antidepressants. Again, it was not possible to know for sure whether the individuals truly had worse long-term glycaemic control (the outcome of interest) or were simply more willing to start insulin. It is estimated that one in four people with T2DM are not willing to take insulin (407). However, I confirmed the association between antidepressant prescribing and worse physical health outcomes, with a second case-control study showing that people with comorbid depression and T2DM who were prescribed antidepressants had higher rates of mortality than those who were not prescribed antidepressants. I derived the outcome of mortality using linked data from ONS death registrations. As it is mandatory by law to record death in the UK, this ensures full confidence in the reliability of mortality as an outcome variable.

8.3.6 Defining prescribing exposures

All prescriptions issued in primary care are done so electronically, and so, are automatically recorded in a patients EHR. Therefore, I have high confidence in the completeness and accuracy of all prescribing exposures and outcomes.

8.3.6.1 Polypharmacy exposure (number of concurrent medications prescribed)

In my first two observational studies (**Chapters 4-5**), I aimed to compare antidepressant prescribing patterns (stopping and restarting) in individuals with comorbid depression and T2DM, according to the number of concurrent medications prescribed at an index date.

I counted the number of different individual medication classes prescribed within 90 days of the relevant index date. However, a single prescription for any medication does not necessarily mean that the individual is taking that medication. I accounted for this by performing sensitivity analysis whereby I only included repeat prescriptions. The findings of this analysis were consistent with the main analysis in both studies.

In the first of these studies (investigating stopping antidepressants) the outcome was measured up to 7 months after the number of concurrent medications were counted. In the second of these studies (investigating restarting antidepressants) the outcome was measured up to 12 months after the number of concurrent medications were counted. The number of concurrent medications could have been subject to change during this time. Therefore, the findings of these studies should be interpreted as the likelihood of stopping and restarting antidepressant treatment, given the number of concurrent medications prescribed at the time of starting and stopping antidepressant treatment respectively.

8.3.6.1 Antidepressant exposure

In **Chapters 6-7** I compared long-term physical health outcomes in people who were or were not prescribed antidepressants. I explained in detail in these chapters that the indication of the antidepressant prescribed may be ambiguous, particularly in individuals with comorbid depression and T2DM who may be prescribed certain antidepressants to treat diabetic neuropathic pain (80,173). Therefore, I could not be certain that any antidepressant was prescribed to treat depression. However, I included in the study only individuals who had a diagnosis, symptom or process of care code for depression recorded during the observed period for which

antidepressant treatment was measured. Therefore, all participants had depression as an indication for potential antidepressant prescribing during this time.

A key strength of the studies included in **Chapters 6-7** is the number of analyses performed (described below) looking at different patterns of exposure to antidepressant treatment. These allowed me to examine the validity of antidepressant prescribing as an exposure in EHR data. They also allowed me to suggest potential explanations for my unexpected findings.

I included any (one or more) antidepressant prescription during the observed period as my primary exposure in these studies. However, a single prescription for any medication does not necessarily mean that the individual is taking that medication. I accounted for this in secondary analyses, where I investigated exposure to different cumulative durations of antidepressant prescribing. People who were prescribed antidepressants even for very short cumulative durations still had considerably worse physical health outcomes. This suggests that these outcomes were not caused by exposure to the antidepressant itself, but rather that antidepressant exposure was a marker for other risk factors that may cause worse health.

Being prescribed an antidepressant, also does not necessarily indicate that depression is being successfully treated, which is what I based my hypotheses (that successfully treating depression would improve physical health) on. I accounted for this in secondary analyses, where I investigated exposure to different numbers of antidepressant agents, with the idea that being prescribed higher numbers of different antidepressant agents would represent complex-to-treat depression. I observed higher rates of all physical health outcomes in people who were prescribed more different antidepressant agents. This suggests that exposure to antidepressant prescribing may not indicate the successful treatment of depression as I had hypothesised.

I further attempted to elucidate whether or not my long-term outcomes of interest were directly caused by the antidepressant agents themselves through secondary analyses that compared the timing of antidepressant exposure (**Chapters 6-7**) and through a subgroup analysis comparing different antidepressant agents head-to-head (**Chapter 6 only**). If worse health outcomes were directly caused by the antidepressant agent itself, I would have expected to see differences in antidepressants with different

mechanisms of action, however, this was not the case. I also would have expected to see increased rates of worse health outcomes in people who were recently prescribed antidepressants, compared to those who only received antidepressants in the past. This was only the case for mortality caused by unnatural causes and by diabetic crises.

8.3.7 Confounding bias

RCTs are the gold standard method for evaluating causal effects of an intervention, such as antidepressant treatment, on an outcome, such as mortality. This is due to the fact that randomisation of participants to an intervention or control group is an effective tool for minimizing bias, by attempting to balance both measured and unmeasured confounders between groups. In real-world data, patients are not randomised to either an intervention or control group, but receive an intervention based on an indication of requiring treatment. For medication prescribing, this could be based on depression severity or subtype, patient characteristics (clinical, demographic, socioeconomic, wider determinants, attitudes to treatment), clinician prescribing habits, or local pressures in access to treatment (e.g. local waiting times for talking therapies), for example. These factors may introduce bias, if they also offer alternative explanations for the outcome of interest.

8.3.7.1 Measured confounding

In all four of my EHR studies I adjusted for confounding by age, gender, ethnicity and GP practice. The dataset does contain linkage to practice-level deprivation scores for a number of participating practices in England, however, this only includes approximately 35% of individuals. As this would significantly reduce my sample size, I decided not to include it. Instead, throughout all studies, I accounted for clustering by GP practice, by including the GP practice ID as a stratum term in my models. In this way, I accounted for practice level deprivation and prescribing trends.

In my final two EHR studies (**Chapters 6-7**) I further attempted to balance confounders by adjusting for a large number of confounders that were associated with both antidepressant prescribing and physical health outcomes. These included comorbidities, polypharmacy, history of antidepressant prescribing, primary care contacts, smoking, drinking, drug use, BMI, and T2DM duration. I did not adjust for confounders related to comorbidities or health behaviours in my first to EHR studies (**Chapters 4-5**), as these were considered to be highly collinear with my exposure

variable (the number of concurrent medications). I discuss potential problems with this below in **Section 8.3.7.2**.

There was very little difference in the results in any of my studies after confounder adjustment. However, there may have been unmeasured confounding leading to bias in my findings. This is discussed in the following two **Sections 8.3.7.2-3**.

8.3.7.2 Confounding by indication

Confounding by indication is where the decision to prescribe a treatment is based on a factor which may increase the risk of the outcome of interest, without being an intermediate step on the causal pathway between the exposure and outcome. For example, people who are more severely depressed may be more likely to be prescribed an antidepressant, as well as having a higher risk of worse physical health outcomes (325). If such factors are unaccounted for they may introduce bias.

There is no routinely recorded variable for depression severity in the CPRD dataset. Neither are there recorded specific symptoms and characteristics of depression that may be associated with antidepressant prescribing. In my final two studies where antidepressant prescribing was the exposure, I attempted to account for depression severity by adjusting for a large number of confounders that are known to be associated with depression severity. This included demographic factors, comorbidities, history of antidepressant prescribing, health behaviours (e.g. primary care contacts, smoking). Adjustment for these factors had little effect on the findings of my studies. However, they are not systematic assessments of depression severity or subtype. In people with physical comorbidities, antidepressants are only recommended when depression is moderate-to-severe (81). Therefore, it is likely that individuals included in my studies who were prescribed antidepressants were more severely depressed than those who were not prescribed antidepressants. As such, the worse physical health outcomes that I observed in these individuals may be, at least in part, attributable to worse depression severity, rather than antidepressant prescribing itself. It was also not available from the data to see who might be receiving other treatments for depression, such as psychological therapies. Without the systematic recording of depression severity, confounding by indication is a serious limitation for antidepressant research using EHR data.

Similar cases of this have been reported previously in EHR data. A recent study by Bansal et al using UK EHR data found that SSRIs were associated with increased rates of all-cause mortality, however, they too were unable to adjust for depression severity due to lack of a suitable variable in the dataset, and so, suggested that their findings may also have been confounded by depression severity (447). Freemantle et al describe a study that attempted to replicate RCTs investigating the effect of spironolactone on mortality in people with heart failure using UK EHR data (448). RCTs showed that spironolactone had a protective effect against mortality, whereas the EHR study showed that people who were prescribed spironolactone had an increased risk of mortality. Freemantle et al suggested that the decision to prescribe spironolactone was made using information on the severity of heart failure which was not available in EHR data. Therefore, their control group contained inappropriately low-risk individuals.

Similarly, the prescribing of concurrent medications is caused by the need to treat comorbid conditions. It was not possible to distinguish between increasing numbers of medications and increasing numbers of comorbidities. While data were available on comorbidities, these were directly collinear with the exposure of concurrent medications, and so would not have been suitable to adjust for. As such, it was not possible to tell whether the increased rates of stopping and restarting antidepressants that I observed was associated specifically with polypharmacy, or instead with worse overall health.

8.3.7.3 Other unmeasured confounding

A key limitation of the CPRD dataset is the lack variables concerning socioeconomic characteristics or wider determinants of health. In my final two EHR studies there may have been unmeasured socioeconomic factors influencing the relationship between antidepressant prescribing and worse physical health. There are a number of markers of socioeconomic status, including quality of housing, employment, household income, and education, for example. I use the examples of housing and employment below to explain how these both may be linked to antidepressant prescribing and poor diabetic outcomes. A report by the Health Foundation on antidepressant prescribing trends in UK primary care, found that people were more likely to be prescribed antidepressants in areas with poor housing and high unemployment (449). Inadequate housing situations are known to be wider determinants of poor mental health (41). In addition,

it has been shown that people in the UK with T2DM are less likely to engage with diabetic health checks or to exercise if they have housing insecurity (148). Outside the UK, poor quality and unstable housing has been linked to uncontrolled T2DM (149,150,450). It has also been shown that people in the UK with T2DM are less likely to engage with diabetic health checks if they are unemployed (148). I am aware of no studies that investigate the effect of unemployment on glycaemic control. However, a meta-analysis of the association between unemployment and T2DM risk, found that people who were unemployed were more likely to develop T2DM (151). Unemployment has also been shown to lead to the deterioration of physical health generally (451–453). Both poor housing and unemployment are known predictors of premature mortality (454). Thus, antidepressant prescribing may be a marker for adverse socioeconomic conditions that lead to a deterioration of physical health in individuals with comorbid depression and T2DM.

People with comorbid depression and T2DM who are prescribed more concurrent medications and who are prescribed antidepressants may have a clustering of risk factors which are associated with depression severity, medication taking behaviours and worse physical health outcomes. Disentangling the effects of polypharmacy and antidepressant treatment from these other risk factors in order to understand the causal mechanisms that lead to worse health outcomes is not possible using CPRD data.

8.3.8 Approach to missing data

Throughout all studies included in this thesis, where ethnicity was missing, I recoded this as “White”. As the CPRD population has been found to be representative of the UK population in terms of ethnicity (242,243), 93% or more individuals with missing ethnicity would be expected to be of White ethnicity; this approach is in line with other research studies using the CPRD (389). I performed sensitivity analyses to examine the effect of missing ethnicity, by including individuals with completed data on ethnicity only. I found no difference in the findings of any of my studies, between the main analysis and this sensitivity analysis.

In the final two studies in my thesis, investigating the association between antidepressant prescribing and long-term physical health outcomes, I adjusted for a number of health characteristics. For comorbidities, I considered the absence of a

relevant record to indicate that the comorbidity was not present. This included smoking, where I considered people with no records relevant to smoking to be non-smokers, in line with existing research (455). I used multiple imputation to impute missing BMI categories. I performed sensitivity analyses to examine the effect of missing BMI, by including individuals with completed data on BMI only. I found no difference in the findings of any of my studies, between the main analysis and this sensitivity analysis.

8.3.9 Study design choice

8.3.9.1 Cohort studies investigating the association between the number of concurrent medications and antidepressant treatment trajectories

My first two observational studies used cohort study designs where I followed people with comorbid depression and T2DM who had different levels of polypharmacy from a specific time point to compare different antidepressant treatment trajectories (stopping treatment, switching drugs, restarting treatment). I chose to model polypharmacy as the continuous number of concurrent medications prescribed. As there was not a linear relationship between the number of concurrent medications prescribed and my antidepressant trajectory outcomes, I used a spline function to estimate distinct hazard ratios as the number of concurrent medications increased. I explain this method in detail in my **Methods Chapter 3** and in the relevant **Chapters 4-5**. The benefit of this approach is that it allowed me to show changes in effect size for each additional medication prescribed, as well as the number of medications required before any difference was seen, and the maximum number of medications at which a difference was seen.

Other research in polypharmacy has typically defined exposure to polypharmacy as a categorised variable (e.g.. 0-4 medications, 5-9 medications, 10+ medications) (192,194,393). The benefit of this approach is that it uses a more traditional comparison to a control group of people with no or low levels of polypharmacy. The comparison between control and exposed groups, as opposed to looking at a continuous exposure (my approach described above), could enable more precise matching between individuals thereby better balancing confounding factors. However, potential confounders such as comorbidities and health behaviours would still be

collinear with the exposure to polypharmacy. Therefore, this more traditional approach is unlikely to have been better able to address confounding bias.

RCTs attempt to balance both measured and unmeasured confounding through the use of randomisation. RCTs would not be suitable to investigate exposure to different numbers of concurrent medications, as randomisation that assigns people to take between 0 to 18+ concurrent medications would be neither ethical nor feasible. “Trial emulation” is a method that uses observational data to attempt to mimic an RCT (456). These methods may be beneficial when comparing the effects of specific interventions. However, the number of concurrent medications can be highly heterogenous, as it could include a wide range of pharmacological treatment. Therefore, these methods would not be appropriate.

The investigation of the effect of polypharmacy on antidepressant treatment trajectories may be better suited to research using primary data collection. EHRs do not typically contain information on reasons for stopping and starting medications. While primary data collection is unlikely to be able to include numbers sufficient to model the increasing number of concurrent medications as a continuous variable, it could provide useful information on patient attitudes to pharmacological treatment, perceived tolerability (in terms of side-effects) of antidepressants alongside other medication and perceived effectiveness of antidepressant treatment.

Nevertheless, my studies have identified for the first time that adherence to antidepressant treatment is suboptimal in people with comorbid depression and T2DM (particularly in those who take fewer concurrent medications); and that people in this patient group who are prescribed more concurrent medications are more likely to need to restart antidepressant treatment if they stop.

8.3.9.2 Nested case-control studies examining the association between antidepressant prescribing and long-term physical health outcomes

In my final two observational studies examining the association between antidepressant prescribing and long-term physical health outcomes, I aimed to compare people with comorbid depression and T2DM who were prescribed antidepressants to those who were not prescribed antidepressants. I initially intended to perform propensity score matched cohort studies, where I would balance confounding by matching individuals who were prescribed antidepressants to those

who were not prescribed antidepressants, based on their propensity to be prescribed antidepressants. The use of propensity scores is a quasi-randomised correction strategy aiming to reduce confounder bias (457). They can be used for target trial emulation. They are calculated at a static time point at which individuals are classified as treated (e.g. with antidepressants) or untreated, and from which follow-up is started. As I described in my **Methods Chapter 3**, the majority of individuals prescribed antidepressants did not receive a clinical code for depression within 6 months of their antidepressant prescription. Depression symptoms are subject to frequent change. Therefore, clinical coding of depression is not suitable to identify people who are depressed at a specific static time point in EHRs. This meant that it was not possible to identify a sufficiently sized control group of individuals who had untreated depression at a specific point in time where propensity scores could be calculated.

An alternative approach to address unmeasured confounding whilst still using EHR data could have been the use of an instrumental variable (458,459). An instrumental variable is an additional variable used to estimate the causal effect of the exposure of interest on the outcome of interest. The instrumental variable must be independent of all variables that have an influence on the outcome except the exposure itself. In this way, the instrumental variable can only affect the outcome through the exposure of interest. However, finding a suitable instrumental variable that meets these assumptions is challenging, especially when the relationship between unmeasured confounders is not well understood . Indeed, I could identify no suitable instrumental variables in the data available.

I instead decided to use a nested-case control study design. Nested case-control studies are nested within a defined cohort. Therefore, they have the same benefit as cohort studies in allowing for the adjustment of confounders at the point of study entry through multivariable modelling. They also follow-up participants from the point of study entry until they reach a subsequent outcome or not. Cohort studies typically assess an exposure at pre-defined baseline and compare people with and without the exposure over a follow-up period during which an outcome can occur at any time. Case-control studies on the other hand assess an outcome at a pre-defined index date, and then compare people with and without the outcome during a retrospective observational period during which an exposure can occur at any time. This is a preferable design for exposures that are time varying in nature (364–366), such as

antidepressant treatment (due to the time varying nature of depression itself). While cohort studies do allow for the investigation of time-varying exposures, this is computationally complex, and typically suited to exposures that vary only a small number of times during the follow-up (364). Antidepressant prescribing may vary a considerable number of times over longer follow-up periods. Furthermore, case-control studies allow for the investigation of more than one exposure, enabling the investigation of multiple different types of antidepressant prescribing patterns during the follow-up period, including whether an individual had ever been prescribed an antidepressant, the cumulative duration of antidepressant treatment, the number of different antidepressant agents prescribed and the timing of the antidepressant prescribing relative to the outcome. This allowed me to further understand potential mechanisms behind my findings.

This approach was not able to account for unmeasured confounding, as I discussed above in **Sections 8.3.7.2-3**. Therefore, I was unable to make causal inferences concerning the effect of antidepressant treatment on long-term physical health outcomes in people with comorbid depression and T2DM. Nevertheless, my thesis has identified antidepressant prescribing as a marker for considerably worse long-term physical health outcomes in this patient group. This is still valuable information, as it may enable these individuals to be targeted for enhanced care, as I discuss below in **Section 8.4**.

8.3.10 Peer review

All studies in this thesis, with the exception of the final study investigating mortality, have been submitted to journals and received feedback from peer review. They have all been amended according to peer review feedback.

8.4 Implications of the findings in this thesis for clinical practice, policy and research

In this section I summarise the findings of my thesis in the context of clinical practice, healthcare policy and research, making recommendations for each.

8.4.1 Implications for clinical practice

8.4.1.1 Optimising antidepressant prescribing in individuals with comorbid depression and T2DM

I found that people with comorbid depression and T2DM commonly did not continue antidepressant treatment for the duration recommended by NICE antidepressant guidelines. This was particularly the case in individuals who are prescribed fewer concurrent medications. This may prevent depression being successfully treated, which in turn could lead to considerably worse long-term health outcomes. These individuals could benefit from primary care services monitoring of missed appointments and overdue repeat prescriptions, and/or adherence support.

A survey of antidepressant users in UK primary care found that while they were being treated with antidepressants, primary care appointments still typically focused on physical health problems without reviewing their antidepressant medication (460). This is presumably more likely to be the case in individuals who have physical long-term comorbidities such as T2DM. Regularly reviewing antidepressant medication in individuals with comorbid depression and T2DM could be beneficial. Where antidepressants are appropriately prescribed, it could identify and address issues that would otherwise result in non-adherence. Psychoeducation which informs patients on the consequences of non-adherence, addresses psychological barriers to adherence, and/or offers behavioural interventions to improve adherence may also be effective (461). This could be offered to all individuals with comorbid depression and T2DM who are prescribed antidepressants. In addition, habit and behavioural based adherence interventions, such as prompts or linking medication taking with existing habits may be effective in individuals who take fewer concurrent medications and so do not have established medication taking behaviours/habits (462). Regularly reviewing antidepressant medication in individuals with comorbid depression and T2DM could also identify where antidepressants are ineffective or inappropriately prescribed.

I found in patients with comorbid depression and T2DM who do stop antidepressant treatment, subsequently restarting treatment is common. This may represent clinically identified depression relapse. The long-term maintenance of antidepressant treatment has been shown in multiple meta-analytic studies of RCTs in the general population to be an effective way to prevent depression relapse (207,211,400,463). This could be considered to prevent depression relapse in individuals with comorbid depression and T2DM. Although I found that individuals with comorbid depression and T2DM were

more likely to restart antidepressant treatment if they had previously been taking antidepressants for longer durations, this may simply highlight a need for the *continued* maintenance of antidepressant medication in these individuals.

I found that the rate of restarting antidepressant treatment for individuals with comorbid depression and T2DM was considerably lower than the expected rate of depression relapse, after stopping antidepressants, particularly in individuals who are prescribed fewer concurrent medications. It is possible that these individuals experienced depression relapse but did not seek or accept antidepressant treatment a second time. As such, depression may be undertreated in these individuals. This may lead to the development of considerably worse long-term health outcomes. If an individual is identified as having stopped antidepressant treatment, close monitoring of their mental health may be required to prevent untreated depression relapse.

8.4.1.2 Enhanced holistic support for individuals with comorbid depression and T2DM who are prescribed antidepressants

Whatever the causal mechanisms, I found that antidepressant prescribing in individuals with comorbid depression and T2DM is a marker for considerably worse health outcomes. These outcomes included the long-term deterioration of physical health, as well as acute diabetic and mental health crises. Individuals with comorbid depression and T2DM who have been prescribed an antidepressant at any point since starting treatment for T2DM could benefit from enhanced holistic support, which I describe below.

According to the American Association for Diabetes Education, there are seven essential self-care activities which improve the health status of individuals T2DM – physical activity, healthy eating, medication adherence, blood glucose monitoring, problem solving skills for changes in glycaemic control, risk reduction for diabetic complications and psychological coping (464). However, a number of depression symptoms are known to make self-care more challenging. These include loss of interest, reduced decision-making ability and fatigue (465). This may be contributing to the worse physical health outcomes that I observed in people with comorbid depression and T2DM who were prescribed antidepressants compared to those who were not, if this association is indeed attributable to depression severity. Antidepressant prescribing could be used to identify individuals with comorbid

depression and T2DM who may benefit the most from enhanced support in each element of self-care. I discuss these further in the following paragraphs.

In the general population of England, it is estimated that 23.4% of adults are physically inactive (466). This suggests that even healthy individuals find it difficult to maintain sufficient levels of physical activity. Physical inactivity is a risk factor for both depression and T2DM . It is also a potential effect of depression (6). As such, individuals with comorbid depression and T2DM are likely to find it harder to maintain sufficient levels of physical activity. Social prescribing is a means for primary care practitioners in the UK to refer patients to community led activities, including a range of exercise activities and sports (467). Social prescribing to exercise schemes has been shown to be effective at improving a range of diabetic outcomes (468). Exercise interventions have also been shown to be effective in decreasing depression severity whilst used alongside antidepressant medication (469). Therefore, community-based exercise schemes may be of benefit to this high risk group of individuals with comorbid depression and T2DM who are prescribed antidepressants. These individuals could be prioritised for social prescribing to such schemes.

In the general population of England it is estimated that 45.6% of adults do not meet healthy diet recommendations (470). This figure highlights the difficulties that people have maintaining a healthy diet. Again, this is likely to be more challenging for people with comorbid depression and T2DM. T2DM is usually caused by unhealthy diet and physical inactivity (141) and people with depression are less likely to eat healthy diets (7,8). A range of healthy eating interventions have been found to be effective for people with T2DM (471) However, long-term behaviour change may be difficult to maintain (471). This may particularly be the case in individuals with comorbid depression, who have reduced levels of motivation (465). Furthermore, a common side-effect of many antidepressants is changes to appetite (153,154). This may add to the motivational challenges of healthy eating. As such, regular support to encourage healthy eating may be required for this high risk group of individuals with comorbid depression and T2DM who are prescribed antidepressants. Ongoing peer support groups have been shown to encourage the maintenance of healthy eating motivation (472).

Depression has been shown to negatively impact an individual’s ability to adhere to antidiabetic medication (143). I found that individuals with comorbid depression and

T2DM who were currently taking antidepressants were at considerably high risk of experiencing fatal diabetic crises, the main cause of which in high income Western countries is the lack of adherence to antidiabetic medication (6,84). I previously described, in **Section 8.4.3.1**, how individuals with comorbid depression and T2DM may require enhanced support in adherence to antidepressant medication. Adherence support for antidiabetic medication could be very similar to and combined with adherence support for antidepressant medication. This could include education as to the consequences of non-adherence, follow-up of missed appointments or overdue repeat prescriptions, and regular medication reviews.

Depression is a known barrier to personal glucose monitoring in individuals with comorbid T2DM (473). “Flash glucose monitors” are now available on the NHS, where individuals wear a small sensor on their body that regularly checks their glucose levels (474). This information can be digitally shared with the individual’s healthcare team who can then monitor the patient’s glycaemic control without relying on the individual to adhere to personal glucose monitoring (474). Flash glucose monitors with remote healthcare team monitoring could be offered to all individuals in this high risk group with comorbid depression and T2DM who are prescribed antidepressants.

Problem solving skills to identify and change lifestyle habits that negatively affect glycaemic control are an important element of diabetes self-management (131). Reduced decision-making ability is a known effect of depression that may result in poor self-care (465). This is particularly relevant to an individual’s capacity for problem solving. RCTs of interventions where problem-solving psychotherapy is combined with antidepressant treatment has shown positive impacts on both physical and mental health outcomes in comorbid depression and T2DM (475,476). Where such care is available, this could be offered to and prioritised for this high risk group of individuals with comorbid depression and T2DM who are prescribed antidepressants.

Reducing risks that lead to diabetic complications is also an important element of diabetes self-management. This primarily includes smoking cessation, foot care, dental care, eye checks, and vaccination (477). Other risk reduction methods include taking medications, healthy eating, and exercise – I have discussed these above. People with depression are more likely to smoke and less likely to quit smoking than people without depression (478). People with depression symptoms also have lower rates of vaccination uptake (479). Amongst people with T2DM, those with comorbid

depression are less likely to perform adequate foot care (480), potentially due to depression causing reduced motivation (481) and/or reduced self-efficacy (482). These individuals are also more likely to miss health check appointments than those without depression (483). When individuals with comorbid depression and T2DM are prescribed antidepressants, they could be prioritised for smoking cessation support if required. They could also be monitored to ensure adequate engagement with diabetic foot checks, eye checks, dental checks and vaccination services.

The final essential self-care activity named by the American Association of Diabetes Education is coping with psychological distress (131). Diabetes distress is "a rational emotional response to the threat of a life-changing illness" (412). People with comorbid depression and T2DM are more likely to suffer from diabetes distress than those without depression, and people with diabetes distress are more likely to develop depression than those without diabetes distress (414). Both diabetes distress (411,414,484) and depression (465) negatively impact self-care behaviours in people with T2DM. In a large survey of individuals with T2DM in the UK, lack of perceived support from healthcare services increased levels of diabetes distress (412). Furthermore, the most commonly used type of diabetes education programmes in the UK tend not to include psychological aspects of diabetes self-management (412). There is evidence that psychological treatments focusing on diabetes distress may improve depression symptoms in people with T2DM (485). People with comorbid depression and T2DM who are prescribed antidepressants represent a group of individuals who are at considerable risk of worse physical and mental health outcomes. Targeting these individuals for enhanced depression treatment, where antidepressant treatment is combined with psychological treatment focusing specifically on diabetes distress may be of benefit to improve both physical and mental health outcomes.

It is also important to be aware that individuals with comorbid depression and T2DM who are currently prescribed antidepressants have considerably higher risk of suicide than those who are not prescribed antidepressants. Regular depression severity monitoring in people with comorbid depression and T2DM who are prescribed antidepressants may be required. These individuals could complete a self-administered depression symptom questionnaire whilst waiting for any primary care appointment. This will enable the primary care practitioner to monitor the individual's

depression severity without any impact on the appointment time, unless a problem is identified, in which case action can be taken. Self-administered depression symptom questionnaires such as the PHQ-9 contain a question related to suicide (486) which would also enable suicide screening in this high risk group.

Finally, antidepressant prescribing may be a marker for adverse socioeconomic conditions in individuals with comorbid depression and T2DM. This may differ by individual patient. Socioeconomic deprivation, such as housing, unemployment and food insecurity, is known to lead to worse outcomes for people with T2DM (148–151). Socioeconomic support is available from government funded benefits payments, social services and charities (487). However, depression may be a barrier to accessing socioeconomic support (488). Signposting to relevant services that help people access socioeconomic support could be beneficial for this high risk group of individuals with comorbid depression and T2DM who are prescribed antidepressants.

8.4.1.3 Prescribing antidepressants alongside other medications in people with comorbid depression and T2DM

In my thesis, I set out to explore whether antidepressant prescribing added to and/or was impacted by the risks associated with inappropriate polypharmacy. These include increased risk of drug side effects (184), drug-drug or drug-disease interactions (178–180,184,202), poor quality of life from higher treatment burden (184,194–196), and reduced adherence to treatment (186,192,193,203). I found no evidence that polypharmacy negatively impacted antidepressant acceptability in this patient group. Conversely, people who were prescribed more medications were more likely to adhere to antidepressant treatment and restart antidepressants after stopping. However, without understanding the reasons for stopping and restarting antidepressant treatment, it is not possible to say that antidepressants were more acceptable to people who were taking more concurrent medications. In the final two studies of my thesis, I found that people who were prescribed antidepressants had considerably worse physical health outcomes. This finding was not affected by the number of concurrent medications prescribed. As such, I found no evidence to suggest that the worse health outcomes observed in people with comorbid depression and T2DM who were prescribed antidepressants was attributable to polypharmacy. However, my studies did not investigate specific combinations of medication prescribing and did not account for the timing of polypharmacy relative to antidepressant treatment. Therefore,

there is still a gap in the evidence regarding the long-term safety of antidepressant treatment alongside other medications prescribed to people with comorbid depression and T2DM.

8.4.2 Implications for policy makers

My thesis has identified that antidepressant treatment in individuals with comorbid depression and T2DM is a marker of considerably worse health outcomes and potentially unmet need. Optimising holistic support for these individuals may significantly reduce the burden of this comorbidity on population health and healthcare services. However, current policy neglects this high-risk patient group.

8.4.2.1 T2DM-specific NICE guidelines for the treatment of depression

There are no NICE guidelines for the treatment of depression specifically in people with T2DM. NICE guidelines for T2DM provide recommendations for the management of a range of complications that are associated with diabetes, including gastroparesis, periodontitis, retinopathy, painful neuropathy, erectile dysfunction, chronic kidney disease, autonomic neuropathy and foot problems (83). However, NICE guidelines for T2DM do not mention depression as a common comorbidity. The prevalence of depression in people with T2DM is approximately 25% (334) – my thesis has shown that this population needs specific attention. My thesis has identified that antidepressant prescribing in people with comorbid depression and T2DM is suboptimal, which is potentially resulting in considerably worse health outcomes. However, there is still a significant gap in the evidence concerning interventions that may improve this. Further research is urgently required to enable the development of NICE guidelines for the treatment of depression specifically in this patient group.

8.4.2.2 Improved QOF indicators for the monitoring of depression in individuals with T2DM

QOF indicators incentivise primary care practices in the UK to perform a number of annual health checks in people with T2DM. They do not include depression screening or monitoring, despite depression being common in people with T2DM (334) and increasing risks in (220,221) this patient group. Furthermore, QOF indicators for depression only recommend that an individual with depression is reviewed once within 56 days of diagnosis (489). This is unlikely to be sufficient for a long-term condition.

My thesis has identified that people with comorbid depression and T2DM who are prescribed antidepressants are a high-risk group with serious unmet need. Regular depression severity monitoring in these individuals could identify people whose current antidepressant treatment is inadequate and who need more support. Primary care practices may need to be incentivised to do this.

8.4.2.3 Improved mental health content of diabetes education

Primary care practices are incentivised through QOF to provide diabetes education for everyone who is diagnosed with T2DM (489). However, diabetes education provided in the UK commonly does not contain information on psychological coping (412) and rarely contains information on antidepressant treatment adherence (490). These are both critical elements of self-management for people with comorbid depression and T2DM who are prescribed antidepressants. Reduced psychological coping increases rates of depression in people with T2DM (491) which may jeopardise the effectiveness of antidepressant treatment. Diabetes education may be effective in improving both psychological coping skills (492,493) and antidepressant adherence (461). As such, the minimum requirements for diabetes education that is offered to people with T2DM in the UK could be improved to include psychological coping and antidepressant adherence.

8.4.2.4 Longer appointments with the opportunity to refer to enhanced holistic support

In **Section 8.4.1**, I made a number of suggestions to clinical practice for enhanced holistic support that may improve outcomes for individuals with comorbid depression and T2DM who are prescribed antidepressants. This included mental health checks, medication reviews, adherence support, and referral to a range of external self-care support services. With the average duration of primary care appointments currently running at 9.2 minutes (494), this is not enough time for these opportunities to be discussed with the patient. This may be partially responsible for the serious unmet need in this complex patient group with comorbid depression and T2DM who are being treated with antidepressants. Offering extended primary care appointments to individuals with comorbid depression and T2DM if they are prescribed antidepressants might help primary care practitioners identify and address specific needs for enhanced holistic care. The NHS Long Term Plan states that “the NHS will offer a ‘digital first’ option for most, allowing for longer and richer face-to-face consultations with clinicians

where patients want or need it" (495). Individuals with comorbid depression and T2DM who are prescribed antidepressants should be considered as a group of people eligible for these extended appointments.

8.4.3 Recommendations for researchers

In this section, I discuss the implications of my thesis on future research. I first discuss the urgent need to prioritise research in people with depression and T2DM. I discuss the contribution of my thesis to advancing the use of EHR data in research concerning depression, multimorbidity and polypharmacy. I then discuss future research questions that have arisen from this thesis, including the use of different study designs and data sources.

8.4.3.1 Depression in people with T2DM as a priority for research

In 2017, the Lancet Psychiatry Commission on protecting physical health in people with mental illness highlighted that we know less about the physical health of people with depression than we do about the physical health of people with severe mental illness (such as schizophrenia or bipolar disorder) (496). My thesis has identified a group of individuals – people with comorbid depression and T2DM who are prescribed antidepressants – that have considerably higher risk of poor health outcomes and serious unmet needs. These are two of the most common conditions globally with some of the highest contribution to the global burden of disease (1). However, this is still a neglected area of research. A number of further research questions have arisen as a result of my thesis. I describe these in detail in the following **Sections 8.4.3.2-6**. I make recommendations with regards to data sources in **Sections 8.4.3.7-8**.

8.4.3.2 What are the factors that influence decisions to start and stop antidepressants in in individuals with comorbid depression and T2DM?

i) **When given a diagnosis of depression, is receipt of antidepressant treatment as likely in people with T2DM compared to people without T2DM?** Antidepressant prescribing in people with comorbid depression and T2DM is suboptimal and is a marker for considerably worse health outcomes. It is not known, however, whether individuals with T2DM are prescribed antidepressants as frequently as people without T2DM. It is important to understand whether there are issues with over or under-treating depression in

this patient group. There is one study that I am aware of by Pal et al examining the prevalence of antidepressant prescribing in the UK in people with T2DM compared to those without T2DM (497). This found that people with T2DM were 30% more likely to be prescribed an antidepressant compared to those without T2DM. However, this study did not restrict its inclusion criteria to individuals with depression, and did not account for depression in statistical analysis. Therefore, the increased rates of antidepressant prescribing are likely to reflect increased prevalence of depression in individuals with T2DM compared to those without T2DM. Research is required to address this question in people with comorbid depression and T2DM.

ii) What factors influence antidepressant prescribing in people with comorbid depression and T2DM in the UK? My first systematic review attempted to understand the factors associated with antidepressant prescribing in individuals with comorbid depression and T2DM. However, I found no UK-based studies suitable for inclusion. In my studies that examined the outcomes associated with antidepressant prescribing in people with comorbid depression and T2DM, I found that individuals in this patient group who were prescribed antidepressants were more likely to be female, of White ethnicity and have more comorbidities. However, even after accounting for these factors, antidepressant prescribing was still associated with considerably worse health outcomes. Therefore, there must be other unmeasured characteristics of people with comorbid depression and T2DM who are prescribed antidepressants that are driving this effect of worse health outcomes. Identifying other characteristics that influence antidepressant prescribing in this patient group could enable the generation of hypotheses as to the mechanisms involved in these worse health outcomes. In particular, depression severity, depression subtype, access to other depression treatment, socioeconomic characteristics, and wider determinants of health should be explored.

iii) What factors influence patient decisions to start and stop antidepressants in people with comorbid depression and T2DM? The findings of my thesis suggested that people with comorbid depression and T2DM are more likely to accept antidepressant treatment if they are taking more concurrent medications. I suggested that this could be because these individuals have worse depression requiring treatment or because they are more accepting of

pharmacological treatment generally. However, given the limitations of my research, these interpretations can only be speculative. Qualitative research is required to understand attitudes to antidepressant medication in this patient group. This information could inform interventions to improve access and adherence to antidepressant treatment in individuals with comorbid depression and T2DM.

8.4.3.3 Are antidepressants safe to prescribe alongside other medications commonly prescribed to individuals with comorbid depression and T2DM?

I found no evidence that concurrent medication use negatively affected antidepressant acceptability in individuals with comorbid depression and T2DM. On the other hand, I found that people in this patient group who were prescribed antidepressants had higher rates of suicide, fatal diabetic crises, falls, traffic accidents and accidental poisoning. In my first observational study I reported the medication classes concurrently prescribed to people starting antidepressant treatment for the first time. A number of these medications, such as opiates and NSAIDs, have been linked to preventable hospital admissions when prescribed in combination with antidepressants (170). It is important to understand whether these polypharmacy combinations are causing serious adverse effects in individuals with comorbid depression and T2DM. It is also important that such research accounts for current depression and depression severity, as many acute adverse effects, such as mortality from unnatural causes or diabetic crises may be caused by depression, rather than the antidepressant itself.

8.4.3.4 To what extent does successful antidepressant treatment moderate the effects of depression on physical health outcomes in individuals with comorbid depression and T2DM?

i) **To what extent is depression successfully treated in individuals with comorbid depression and T2DM?** I hypothesised that antidepressant treatment would improve physical health outcomes in people with comorbid depression and T2DM, by improving their diabetic management and self-care, through the improvement of their mental health. However, I found the opposite to this. It is important to understand the extent to which depression is successfully treated in individuals with comorbid depression and T2DM, as this

may be the reason that antidepressant treatment does not improve physical health outcomes in this patient group.

ii) **Does the association between antidepressant treatment and physical health outcomes in people with comorbid depression and T2DM vary according to whether or not depression was successfully treated?** To do this, further research is required that first compares physical health outcomes in people with comorbid depression and T2DM, to those in people with T2DM but no depression. The modifying effect of antidepressant treatment could then be compared between individuals for whom antidepressant treatment was considered successful and in those for whom it was not.

iii) **Does the timing of antidepressant treatment relative to T2DM disease stage improve mental and physical health outcomes in people with comorbid depression and T2DM?** The characteristics of people included in my studies who were prescribed antidepressants compared to those who were not, suggested that people with comorbid depression and T2DM are more likely to be prescribed antidepressants if they have worse overall health. Further research is required to compare the association between antidepressants and worse physical health outcomes, in people who are first prescribed antidepressants when they are healthier with early stage T2DM, compared to those who are prescribed antidepressants when they are less healthy, with later stage T2DM. This would highlight whether the earlier initiation of antidepressant treatment could prevent worse health outcomes in people with comorbid depression and T2DM.

8.4.3.5 How do wider determinants of health influence the relationship between antidepressant prescribing and worse health outcomes in individuals with comorbid depression and T2DM?

I was unable to account for person-level socioeconomic status or specific elements of socioeconomic status, such as housing or employment. Socioeconomic status may effect an individual's likelihood of being prescribed an antidepressant (239,497). Socioeconomic deprivation can also lead to worse physical health outcomes in individuals with T2DM (148–151,451–453). As such, antidepressant prescribing may be a marker of adverse socioeconomic status in individuals with comorbid depression and T2DM, which could lead to worse physical health outcomes. Further research is

required that measures socioeconomic status and specific socioeconomic characteristics at person-level, to identify causal pathways between socioeconomic characteristics, depression, antidepressant prescribing and worse physical health outcomes in individuals with comorbid depression and T2DM.

8.4.3.6 Evaluation of enhanced holistic care interventions

In **Sections 8.4.1-2** I discussed interventions for enhanced holistic care that may improve physical and mental health outcomes for the high risk group of individuals that I identified with comorbid depression and T2DM who are prescribed antidepressants. However, these interventions have not yet be evaluated in this patient group. Evaluation of these interventions in individuals with comorbid depression and T2DM who are prescribed antidepressants would provide evidence to support their implementation:

- Monitoring and follow-up of missed appointments and overdue repeat prescriptions;
- Regular antidepressant medication reviews and closer monitoring of mental health, including risk of suicide;
- Long-term maintenance of antidepressant treatment;
- Psychoeducation on the necessity of medication adherence, problem solving skills and coping with diabetes distress;
- Access to habit or behaviour-focused adherence interventions for individuals who are prescribed fewer concurrent medications and may not have established medication taking habits;
- Social prescribing for community-based exercise schemes;
- Regular support to maintain healthy eating;
- Referral to smoking cessation;
- Signposting to socioeconomic support.

8.4.3.7 Other research approaches using additional data sources

In this section, I discuss other data sources that may be able to answer the further research questions that I recommended in **Sections 8.4.3.2-6**. The triangulation of multiple sources and approaches is likely to be necessary to develop a comprehensive understanding of the relationship between antidepressant prescribing, polypharmacy and long-term health outcomes for people with comorbid depression and T2DM.

i) **International datasets:** EHR datasets from international populations may have different distributions of confounding variables, particularly with regards to the wider determinants of health. Replication of my studies in international datasets could highlight wider determinants of health that may be driving the association between antidepressant prescribing and worse health outcomes in people with comorbid depression and T2DM. Furthermore, international datasets may contain more routine recording of depression episodes and severity that would allow me to investigate the confounding effect of depression.

ii) **Primary data collection:** Primary data collection may be required to collect information on changing depression severity, depression subtype, wider determinants of health and patient reasons for starting/stopping antidepressant medication.

iii) **Incorporation of prior information using Bayesian methods:** Bayesian methods enable the synthesis of information from different data sources to incorporate prior information concerning potential confounding effects that may not be available from one data source (498–500). These methods are not well explored in pharmacoepidemiology but could be promising to account for previously unmeasurable confounding.

8.4.3.8 The development of EHR data sources for research purposes

EHR systems are currently not designed for research but for clinical practice (439,440). The lack of randomisation results in confounding bias and missing data results in selection bias (439). Expanding EHR systems to make them more suitable for research could lead to huge advances in public health practice and policy (440). In the long-term, the incorporation of regularly collected psychosocial elements would provide valuable information. However, primary care workflow would need to be adapted to find an efficient way to collect these data (440). In the short-term, linkage to other data sources could improve validity and provide information on potential confounders. These could include, for example, socioeconomic data held by local authorities or the national improving access to psychological therapies (IAPT) dataset.

8.5 Dissemination

At the time of submitting this thesis, modified versions of the following chapters had been published, submitted for publication or were being prepared for publication:

i) A version of the meta-analysis in **Chapter 2**, investigating the prevalence of antidepressant prescribing and associated polypharmacy characteristics in individuals with comorbid depression and T2DM, has been published in Health Science Review;

ii) A version of the systematic review in **Chapter 2**, investigating long-term physical health outcomes associated with antidepressant prescribing in individuals with comorbid depression and T2DM, has been published as a preprint;

iii) A version of the EHR study in **Chapter 4**, investigating the association between polypharmacy and early antidepressant discontinuation in individuals with comorbid depression and T2DM, is currently at the second stage of peer review at the British Journal of General Practice;

iv) A version of the EHR study in **Chapter 5**, investigating the association between polypharmacy and restarting antidepressants in individuals with comorbid depression and T2DM, is currently at the second stage of peer review at the British Journal of Psychiatry;

v) A version of the EHR study in **Chapter 6**, investigating the association between antidepressant prescribing and starting insulin in individuals with comorbid depression and T2DM, is currently under peer review at PLOS Medicine;

vi) A version of the EHR study in **Chapter 7**, investigating the association between antidepressant prescribing and mortality in individuals with comorbid depression and T2DM, is currently being drafted.

Additionally, I presented elements of this research at international conferences:

i) A poster and spotlight presentation of the EHR study in **Chapter 4**, investigating the association between polypharmacy and early antidepressant discontinuation in individuals with comorbid depression and T2DM, at the International Conference of Pharmacoepidemiology in August 2022;

ii) A poster of the EHR study in **Chapter 5**, investigating the association between polypharmacy and restarting antidepressants in individuals with

comorbid depression and T2DM, at the International Conference of Pharmacoepidemiology in August 2022;

iii) A poster of the EHR study in **Chapter 6**, investigating the association between antidepressant prescribing and starting insulin in individuals with comorbid depression and T2DM, at the International Conference of Pharmacoepidemiology in August 2022;

Dissemination to a wider audience, including members of the public, includes:

i) I have presented the findings of my thesis to the NIHR Applied Research Collaboration (ARC) North Thames Patient and Public Research Advisory Panel who provided feedback which has informed the **Discussion Chapter** of my thesis, particularly in regards to the clinical implications and future research directions. This group also suggested a number of channels for the dissemination of my thesis findings to a wider audience, including the NIHR and diabetes charities. Since this session I have met with the NIHR ARC North Thames's Implementation and Public and Patient Involvement Managers to plan further dissemination via these channels.

ii) During my PhD I founded the UCL Pharmaco-Epi Data Collaborative – a network of international and multidisciplinary researchers working in the field of pharmacoepidemiology. This has enabled the transfer of knowledge throughout UCL and other universities around the world via a number of seminars, workshops and training sessions. As part of this initiative I am also in the process of setting up an online knowledge hub where I will make all of the code lists and statistical code used in this PhD open source.

8.6 Conclusions

Through the studies in this thesis, I established that antidepressant prescribing in people with comorbid depression and T2DM is suboptimal in UK primary care. People who are prescribed fewer concurrent medications are at higher risk of stopping antidepressant treatment before the NICE recommended duration. While people who are prescribed more concurrent medications may be more severely depressed and have greater need of depression treatment. This information can be used by clinicians to optimise depression care in these individuals. I also found that antidepressant prescribing is marker of considerably worse physical health outcomes in this patient

group. This information can be used by clinicians to a group of people who are in urgent need of enhanced holistic support.

The use of EHR data has enabled me to explore real-world antidepressant and polypharmacy patterns and outcomes, in people with comorbid depression and T2DM, for the first time. My thesis has highlighted limitations of this data – particularly confounding by the indication of depression severity and unmeasured behavioural or socioeconomic confounders. However, it has also shown that EHR data can be a valuable source of information to identify groups of people with worse health outcomes, suboptimal treatment and unmet needs.

References

1. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2018 Nov 10;392(10159):1789–858. Available from: http://www.thelancet.com/article/S0140673618322797/fulltext
2. Archer G, Kuh D, Hotopf M, Stafford M, Richards M. Association Between Lifetime Affective Symptoms and Premature Mortality. JAMA Psychiatry. 2020 Aug 1;77(8):806–13. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2763796
3. World Health Organisation. Depression. [Internet] [cited 2022 October 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. [Internet] 2013 May 22 [cited 2022 Apr 12]; Available from: https://psychiatryonline.org/doi/book/10.1176/appi.books.9780890425596
5. World Health Organisation. ICD-11 for Mortality and Morbidity Statistics. [Internet] [cited 2022 October 13]. Available from: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f1563440232
6. Cooney GM, Dwan K, Greig CA, Lawlor DA, Rimer J, Waugh FR, et al. Exercise for depression: Some benefits but better trials are needed. Saudi Med J. 2013 Nov;34(11):1203. Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004366.pub6/full
7. Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. J Acad Nutr Diet. 2012 Dec;112(12):2022–7. Available from: https://pubmed.ncbi.nlm.nih.gov/23174689/
8. McMartin SE, Jacka FN, Colman I. The association between fruit and vegetable consumption and mental health disorders: evidence from five waves of a national survey of Canadians. Prev Med (Baltim). 2013 Mar;56(3–4):225–30. Available from: https://pubmed.ncbi.nlm.nih.gov/23295173/
9. Luger TM, Suls J, vander Weg MW. How robust is the association between smoking and depression in adults? A meta-analysis using linear mixed-effects models.

Addictive behaviors. 2014;39(10):1418–29. Available from: https://pubmed.ncbi.nlm.nih.gov/24935795/

10. Weinberger AH, Kashan RS, Shpigel DM, Esan H, Taha F, Lee CJ, et al. Depression and cigarette smoking behavior: A critical review of population-based studies. Am J Drug Alcohol Abuse. 2017 Jul 4;43(4):416–31. Available from: https://pubmed.ncbi.nlm.nih.gov/27286288/
11. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006;67(2):247–57. Available from: https://pubmed.ncbi.nlm.nih.gov/16566620/
12. Jaracz J, Gattner K, Jaracz K, Górna K. Unexplained Painful Physical Symptoms in Patients with Major Depressive Disorder: Prevalence, Pathophysiology and Management. CNS Drugs. 2016 Apr 1;30(4):293–304. Available from: https://pubmed.ncbi.nlm.nih.gov/27048351/
13. Archer G, Kuh D, Hotopf M, Stafford M, Richards M. Association Between Lifetime Affective Symptoms and Premature Mortality. JAMA Psychiatry. 2020 Aug 1;77(8):806–13. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2763796
14. HM Government. No health without mental health: A cross-Government mental health outcomes strategy for people of all ages. [Internet]. [Cited 2022 October 13].
15. National Institute for Health and Care Excellence. Recommendations: Depression in adults: treatment and management. [Internet] [cited 2022 October 13]. Available from: https://www.nice.org.uk/guidance/ng222/chapter/recommendations#starting-antidepressant-medication
16. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet. 2018 Apr 7;391(10128):1357–66. Available from: http://www.thelancet.com/article/S0140673617328027/fulltext
17. National Institute for Health and Care Excellence. BNF: Treatment summary: Antidepressant drugs. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/treatment-summary/antidepressant-drugs.html

18. Royal College of Psychiatrists. Antidepressants. [Internet] [cited 2022 October 14]. Available from: https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/antidepressants
19. National Institute for Health and Care Excellence. BNF: Drug: Venlafaxine. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/venlafaxine/
20. National Institute for Health and Care Excellence. BNF: Drug: Duloxetine. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/duloxetine/
21. National Institute for Health and Care Excellence. Depression in adults with a chronic physical health problem: recognition and management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/cg91
22. National Institute for Health and Care Excellence. Depression in adults: recognition and management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/cg90/chapter/Recommendations
23. National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng28/chapter/Recommendations
24. Heald AH, Stedman M, Davies M, Livingston M, Taylor D, Gadsby R. Antidepressant Prescribing in England: Patterns and Costs. Prim Care Companion CNS Disord. 2020 Apr 16;22(2):26631. Available from: https://www.psychiatrist.com/pcc/depression/antidepressant-prescribing-in-england
25. NHS Digital. Waiting Times. [Internet] [cited 2022 October 14]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/psychological-therapies-report-on-the-use-of-iapt-services/march-2021-final-including-a-report-on-the-iapt-employment-advisors-pilot-and-quarter-4-2020-21-data/waiting-times
26. World Health Organisation. Diabetes. [Internet] [cited 2022 October 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes
27. KAISER AB, ZHANG N, der PLUIJM W van. Global Prevalence of Type 2 Diabetes over the Next Ten Years (2018-2028). Diabetes. 2018 Jul 1;67(Supplement_1). Available from: https://diabetesjournals.org/diabetes/article/67/Supplement_1/202-LB/55092/Global-Prevalence-of-Type-2-Diabetes-over-the-Next
28. THE COST OF DIABETES.
29. Sterrett JJ, Bragg S, Weart CW. Type 2 Diabetes Medication Review. Am J Med Sci. 2016 Apr 1;351(4):342–55. Available from: http://www.amjmedsci.org/article/S0002962915410584/fulltext

30. Association AD. 7. Approaches to Glycemic Treatment. Diabetes Care. 2015 Jan 1;38(Supplement_1):S41–8. Available from: https://diabetesjournals.org/care/article/38/Supplement_1/S41/37287/7-Approaches-to-Glycemic-Treatment
31. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. AACE/ACE comprehensive diabetes management algorithm 2015. Endocr Pract. 2015 Apr 1;21(4):438–47. Available from: https://pubmed.ncbi.nlm.nih.gov/25877012/
32. Diabetes Canada. Clinical Practice Guidelines - Chapter 13: Pharmacologic Glycemic Management of Type 2 Diabetes in Adults. [Internet] [cited 2022 October 14]. Available from: http://guidelines.diabetes.ca/browse/Chapter13
33. National Institute for Health and Care Excellence. BNF: Drug: METFORMIN HYDROCHLORIDE. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/metformin-hydrochloride.html
34. EMC. Electronic medicines compendium. [Internet] [cited 2022 October 14]. Available from: https://www.medicines.org.uk/emc
35. National Institute for Health and Care Excellence. Type 2 diabetes in adults: choosing medicines Factors to take into account when choosing, reviewing and changing medicines. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng28/resources/visual-summary-full-version-choosing-medicines-for-firstline-and-further-treatment-pdf-10956472093
36. National Institute for Health and Care Excellence. BNF: Drug: CANAGLIFLOZIN [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/canagliflozin.html
37. National Institute for Health and Care Excellence. BNF: Drug: SITAGLIPTIN [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/sitagliptin.html
38. National Institute for Health and Care Excellence. BNF: Drug: PIOGLITAZONE [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/pioglitazone.html
39. National Institute for Health and Care Excellence. BNF: Drug: GLICLAZIDE [Internet] [cited 2022 October 14]. from: https://bnf.nice.org.uk/drug/gliclazide.html

40. National Institute for Health and Care Excellence. BNF: Drug: DULAGLUTIDE [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/dulaglutide.html
41. National Institute for Health and Care Excellence. Insulin therapy in type 2 diabetes. [Internet] [cited 2022 October 14]. Available from: https://cks.nice.org.uk/topics/insulin-therapy-in-type-2-diabetes/
42. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. The Lancet. 2012 Aug 11; 380(9841):601–10. Available from: http://www.thelancet.com/article/S0140673612609878/fulltext
43. Yamazaki D, Hitomi H, Nishiyama A. Hypertension with diabetes mellitus complications. Hypertens Res. 2018 Mar 1;41(3):147–56. Available from: https://pubmed.ncbi.nlm.nih.gov/29353881/
44. National Institute for Health and Care Excellence. BNF: Drug: Ramipril. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/ramipril/
45. National Institute for Health and Care Excellence. BNF: Drug: Telmisartan. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/telmisartan/
46. National Institute for Health and Care Excellence. BNF: Drug: Amlodipine. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/amlodipine/#side-effects
47. National Institute for Health and Care Excellence. BNF: Drug: Hydrochlorothiazide. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/hydrochlorothiazide/
48. Wylie TAF, Shah C, Connor R, Farmer AJ, Ismail K, Millar B, et al. Transforming mental well-being for people with diabetes: research recommendations from Diabetes UK's 2019 Diabetes and Mental Well-Being Workshop. Diabetic Medicine. 2019 Dec 1;36(12):1532–8.
49. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular Diabetology 2018 17:1. 2018 Jun 8 [cited 2022 Apr 22];17(1):1–19. Available from: https://cardiab.biomedcentral.com/articles/10.1186/s12933-018-0728-6
50. QRISK3. [Internet] [cited 2022 October 14]. Available from: https://www.qrisk.org/three/index.php

51. National Institute for Health and Care Excellence. BNF: Drug: Atorvastatin. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/atorvastatin/
52. British Heart Foundation. Medicines for my heart - Heart conditions. [Internet] [cited 2022 October 14]. Available from: https://www.bhf.org.uk/informationsupport/publications/heart-conditions/medicines-for-your-heart#
53. National Institute for Health and Care Excellence. BNF: Drug: Aspirin. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/aspirin/
54. National Institute for Health and Care Excellence. BNF: Drug: Atenolol. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/atenolol/
55. National Institute for Health and Care Excellence. BNF: Drug: Glyceryl trinitrate. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/glyceryl-trinitrate/
56. American Diabetes Association. Chronic Kidney Disease and Type 2 Diabetes. Chronic Kidney Disease and Type 2 Diabetes. American Diabetes Association. Chronic. Arlington VA. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK571714/
57. National Kidney Foundation. Diabetes - A Major Risk Factor for Kidney Disease. [Internet] [cited 2022 October 14]. Available from: https://www.kidney.org/atoz/content/diabetes
58. Bharucha AE, Kudva YC, Prichard DO. Diabetic Gastroparesis. Endocr Rev. 2019 May 10;40(5):1318. Available from: /pmc/articles/PMC6736218/
59. National Institute for Health and Care Excellence. BNF: Drug: Erythromycin. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/erythromycin/#side-effects
60. National Institute for Health and Care Excellence. BNF: Drug: Metoclopramide hydrochloride. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/metoclopramide-hydrochloride/#side-effects
61. Ziegler D. Painful diabetic neuropathy: treatment and future aspects. Diabetes Metab Res Rev. 2008 May 1;24(S1):S52–7. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/dmrr.817
62. Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. Diab

Vasc Dis Res. 2006 Sep;3(2):108–19. Available from: https://pubmed.ncbi.nlm.nih.gov/17058631/

63. National Institute for Health and Care Excellence. Neuropathic pain in adults: pharmacological management in non-specialist settings. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/cg173/chapter/1-Recommendations
64. National Institute for Health and Care Excellence. BNF: Drug: Carbamazepine. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/carbamazepine/#side-effects
65. Diabetes UK. Diabetes and Erectile Dysfunction. [Internet] [cited 2022 October 14]. Available from: https://www.diabetes.co.uk/diabetes-erectile-dysfunction.html
66. National Institute for Health and Care Excellence. BNF: Drug: Sildenafil. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/sildenafil/#side-effects
67. Diabetic foot problems: prevention and management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng19/chapter/Recommendations#diabetic-foot-infection
68. National Institute for Health and Care Excellence. BNF: Treatment summary: Diarrhoea (acute). [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/treatment-summary/diarrhoea-acute.html
69. National Institute for Health and Care Excellence. BNF: Drug: Loperamide hydrochloride. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/loperamide-hydrochloride/#side-effects
70. National Institute for Health and Care Excellence. BNF: Treatment summary: Urinary-tract infections. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/treatment-summary/urinary-tract-infections.html
71. Kolb L. An Effective Model of Diabetes Care and Education: The ADCES7 Self-Care BehaviorsTM. The Science of Diabetes Self-Management and Care. 2021;47(1):30-53. Available from: https://journals.sagepub.com/doi/full/10.1177/0145721720978154
72. Ali S, Stone MA, Peters JL, Davies MJ, Khunti K. The prevalence of co-morbid depression in adults with Type 2 diabetes: a systematic review and meta-analysis. Diabet Med. 2006 Nov;23(11):1165–73. Available from: https://pubmed.ncbi.nlm.nih.gov/17054590/

73. Lin EH, Von Korff M, Alonso J, Angermeyer MC, Anthony J, Bromet E, Bruffaerts R, Gasquet I, de Girolamo G, Gureje O, Haro JM, Karam E, Lara C, Lee S, Levinson D, Ormel JH, Posada-Villa J, Scott K, Watanabe M, Williams D. Mental disorders among persons with diabetes--results from the World Mental Health Surveys. J Psychosom Res. 2008;65(6):571–80. Available from: https://pubmed.ncbi.nlm.nih.gov/19027447/
74. Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. Diabetes Care. 2008 Dec;31(12):2383–90. Available from: https://pubmed.ncbi.nlm.nih.gov/19033418/
75. Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. Curr Diab Rep. 2010 Dec;10(6):396–405. Available from: https://pubmed.ncbi.nlm.nih.gov/20878274/
76. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008 Jan;9(1):46–56. Available from: https://pubmed.ncbi.nlm.nih.gov/18073775/
77. Courtet P, Olié E. Circadian dimension and severity of depression. Eur Neuropsychopharmacol. 2012;22 Suppl 3(SUPPL3). Available from: https://pubmed.ncbi.nlm.nih.gov/22959112/
78. Gangwisch JE. Epidemiological evidence for the links between sleep, circadian rhythms and metabolism. Obes Rev. 2009 Nov;10 Suppl 2(0 2):37–45. Available from: https://pubmed.ncbi.nlm.nih.gov/19849800/
79. Harris MD. Psychosocial aspects of diabetes with an emphasis on depression. Curr Diab Rep. 2003;3(1):49–55. Available from: https://pubmed.ncbi.nlm.nih.gov/12643146/
80. Nouwen A, Winkley K, Twisk J, Lloyd CE, Peyrot M, Ismail K, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. Diabetologia. 2010 Dec;53(12):2480–6. Available from: https://pubmed.ncbi.nlm.nih.gov/20711716/
81. WHO Global Report on Diabetes. Global Report on Diabetes. [Internet] 2016 [cited 2022 October 14];978:6–86. Available from: https://sci-hub.si/https://apps.who.int/iris/handle/10665/204874%0Ahttps://apps.who.int/iris/bitstream/handle/10665/204874/WHO_NMH_NVI_16.3_eng.pdf?sequence=1%0Ahttp://

www.who.int/about/licensing/copyright_form/index.html%0Ahttp://www.who.int/about/licens

82. World Health Organisation. Depression. [Internet] [cited 2022 October 14]. Available from: https://www.who.int/news-room/fact-sheets/detail/depression
83. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and Diabetes Treatment Nonadherence: A Meta-Analysis. Diabetes Care. 2008 Dec;31(12):2398. Available from: /pmc/articles/PMC2584202/
84. de Groot, Mary PhD; Anderson, Ryan BA; Freedland, Kenneth E. PhD; Clouse, Ray E. MD; Lustman, Patrick J. PhD. Association of Depression and Diabetes Complications: A Meta-Analysis. Psychosom Med. 2001 Jul;63(4):619–30. Available from: https://journals.lww.com/psychosomaticmedicine/Fulltext/2001/07000/Association_of_Depression_and_Diabetes.15.aspx
85. Salvi V, Grua I, Cerveri G, Mencacci C, Barone-Adesi F. The risk of new-onset diabetes in antidepressant users - A systematic review and meta-analysis. PLoS One. 2017 Jul 1;12(7). Available from: https://pubmed.ncbi.nlm.nih.gov/28759599/
86. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. BMJ. 2015 Mar 11;350. Available from: https://www.bmj.com/content/350/bmj.h1059
87. National Institute for Health and Care Excellence. BNF: Drug: MIRTAZAPINE. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/mirtazapine.html
88. National Institute for Health and Care Excellence. BNF: Drug: SERTRALINE. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/sertraline.html
89. Baumeister H, Hutter N, Bengel J. Psychological and pharmacological interventions for depression in patients with diabetes mellitus and depression. Cochrane Database of Systematic Reviews. 2012 Dec 12; Available from: http://doi.wiley.com/10.1002/14651858.CD008381.pub2
90. Roopan S, Larsen ER. Use of antidepressants in patients with depression and comorbid diabetes mellitus: a systematic review. 2016; Available from: https://doi.org/10.1017/neu.2016.54

91. Duerden M, Payne R. Polypharmacy and medicines optimisation Making it safe and sound Authors. [Internet] [cited on 2022 October 14]. Available from: http://www.kingsfund.org.uk/publications
92. NHS Digital. Health Survey for England, 2016. [Internet] [cited on 2022 October 14]. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/health-survey-for-england/health-survey-for-england-2016
93. Gao L, Maidment I, Matthews FE, Robinson L, Brayne C. Medication usage change in older people (65+) in England over 20 years: findings from CFAS I and CFAS II. Age Ageing. 2018 Mar 1;47(2):220–5. Available from: https://academic.oup.com/ageing/article/47/2/220/4237359
94. Aronson JK. In defence of polypharmacy. Br J Clin Pharmacol. 2004 Feb;57(2):119. Available from: /pmc/articles/PMC1884429/
95. Aronson JK. Polypharmacy, appropriate and inappropriate. The British Journal of General Practice. 2006 Jul;56(528):484. Available from: /pmc/articles/PMC1872056/
96. Payne RA, Abel GA, Avery AJ, Mercer SW, Roland MO. Is polypharmacy always hazardous? A retrospective cohort analysis using linked electronic health records from primary and secondary care. Br J Clin Pharmacol. 2014 ;77(6):1073–82. Available from: https://pubmed.ncbi.nlm.nih.gov/24428591/
97. World Health Organisation. Promoting rational use of medicines. [Internet] [cited on 2022 October 14]. Available from: https://www.who.int/activities/promoting-rational-use-of-medicines
98. Royal Pharmaceutical Society. Polypharmacy: Getting our medicines right. [Internet] [cited on 2022 October 14]. Available from: https://www.rpharms.com/recognition/setting-professional-standards/polypharmacy-getting-our-medicines-right#background
99. Petty DR, Zermansky AG, Alldred DP. The scale of repeat prescribing - Time for an update. BMC Health Serv Res. 2014 Feb 19;14(1):1–4. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/1472-6963-14-76
100. Baird B, Charles A, Honeyman M, Maguire D, Das P. The King's Fund; 2016. Understanding pressures in general practice. Available from: https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/Understanding-GP-pressures-Kings-Fund-May-2016.pdf

101. Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs Aging. 2014 Apr;31(4):283–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24604085/
102. Garfinkel D, IGRIMUP. Overview of current and future research and clinical directions for drug discontinuation: psychological, traditional and professional obstacles to deprescribing. European Journal of Hospital Pharmacy. 2017 Jan 1;24(1):16–20. Available from: https://ejhp.bmj.com/content/24/1/16
103. Angamo MT, Chalmers L, Curtain CM, Bereznicki LRE. Adverse-Drug-Reaction-Related Hospitalisations in Developed and Developing Countries: A Review of Prevalence and Contributing Factors. Drug Saf. 2016 Sep 1;39(9):847–57. Available from: https://link.springer.com/article/10.1007/s40264-016-0444-7
104. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ. 2004 Jul 1;329(7456):15–9. Available from: https://www.bmj.com/content/329/7456/15
105. Smith R. The drugs don't work. BMJ. 2003 Dec 11;327(7428). Available from: https://www.bmj.com/content/327/7428/0.9
106. Moore A, Derry S, Eccleston C, Kalso E. Expect analgesic failure; pursue analgesic success. BMJ. 2013 May 3;346(7911). Available from: https://www.bmj.com/content/346/bmj.f2690
107. National Institute of Health and Care Excellence. BNF: Drug: AMITRIPTYLINE HYDROCHLORIDE. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/amitriptyline-hydrochloride.html
108. Ruxton K, Woodman RJ, Mangoni AA. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: A systematic review and meta-analysis. Br J Clin Pharmacol. 2015 Aug 1;80(2):209–20. Available from: https://pubmed.ncbi.nlm.nih.gov/25735839/
109. van Spall HGC, Toren A, Kiss A, Fowler RA. Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals: A Systematic Sampling Review. JAMA. 2007 Mar;297(11):1233–40. Available from: https://jamanetwork.com/journals/jama/fullarticle/206151

110. Masoudi FA, Havranek EP, Wolfe P, Gross CP, Rathore SS, Steiner JF, et al. Most hospitalized older persons do not meet the enrollment criteria for clinical trials in heart failure. Am Heart J. 2003 Aug 1;146(2):250–7.
111. Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, et al. External validity of randomized controlled trials in COPD. Respir Med. 2007 Jun 1 [cited 2022 Apr 25];101(6):1313–20. Available from: http://www.resmedjournal.com/article/S0954611106005087/fulltext
112. National Institute for Health and Care Excellence. Multimorbidity: clinical assessment and management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng56
113. U.S. Food and Drug Administration. Drug Interactions: What You Should Know. [Internet] [cited 2022 October 14]. Available from: https://www.fda.gov/drugs/resources-you-drugs/drug-interactions-what-you-should-know
114. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995-2010. BMC Med. 2015 Dec 12;13(1):1–10. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-015-0322-7
115. Zhan C, Correa-De-Araujo R, Bierman AS, Sangl J, Miller MR, Wickizer SW, et al. Suboptimal prescribing in elderly outpatients: potentially harmful drug-drug and drug-disease combinations. J Am Geriatr Soc. 2005 Feb;53(2):262–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15673350/
116. Open Prescribing. Citalopram hydrochloride. [Internet] [cited 2022 October 14]. Available from: https://openprescribing.net/chemical/0403030Z0/
117. National Institute for Health and Care Excellence. BNF: Interactions: Citalopram. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/interaction/citalopram-2.html
118. Age UK. More Harm Than Good. [Internet] [cited 2022 October 14]. Available from: https://www.ageuk.org.uk/globalassets/age-uk/documents/reports-and-publications/reports-and-briefings/health--wellbeing/medication/190819_more_harm_than_good.pdf
119. Tatonetti NP, Denny JC, Murphy SN, Fernald GH, Krishnan G, Castro V, et al. Detecting Drug Interactions From Adverse-Event Reports: Interaction Between Paroxetine and Pravastatin Increases Blood Glucose Levels. Clin Pharmacol Ther.

2011 Jul 1;90(1):133–42. Available from: https://onlinelibrary.wiley.com/doi/full/10.1038/clpt.2011.83

120. Farrell B, French Merkley V, Ingar N. Reducing pill burden and helping with medication awareness to improve adherence. Canadian Pharmacists Journal : CPJ. 2013 Sep 1;146(5):262. Available from: /pmc/articles/PMC3785195/
121. National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/cg76/chapter/Introduction
122. World Health Organisation. Adherence to Long-Term Therapies - Evidence for Action. [Internet] [cited 2022 October 14]. Available from: http://apps.who.int/iris/bitstream/handle/10665/42682/9241545992.pdf?sequence=1
123. Ho PM, Rumsfeld JS, Masoudi FA, McClure DL, Plomondon ME, Steiner JF, et al. Effect of medication nonadherence on hospitalization and mortality among patients with diabetes mellitus. Arch Intern Med. 2006 Sep 25;166(17):1836–41. Available from: https://pubmed.ncbi.nlm.nih.gov/17000939/
124. World Health Organisation. Medication safety in polypharmacy: technical report. [Internet] [cited 2022 October 14]. Available from: https://www.who.int/publications/i/item/WHO-UHC-SDS-2019.11
125. National Institute for Health and Care Excellence. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/cg76
126. Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs Aging. 2014 Apr 1;31(4):283–9. Available from: https://link.springer.com/article/10.1007/s40266-014-0163-7
127. Stoehr GP, Lu SY, Lavery L, Bilt J vander, Saxton JA, Chang CCH, et al. Factors associated with adherence to medication regimens in older primary care patients: the Steel Valley Seniors Survey. Am J Geriatr Pharmacother. 2008 Dec;6(5):255–63. Available from: https://pubmed.ncbi.nlm.nih.gov/19161928/
128. Schenker Y, Park SY, Jeong K, Pruskowski J, Kavalieratos D, Resick J, et al. Associations Between Polypharmacy, Symptom Burden, and Quality of Life in Patients with Advanced, Life-Limiting Illness. J Gen Intern Med. 2019 Apr 15 [cited

2022 Apr 28];34(4):559–66. Available from: https://link.springer.com/article/10.1007/s11606-019-04837-7

129. Machón M, Larrañaga I, Dorronsoro M, Vrotsou K, Vergara I. Health-related quality of life and associated factors in functionally independent older people. BMC Geriatr. 2017 Jan 14 ;17(1). Available from: /pmc/articles/PMC5237562/
130. McLean S, Sheehy-Skeffington B, O'Leary N, O'Gorman A. Pharmacological management of co-morbid conditions at the end of life: is less more? Ir J Med Sci. 2013 Mar;182(1):107–12. Available from: https://pubmed.ncbi.nlm.nih.gov/22843427/
131. Palapinyo S, Methaneethorn J, Leelakanok N. Association between polypharmacy and depression: a systematic review and meta-analysis. Journal of Pharmacy Practice and Research. 2021 Aug 1;51(4):280–99. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/jppr.1749
132. Kuijpers MAJ, van Marum RJ, Egberts ACG, Jansen PAF. Relationship between polypharmacy and underprescribing. Br J Clin Pharmacol. 2008 Jan ;65(1):130. Available from: /pmc/articles/PMC2291281/
133. Tournier M, Cougnard A, Boutouaba-Combe S, Verdoux H. [Duration of antidepressant drug treatment and its determinants in France]. Encephale. 2011;37 Suppl 1(SUPPL. 1). Available from: https://pubmed.ncbi.nlm.nih.gov/21600331/
134. Olfson M, Marcus SC, Tedeschi M, Wan GJ. Continuity of antidepressant treatment for adults with depression in the United States. Am J Psychiatry. 2006 Jan;163(1):101–8. Available from: https://pubmed.ncbi.nlm.nih.gov/16390896/
135. Mars B, Heron J, Kessler D, Davies NM, Martin RM, Thomas KH, et al. Influences on antidepressant prescribing trends in the UK: 1995-2011. Soc Psychiatry Psychiatr Epidemiol. 2017 Feb 1;52(2):193–200. Available from: https://pubmed.ncbi.nlm.nih.gov/27885400/
136. Zhan C, Correa-De-Araujo R, Bierman AS, Sangl J, Miller MR, Wickizer SW, et al. Suboptimal prescribing in elderly outpatients: potentially harmful drug-drug and drug-disease combinations. J Am Geriatr Soc. 2005 Feb;53(2):262–7. Available from: https://pubmed.ncbi.nlm.nih.gov/15673350/
137. National Institute for Health and Care Excellence. Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence.. NICE Guidelines. 2009. p. 1–31. Available from: https://www.nice.org.uk/guidance/cg76
138. Buckman JEJ, Underwood A, Clarke K, Saunders R, Hollon SD, Fearon P, et al. Risk factors for relapse and recurrence of depression in adults and how they

operate: A four-phase systematic review and meta-synthesis. Clin Psychol Rev. 2018 Aug 1;64:13–38. Available from: https://pubmed.ncbi.nlm.nih.gov/30075313/

139. Saunders R, Cohen ZD, Ambler G, DeRubeis RJ, Wiles N, Kessler D, et al. A Patient Stratification Approach to Identifying the Likelihood of Continued Chronic Depression and Relapse Following Treatment for Depression. Journal of Personalized Medicine 2021, Vol 11, Page 1295. 2021 Dec 4;11(12):1295. Available from: https://www.mdpi.com/2075-4426/11/12/1295/htm
140. Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, et al. Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? American Journal of Psychiatry. 2000 Sep 1;157(9):1501–4. Available from: https://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.157.9.1501
141. Sim K, Lau WK, Sim J, Sum MY, Baldessarini RJ. Prevention of Relapse and Recurrence in Adults with Major Depressive Disorder: Systematic Review and Meta-Analyses of Controlled Trials. Int J Neuropsychopharmacol. 2015 Feb 1;19(2). Available from: https://pubmed.ncbi.nlm.nih.gov/26152228/
142. Iosifescu D v., Nierenberg AA, Alpert JE, Papakostas GI, Perlis RH, Sonawalla S, et al. Comorbid Medical Illness and Relapse of Major Depressive Disorder in the Continuation Phase of Treatment. Psychosomatics. 2004 Sep 1;45(5):419–25.
143. Walker AE. Multiple chronic diseases and quality of life: patterns emerging from a large national sample, Australia. Chronic Illn. 2007 Sep;3(3):202–18. Available from: https://pubmed.ncbi.nlm.nih.gov/18083677/
144. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. The Lancet. 2003 Feb 22;361(9358):653–61.
145. Glue P, Donovan MR, Kolluri S, Emir B. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. Australian and New Zealand Journal of Psychiatry. 2010 Aug 1;44(8):697–705. Available from: https://journals.sagepub.com/doi/10.3109/00048671003705441
146. Williams N, Simpson AN, Simpson K, Nahas Z. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. Hum Psychopharmacol. 2009;24(5):401–8. Available from: https://pubmed.ncbi.nlm.nih.gov/19526453/
147. Lee HM, Yang YC, Chen SF, Hsu CY, Shen YC. Risk of hyperglycemic crisis episode in diabetic patients with depression: A nationwide population-based cohort study. J Diabetes Complications. 2020 Mar 1;34(3).

148. Noordam R, Aarts N, Peeters RP, Hofman A, Stricker BH, Visser LE. Selective Serotonin Reuptake Inhibitors Decrease Pancreatic Insulin Secretion in Older Adults and Increase the Risk of Insulin Dependence in Type 2 Diabetes Patients. J Clin Psychiatry. 2016 Sep 1;77(9):e1124–9. Available from: https://pubmed.ncbi.nlm.nih.gov/27487004/
149. Derijks HJ, Meyboom RHB, Heerdink ER, de Koning FHP, Janknegt R, Lindquist M, et al. The association between antidepressant use and disturbances in glucose homeostasis: Evidence from spontaneous reports. Eur J Clin Pharmacol. 2008 May 15;64(5):531–8. Available from: https://link.springer.com/article/10.1007/s00228-007-0441-y
150. Our World in Data. Causes of death. [Internet] [cited 2022 October 14]. Available from: https://ourworldindata.org/causes-of-death
151. Arya S, Lee S, Zahner GJ, Cohen BE, Hiramoto J, Wolkowitz OM, et al. The Association Of Co-Morbid Depression With Mortality And Amputation In Veterans With Peripheral Artery Disease. J Vasc Surg. 2018 Aug 1;68(2):536. Available from: /pmc/articles/PMC6057818/
152. Chen HM, Yang YH, Chen KJ, Lee Y, McIntyre RS, Lu ML, et al. Antidepressants Reduced Risk of Mortality in Patients With Diabetes Mellitus: A Population-Based Cohort Study in Taiwan. J Clin Endocrinol Metab. 2019 Oct 1;104(10):4619–25. Available from: https://academic.oup.com/jcem/article/104/10/4619/5526757
153. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of Depression and Diabetes Complications: A Meta-Analysis. Psychosom Med. 2001 Jul;63(4):619–30.
154. Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care. 2000 Jul 1;23(7):934–42. Available from: https://diabetesjournals.org/care/article/23/7/934/23870/Depression-and-poor-glycemic-control-a-meta
155. Brent DA. Antidepressants and Suicidality. Psychiatric Clinics of North America. 2016 Sep 1;39(3):503–12.
156. Sørensen HT, Lash TL, Rothman KJ. Beyond randomized controlled trials: a critical comparison of trials with nonrandomized studies. Hepatology. 2006 Nov;44(5):1075–82. Available from: https://pubmed.ncbi.nlm.nih.gov/17058242/

157. Silverman SL. From randomized controlled trials to observational studies. Am J Med. 2009 Feb;122(2):114–20. Available from: https://pubmed.ncbi.nlm.nih.gov/19185083/
158. Khazaie H, Rahimi M, Tatari F, Rezaei M, Najafi F, Tahmasian M. From the Departments of Psychiatry (Khazaie, Tatari, Tahmasian) and Endocrinology (Rahimi), the Kermanshah Health Research Center. Neurosciences. 2011;16(1):42–5.
159. Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH, et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. Psychosom Med. 1997;59(3):241–50. Available from: https://pubmed.ncbi.nlm.nih.gov/9178335/
160. Komorousová J, Beran J, Rušavý Z, Jankovec Z. Glycemic control improvement through treatment of depression using antidepressant drugs in patients with diabetes mellitus type 1. Neuroendocrinol Lett. 2010;31(6):801–6. Available from: www.nel.edu
161. Echeverry D, Duran P, Bonds C, Lee M, Davidson MB. Effect of Pharmacological Treatment of Depression on A1C and Quality of Life in Low-Income Hispanics and African Americans With DiabetesA randomized, double-blind, placebo-controlled trial. Diabetes Care. 2009 Dec 1;32(12):2156–60. Available from: https://diabetesjournals.org/care/article/32/12/2156/26038/Effect-of-Pharmacological-Treatment-of-Depression
162. Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. Diabetes Care. 2000 May 1;23(5):618–23. Available from: https://diabetesjournals.org/care/article/23/5/618/22392/Fluoxetine-for-depression-in-diabetes-a-randomized
163. Padmanabhan S, Carty L, Cameron E, Ghosh RE, Williams R, Strongman H. Approach to record linkage of primary care data from Clinical Practice Research Datalink to other health-related patient data: overview and implications. Eur J Epidemiol. 2019 Jan 15;34(1):91–9. Available from: https://link.springer.com/article/10.1007/s10654-018-0442-4
164. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed patients with type 2 diabetes treated with paroxetine: A double-blind randomised placebo controlled 6-month trial. BMC Fam Pract. 2007 Jun

15;8(1):1–7. Available from: https://bmcprimcare.biomedcentral.com/articles/10.1186/1471-2296-8-34

165. Paile-Hyvärinen M, Wahlbeck K, Eriksson JG. Quality of life and metabolic status in mildly depressed women with type 2 diabetes treated with paroxetine: A single-blind randomised placebo controlled trial. BMC Fam Pract. 2003 May 14;4(1):1–6. Available from: https://bmcprimcare.biomedcentral.com/articles/10.1186/1471-2296-4-7
166. Gülseren L, Gülseren S, Hekimsoy Z, Mete L. Comparison of Fluoxetine and Paroxetine in Type II Diabetes Mellitus Patients. Arch Med Res. 2005 Mar 4;36(2):159–65.
167. Tamblyn R, Mcleod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. Med Care. 2003 Aug;41(8):895–908.
168. Galdas PM, Cheater F, Marshall P. Men and health help-seeking behaviour: literature review. J Adv Nurs. 2005 Mar;49(6):616–23. Available from: https://pubmed.ncbi.nlm.nih.gov/15737222/
169. Polacsek M, Boardman GH, McCann T v. Help-seeking experiences of older adults with a diagnosis of moderate depression. Int J Ment Health Nurs. 2019 Feb 1;28(1):278–87. Available from: https://pubmed.ncbi.nlm.nih.gov/30120874/
170. Lipson SK, Zhou S, Abelson S, Heinze J, Jirsa M, Morigney J, et al. Trends in college student mental health and help-seeking by race/ethnicity: Findings from the national healthy minds study, 2013-2021. J Affect Disord. 2022 Jun;306:138–47. Available from: https://pubmed.ncbi.nlm.nih.gov/35307411/
171. Inequalities in health care for people with depression and/or anxiety - The Health Foundation. Available from: https://www.health.org.uk/publications/long-reads/inequalities-in-health-care-for-people-with-depression-and-anxiety
172. Tolmie EP, Mungall MMB, Louden G, Lindsay GM, Gaw A. Understanding why older people participate in clinical trials: the experience of the Scottish PROSPER participants. Age Ageing. 2004 Jul 1;33(4):374–8. Available from: https://academic.oup.com/ageing/article/33/4/374/17976
173. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005 Apr 1;58(4):323–37.

174. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, Staa T van, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015 Jun 1;44(3):827–36. Available from: https://pubmed.ncbi.nlm.nih.gov/26050254/
175. Wolf A, Dedman D, Campbell J, Booth H, Lunn D, Chapman J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. Int J Epidemiol. 2019 Dec 1;48(6):1740-1740G.
176. Santos Cavaiola T, Kiriakov Y, Reid T. Primary Care Management of Patients With Type 2 Diabetes: Overcoming Inertia and Advancing Therapy With the Use of Injectables. Clin Ther. 2019 Feb 1;41(2):352–67. Available from: http://www.clinicaltherapeutics.com/article/S0149291818305952/fulltext
177. van der Feltz-Cornelis CM, Nuyen J, Stoop C, Chan J, Jacobson AM, Katon W, et al. Effect of interventions for major depressive disorder and significant depressive symptoms in patients with diabetes mellitus: a systematic review and meta-analysis. Gen Hosp Psychiatry. 2010 Jul 1;32(4):380–95.
178. Derijks HJ, Heerdink ER, de Koning FH, Janknegt R, Klungel OH, Egherts AC. The association between antidepressant use and hypoglycaemia in diabetic patients: a nested case-control study. Pharmacoepidemiol Drug Saf. 2008 Apr;17(4):336–44. Available from: https://pubmed.ncbi.nlm.nih.gov/18302302/
179. Wang J, Wu X, Lai W, Long E, Zhang X, Li W, et al. Prevalence of depression and depressive symptoms among outpatients: a systematic review and meta-analysis. BMJ Open. 2017 Aug 1;7(8):e017173. Available from: https://bmjopen.bmj.com/content/7/8/e017173
180. Search strategies for the identification of clinical studies - Depression in Adults with a Chronic Physical Health Problem - NCBI Bookshelf. Available from: https://www.ncbi.nlm.nih.gov/books/NBK82908/
181. Internal Clinical Guidelines Team N. Type 2 diabetes search strategies. Available from: https://www.nice.org.uk/guidance/ng28/update/NG28/documents/type-2-diabetes-search-strategies2
182. Kato M, Hori H, Inoue T, Iga J, Iwata M, Inagaki T, et al. Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis. Molecular Psychiatry 2020 26:1. 2020 Jul 23;26(1):118–33. Available from: https://www.nature.com/articles/s41380-020-0843-0

183. Li L, Smith HE, Atun R, Tudor Car L. Search strategies to identify observational studies in MEDLINE and Embase. Cochrane Database of Systematic Reviews. 2019 Mar 12;2019(10). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000041.pub2/full
184. Ottawa Hospital Research Institute. [cited 2022 Mar 3]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
185. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: A critical appraisal of guidelines and practice. J Health Serv Res Policy. 2002 Jun 24;7(1):51–61. Available from: https://journals.sagepub.com/doi/10.1258/1355819021927674
186. Binsaleh AY, Perez A, Popovici I, Rabionet SE. Impact of Antidepressant Use on Healthcare Utilization among Individuals with Type 2 Diabetes and Depression Symptoms in the United States: Sociodemographic, Clinical, and Behavioral Factors Matter. International Journal of Environmental Research and Public Health 2018, Vol 15, Page 1904. 2018 Sep 1;15(9):1904. Available from: https://www.mdpi.com/1660-4601/15/9/1904/htm
187. Brieler JA, Lustman PJ, Scherrer JF, Salas J, David Schneider F. Antidepressant medication use and glycaemic control in co-morbid type 2 diabetes and depression. Fam Pract. 2016 Feb 1;33(1):30–6. Available from: https://academic.oup.com/fampra/article/33/1/30/2450462
188. Chen HY, Ruppert K, Charron-Prochownik D, Noullet W v., Zgibor JC. Effects of depression and antidepressant use on goal setting and barrier identification among patients with type 2 diabetes. Diabetes Educator. 2011 May 1;37(3):370–80. Available from: https://journals.sagepub.com/doi/10.1177/0145721711400662
189. Higgins TS, Ritchie CS, Stetson BA, Burke JD, Looney SW. An examination of the moderating effect of treatment with anti-depressants on the association of heart disease with depression in males with type 2 diabetes attending a Veterans Affairs Medical Center. Diabetes Res Clin Pract. 2007 Feb 1;75(2):220–8.
190. Shrestha SS, Zhang P, Li R, Thompson TJ, Chapman DP, Barker L. Medical expenditures associated with major depressive disorder among privately insured working-age adults with diagnosed diabetes in the United States, 2008. Diabetes Res Clin Pract. 2013 Apr 1;100(1):102–10.
191. Wagner JA, Perkins DW, Piette JD, Lipton B, Aikens JE. Racial differences in the discussion and treatment of depressive symptoms accompanying type 2 diabetes.

Diabetes Res Clin Pract. 2009 Nov;2(86):111–6. Available from: https://www.infona.pl//resource/bwmeta1.element.elsevier-bbfd6d3c-b24f-3045-99e5-5aab9f48f470

192. Whitworth SR, Bruce DG, Starkstein SE, Davis WA, Davis TME, Skinner TC, et al. Depression symptoms are persistent in Type 2 diabetes: risk factors and outcomes of 5-year depression trajectories using latent class growth analysis. Diabetic Medicine. 2017 Aug 1;34(8):1108–15. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13372
193. Shrestha M, Al-Ghareeb A, Alenazi F, Gray R. Association between subthreshold depression and self-care behaviour in people with type 2 diabetes: a protocol for systematic review of observational studies. Syst Rev. 2019 Jul 12;8(1):167. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31300045
194. Abrahamian H, Hofmann P, Prager R, Toplak H. Diabetes mellitus and co-morbid depression: Treatment with milnacipran results in significant improvement of both diseases (results from the Austrian MDDM study group). Neuropsychiatr Dis Treat. 2009;5(1):261–6.
195. Abrahamian H, Hofmann P, Kinzl J, Toplak H. Diabetes mellitus and comorbid depression: Improvement of both diseases with milnacipran. a replication study (results of the Austrian major depression diabetes mellitus study group). Neuropsychiatr Dis Treat. 2012 Aug 13;8:355–60.
196. Acee AM, Fahs MC. Can treating depression improve diabetic management? Nurse Practitioner. 2012 Jan 19;37(1):46–52. Available from: https://journals.lww.com/tnpj/Fulltext/2012/01000/Can_treating_depression_improve_diabetic.9.aspx
197. Alenzi EO, Sambamoorthi U. Depression treatment and health-related quality of life among adults with diabetes and depression. Quality of Life Research. 2016 Jun 1;25(6):1517–25.
198. Amital D, Fostick L, Silberman A, Calati R, Spindelegger C, Serretti A, et al. Physical co-morbidity among treatment resistant vs. treatment responsive patients with major depressive disorder. European Neuropsychopharmacology. 2013 Aug 1;23(8):895–901.
199. Bhattacharya R, Shen C, Wachholtz AB, Dwibedi N, Sambamoorthi U. Depression treatment decreases healthcare expenditures among working age patients with comorbid conditions and type 2 diabetes mellitus along with newly-diagnosed

depression. BMC Psychiatry. 2016 Jul 19;16(1):1–14. Available from: https://link.springer.com/articles/10.1186/s12888-016-0964-9

200. Bryan C, Songer T, Brooks MM, Rush AJ, Thase ME, Gaynes B, et al. The impact of diabetes on depression treatment outcomes. Gen Hosp Psychiatry. 2010 Jan 1;32(1):33–41.
201. Caughey GE, Preiss AK, Vitry AI, Gilbert AL, Ryan P, Shakib S, et al. Does antidepressant medication use affect persistence with diabetes medicines? Pharmacoepidemiol Drug Saf. 2013 Jun 1;22(6):615–22. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3424
202. Danhauer SC, Brenes GA, Levine BJ, Young L, Tindle HA, Addington EL, et al. Variability in sleep disturbance, physical activity and quality of life by level of depressive symptoms in women with Type 2 diabetes. Diabetic Medicine. 2019 Sep 1;36(9):1149–57. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.13878
203. Filipčić I, Margetić B, Šimunović I, Jakovljević M. DEPRESSION TREATMENT AND ITS IMPACT UPON THE QUALITY OF LIFE IN PATIENTS WITH DIABETES TYPE 2-THE CROATIAN STUDY. Psychiatr Danub. 2010;22(2):231–5.
204. Hazuda HP, Gaussoin SA, Wing RR, Yanovski SZ, Johnson KC, Coday M, et al. Long-term Association of Depression Symptoms and Antidepressant Medication Use With Incident Cardiovascular Events in the Look AHEAD (Action for Health in Diabetes) Clinical Trial of Weight Loss in Type 2 Diabetes. Diabetes Care. 2019 May 1;42(5):910–8. Available from: https://diabetesjournals.org/care/article/42/5/910/40513/Long-term-Association-of-Depression-Symptoms-and
205. Kammer JR, Hosler AS, Leckman-Westin E, Dirienzo G, Osborn CY. The association between antidepressant use and glycemic control in the Southern Community Cohort Study (SCCS). J Diabetes Complications. 2016 Mar 1;30(2):242–7.
206. Kammer J, Hosler AS, Leckman-Westin E, DiRienzo AG. Use of antidepressant medications not associated with A1C among individuals with diabetes in NHANES sample. Prim Care Diabetes. 2016 Oct 1;10(5):360–8.
207. Kammer J, Hosler AS, Leckman-Westin E, DiRienzo AG. The association between antidepressant use and hemoglobin A1C in older adults. Geriatr Nurs (Minneap). 2017 Mar 1;38(2):141–5.

208. Katon WJ. The Comorbidity of Diabetes Mellitus and Depression. Am J Med. 2008 Nov 1;121(11):S8–15.
209. Katon WJ, Russo JE, von Korff M, Lin EHB, Ludman E, Ciechanowski PS. Long-Term Effects on Medical Costs of Improving Depression Outcomes in Patients With Depression and Diabetes. Diabetes Care. 2008 Jun;31(6):1155–9. Available from: /pmc/articles/PMC3810023/
210. Katon WJ. Epidemiology and treatment of depression in patients with chronic medical illness. Dialogues Clin Neurosci. 2011;13(1):7. Available from: /pmc/articles/PMC3181964/
211. Katon W, Lyles CR, Parker MM, Karter AJ, Huang ES, Whitmer RA. Association of Depression With Increased Risk of Dementia in Patients With Type 2 Diabetes: The Diabetes and Aging Study. Arch Gen Psychiatry. 2012 Apr 1;69(4):410–7. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/1151060
212. Katon W, Pedersen HS, Ribe AR, Fenger-Grøn M, Davydow D, Waldorff FB, et al. Effect of Depression and Diabetes Mellitus on the Risk for Dementia: A National Population-Based Cohort Study. JAMA Psychiatry. 2015 Jun 1;72(6):612–9. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2272732
213. Keating P, O'Connor R, O'Doherty J, Hannigan A, Cullen W, Hickey L, et al. Prescription of psychotropic medication in patients with type two diabetes mellitus: A multi-practice study from Ireland. https://doi.org/101080/1381478820191640208. 2019;25(3):157–63. Available from: https://www.tandfonline.com/doi/abs/10.1080/13814788.2019.1640208
214. Keitner GI, Ryan CE, Miller IW, Kohn R, Epstein NB. 12-month outcome of patients with major depression and comorbid psychiatric or medical illness (compound depression). https://doi.org/101176/ajp1483345. 2006 Apr 1;148(3):345–50. Available from: https://ajp.psychiatryonline.org/doi/abs/10.1176/ajp.148.3.345
215. Knol MJ, Derijks HJ, Geerlings MI, Heerdink ER, Souverein PC, Gorter KJ, et al. Influence of antidepressants on glycaemic control in patients with diabetes mellitus. Pharmacoepidemiol Drug Saf. 2008 Jun 1;17(6):577–86. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/pds.1608
216. Labad J, Price JF, Strachan MWJ, Fowkes FGR, Deary IJ, Seckl JR, et al. Leptin levels and depressive symptoms in people with type 2 diabetes: The Edinburgh type 2 diabetes study. Psychosom Med. 2012 Jan;74(1):39–45.

217. Lee AK, Lee CJ, Huang ES, Sharrett AR, Coresh J, Selvin E. Risk factors for severe hypoglycemia in black and white adults with diabetes: The Atherosclerosis Risk in Communities (ARIC) Study. Diabetes Care. 2017 Dec 1;40(12):1661–7. Available from: /pmc/articles/PMC5711330/
218. Lin EHB, Heckbert SR, Rutter CM, Katon WJ, Ciechanowski P, Ludman EJ, et al. Depression and Increased Mortality in Diabetes: Unexpected Causes of Death. The Annals of Family Medicine. 2009 Sep 1;7(5):414–21. Available from: https://www.annfammed.org/content/7/5/414
219. Lunghi C, Moisan J, Grégoire JP, Guénette L. The Association between Depression and Medication Nonpersistence in New Users of Antidiabetic Drugs. Value in Health. 2017 Jun 1;20(6):728–35. Available from: http://www.valueinhealthjournal.com/article/S1098301516337676/fulltext
220. Lunghi C, Zongo A, Moisan J, Grégoire JP, Guénette L. Factors associated with antidiabetic medication non-adherence in patients with incident comorbid depression. J Diabetes Complications. 2017 Jul 1;31(7):1200–6.
221. Lustman PJ, Griffith LS, Freedland KE, Clouse RE. The course of major depression in diabetes. Gen Hosp Psychiatry. 1997 Mar 1;19(2):138–43.
222. Lustman PJ, Williams MM, Sayuk GS, Nix BD, Clouse RE. Factors influencing glycemic control in type 2 diabetes during acute- and maintenance-phase treatment of major depressive disorder with bupropion. Diabetes Care. 2007 Mar;30(3):459–66.
223. Miller MD, Paradis CF, Houck PR, Rifai AH, Mazumdar S, Pollock B, et al. Chronic Medical Illness in Patients With Recurrent Major Depression. The American Journal of Geriatric Psychiatry. 1996 Sep 1;4(4):281–90.
224. Moulton CD, Murray L, Winkley K, Amiel SA, Ismail K, Patel A. Depression and change in occupational functioning in type 2 diabetes. Occup Med (Lond). 2019 Aug 22;69(5):322–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31087077
225. Nicolau J, Rivera R, Francés C, Chacártegui B, Masmiquel L. Treatment of depression in type 2 diabetic patients: Effects on depressive symptoms, quality of life and metabolic control. Diabetes Res Clin Pract. 2013 Aug 1;101(2):148–52.
226. Novak M, Mucsi I, Rhee CM, Streja E, Lu JL, Kalantar-Zadeh K, et al. Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression. Diabetes Care. 2016 Nov 1;39(11):1940–7. Available from:

https://diabetesjournals.org/care/article/39/11/1940/37301/Increased-Risk-of-Incident-Chronic-Kidney-Disease

227. Osborn CY, Trott HW, Buchowski MS, Patel KA, Kirby LD, Hargreaves MK, et al. Racial Disparities in the Treatment of Depression in Low-Income Persons With Diabetes. Diabetes Care. 2010 May 1;33(5):1050–4. Available from: https://diabetesjournals.org/care/article/33/5/1050/26768/Racial-Disparities-in-the-Treatment-of-Depression
228. Pan A, Lucas M, Sun Q, van Dam RM, Franco OH, Willett WC, et al. Increased Mortality Risk in Women With Depression and Diabetes Mellitus. Arch Gen Psychiatry. 2011 Jan 3;68(1):42–50. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/210971
229. Passamonti M, Musazzi L, Pigni M, Testolin E, Mauro D, Torri S, et al. Treatment of depression improves glycated hemoglobin in patients with type 2 diabetes mellitus. Experience in general practice. 2015;35:279–83. Available from: https://www.researchgate.net/publication/292355978_Treatment_of_depression_improves_glycated_hemoglobin_in_patients_with_type_2_diabetes_mellitus_Experience_in_general_practice/citation/download
230. Peyrot M, Rubin RR. Persistence of depressive symptoms in diabetic adults. Diabetes Care. 1999;22(3):448–52. Available from: https://pubmed.ncbi.nlm.nih.gov/10097927/
231. Popkin MK, Callies AL, Mackenzie TB. The Outcome of Antidepressant Use in the Medically Ill. Arch Gen Psychiatry. 1985 Dec 1;42(12):1160–3. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/493708
232. Radojkovic J, Sikanic N, Bukumiric Z, Tadic M, Kostic N, Babic R. Improvement of Glycemic Control in Insulin-Dependent Diabetics with Depression by Concomitant Treatment with Antidepressants. Med Sci Monit. 2016 Jun 22;22:2133. Available from: /pmc/articles/PMC4920101/
233. Rivich J, Kosirog ER, Billups SJ, Petrie JL, Saseen JJ. Social and Psychosocial Determinants of Health Associated With Uncontrolled Diabetes in a Federally Qualified Health Center Population. Diabetes Spectrum. 2019 May 1;32(2):145–51. Available from: https://diabetesjournals.org/spectrum/article/32/2/145/32440/Social-and-Psychosocial-Determinants-of-Health

234. Rizvi SJ, Grima E, Tan M, Rotzinger S, Lin P, McIntyre RS, et al. Treatment-Resistant Depression in Primary Care Across Canada. The Canadian Journal of Psychiatry. 2014;59(7):349–57. Available from: www.TheCJP.ca
235. Rubin RR, Peyrot M, Gaussoin SA, Espeland MA, Williamson D, Faulconbridge LF, et al. Four-Year Analysis of Cardiovascular Disease Risk Factors, Depression Symptoms, and Antidepressant Medicine Use in the Look AHEAD (Action for Health in Diabetes) Clinical Trial of Weight Loss in Diabetes. 2013; Available from: http://care.diabetesjournals.org/lookup/suppl/
236. Rush WA, Whitebird RR, Rush MR, Solberg LI, O'Connor PJ. Depression in Patients with Diabetes: Does It Impact Clinical Goals? The Journal of the American Board of Family Medicine. 2008 Sep 1;21(5):392–7. Available from: https://www.jabfm.org/content/21/5/392
237. Sambamoorthi U, Olfson M, Wei W, Crystal S. Diabetes and Depression Care among Medicaid Beneficiaries. J Health Care Poor Underserved. 2006;17(1):141–61. Available from: https://doi.org/10.1353/hpu.2006.0034https://muse.jhu.edu/article/193743
238. Shen C, Shah N, Findley PA, Sambamoorthi U. Depression treatment and short-term healthcare expenditures among elderly Medicare beneficiaries with chronic physical conditions. J Negat Results Biomed. 2013 Oct 22;12(1):1–10. Available from: https://link.springer.com/articles/10.1186/1477-5751-12-15
239. Simon GE, von Korff M, Lin E. Clinical and functional outcomes of depression treatment in patients with and without chronic medical illness. Psychol Med. 2005 Feb;35(2):271–9. Available from: https://www.cambridge.org/core/journals/psychological-medicine/article/clinical-and-functional-outcomes-of-depression-treatment-in-patients-with-and-without-chronic-medical-illness/BD18B5EAD86E36737596C7903FAB25B2
240. Song HR, Woo YS, Wang HR, Shim IH, Jun TY, Bahk WM. Does mirtazapine interfere with naturalistic diabetes treatment? J Clin Psychopharmacol. 2014;34(5):588–94. Available from: https://journals.lww.com/psychopharmacology/Fulltext/2014/10000/Does_Mirtazapine_Interfere_With_Naturalistic.9.aspx
241. Tuncel E, Durgun O, Peynirci H, Ersoy C. Sexual dysfunction in female patients with type 2 diabetes mellitus: a cross-sectional single-centre study among Turkish patients. http://dx.doi.org/101080/1464727320161266039. 2016 Jul 3;20(3):192–9.

Available from: https://www.tandfonline.com/doi/abs/10.1080/14647273.2016.1266039

242. Unützer J, Schoenbaum M, Katon WJ, Fan MY, Pincus HA, Hogan D, et al. Healthcare Costs Associated with Depression in Medically Ill Fee-for-Service Medicare Participants. J Am Geriatr Soc. 2009 Mar 1;57(3):506–10. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1532-5415.2008.02134.x
243. Viscogliosi G, Donfrancesco C, lo Noce C, Giampaoli S, Vanuzzo D, Carle F, et al. Association Between Antidepressant Medication Use and Prevalence and Control of Cardiovascular Risk Factors in Community-Dwelling Older Adults: The Italian Health Examination Survey 2008–2012. https://home.liebertpub.com/met. 2020 Feb 28;18(2):73–8. Available from: https://www.liebertpub.com/doi/abs/10.1089/met.2019.0088
244. Wami WM, Buntinx F, Bartholomeeusen S, Goderis G, Mathieu C, Aerts M. Influence of chronic comorbidity and medication on the efficacy of treatment in patients with diabetes in general practice. British Journal of General Practice. 2013 Apr 1;63(609):e267–73. Available from: https://bjgp.org/content/63/609/e267
245. Wickström L, Pettersson K. TREATMENT OF DIABETICS WITH MONOAMINE-OXIDASE INHIBITORS. The Lancet. 1964 Nov 7;284(7367):995–7.
246. Williams LH, Miller DR, Fincke G, Lafrance JP, Etzioni R, Maynard C, et al. Depression and incident lower limb amputations in veterans with diabetes. J Diabetes Complications. 2010 Aug 30;25(3):175–82. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/20801060/?tool=EBI
247. Xing S, Calip GS, Leow AD, Kim S, Schumock GT, Touchette DR, et al. The Impact of Depression Medications on Oral Antidiabetic Drug Adherence in Patients with Diabetes and Depression. J Diabetes Complications. 2018 May 1;32(5):492. Available from: /pmc/articles/PMC5920707/
248. Yekta Z, Xie D, Bogner HR, Weber DR, Zhang X, Harhay M, et al. The association of antidepressant medications and diabetic retinopathy among people with diabetes. J Diabetes Complications. 2015 Nov 1;29(8):1077–84.
249. Howren A, Aviña-Zubieta JA, Puyat JH, Esdaile JM, da Costa D, de Vera MA. Defining Depression and Anxiety in Individuals With Rheumatic Diseases Using Administrative Health Databases: A Systematic Review. Arthritis Care Res (Hoboken). 2020 Feb 1;72(2):243–55. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/acr.24048

250. Goldberg O, Goldberg RJ, Oxman TE. PHYSICIANS POSTGRADUATE PRESS, INC. Billing for the Evaluation and Treatment of Adult Depression by the Primary Care Clinician. Prim Care Companion J Clin Psychiatry. 2004;6(1):21–6.
251. Konrad R, Zhang W, Bjarndóttir M, Proaño R. Key considerations when using health insurance claims data in advanced data analyses: an experience report. https://doi.org/101080/2047696520191581433. 2019;9(4):317–25. Available from: https://www.tandfonline.com/doi/abs/10.1080/20476965.2019.1581433
252. A MANIFESTO FOR BETTER MENTAL HEALTH.
253. Ni Y, Liu S, Li J, Li S, Dong T. Patient-perceived service needs and health care utilization in people with type 2 diabetes: A multicenter cross-sectional study. Medicine. 2020 May 22;99(21):e20322. Available from: https://journals.lww.com/md-journal/Fulltext/2020/05220/Patient_perceived_service_needs_and_health_care.71.aspx
254. Read JR, Sharpe L, Modini M, Dear BF. Multimorbidity and depression: A systematic review and meta-analysis. J Affect Disord. 2017 Oct 15;221:36–46. Available from: https://pubmed.ncbi.nlm.nih.gov/28628766/
255. ICD - ICD-9-CM - International Classification of Diseases, Ninth Revision, Clinical Modification. Centers for Disease Control and Prevention. 2011. Available from: https://www.cdc.gov/nchs/icd/icd9cm.htm
256. Royal College of General Practitioners. Coding, Classification and Diagnosis of Diabetes A review of the coding, classification and diagnosis of diabetes in primary care in England with recommendations for improvement. [Internet] 2011 [cited on 2022 October 14]. Available from: https://orchid.phc.ox.ac.uk/wp-content/uploads/2017/02/nhs_diabetes_and_rcgp_cod_final_report.pdf
257. Mayfield JA. Diagnosis and Classification of Diabetes Mellitus: New Criteria. Am Fam Physician. 1998 Oct 15;58(6):1355.
258. Mehboob S, Mehboob M, Mehjabeen -, Tariq Rafi SM, Khan T, Anser H, et al. Spectroscopic interactions of non-insulin-dependent diabetes mellitus with levocetirizine. Pak J Pharm Sci. 2021 Jul 1;34(4(Supplementary)):1639–44.
259. Choi JY, Shin J, Baek S. Gender-based comparison of factors affecting regular exercise of patients with Non-Insulin Dependent Diabetes Mellitus (NIDDM) based on the 7th Korea National Health and Nutrition Examination Survey (KNHANES). PLoS One. 2021 Sep 1;16(9).

260. National Institute for Health and Care Research. BNF: Drug: METFORMIN HYDROCHLORIDE. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drug/metformin-hydrochloride.html
261. National Institute for Health and Care Research. BNF: Drug: Nortriptyline. [Internet] [cited 2022 October 14]. Available from: https://bnf.nice.org.uk/drugs/nortriptyline/
262. National Institute for Health and Care Research. Depression in adults: treatment and management. [Internet] [cited 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng222/chapter/Recommendations
263. Khaledi M, Haghighatdoost F, Feizi A, Aminorroaya A. The prevalence of comorbid depression in patients with type 2 diabetes: an updated systematic review and meta-analysis on huge number of observational studies. Acta Diabetol. 2019;56(6). Available from: https://pubmed.ncbi.nlm.nih.gov/30903433/
264. Clinical Practice Research Datalink. [Internet] [cited on 2022 October 14]. Available from: https://www.cprd.com/
265. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. Br J Clin Pharmacol. 2010 Jan;69(1):4. Available from: /pmc/articles/PMC2805870/
266. Kontopantelis E, Stevens RJ, Helms PJ, Edwards D, Doran T, Ashcroft DM. Spatial distribution of clinical computer systems in primary care in England in 2016 and implications for primary care electronic medical record databases: a cross-sectional population study. BMJ Open. 2018;8:20738. Available from: http://bmjopen.bmj.com/
267. HM Government. What to do after someone dies: Register the death. [Internet] [cited on 2022 October 14]. Available from: https://www.gov.uk/after-a-death
268. Chisholm J. The Read clinical classification. BMJ. 1990 [cited 2022 Jun 15];300(6732):1092. Available from: https://pubmed.ncbi.nlm.nih.gov/2344534/
269. SNOMED - 5-Step Briefing. [Internet] [cited on 2022 October 14]. Available from: https://www.snomed.org/snomed-ct/five-step-briefing
270. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med. 2002 Nov 15;162(20):2269–76.
271. Shephard E, Stapley S, Hamilton W. The use of electronic databases in primary care research. Fam Pract. 2011 Aug 1;28(4):352–4. Available from: https://academic.oup.com/fampra/article/28/4/352/509050

272. Williams T, van Staa T, Puri S, Eaton S. Recent advances in the utility and use of the General Practice Research Database as an example of a UK Primary Care Data resource. Ther Adv Drug Saf. 2012;3(2):89. Available from: /pmc/articles/PMC4110844/
273. Carbonari DM, Saine ME, Newcomb CW, Blak B, Roy JA, Haynes K, et al. Use of demographic and pharmacy data to identify patients included within both the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). Pharmacoepidemiol Drug Saf. 2015 Sep 1;24(9):999–1003. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3844
274. QResearch. [Internet] [cited on 2022 October 14]. Available from: https://www.qresearch.org/
275. Hippisley-Cox J, Coupland C, Brindle P. The performance of seven QPrediction risk scores in an independent external sample of patients from general practice: a validation study. BMJ Open. 2014 Aug 1;4(8):e005809. Available from: https://bmjopen.bmj.com/content/4/8/e005809
276. Reeves D, Springate DA, Ashcroft DM, Ryan R, Doran T, Morris R, et al. Can analyses of electronic patient records be independently and externally validated?: The effect of statins on the mortality of patients with ischaemic heart disease: a cohort study with nested case-control analysis. BMJ Open. 2014;4(4):e004952. Available from: https://research-information.bris.ac.uk/en/publications/can-analyses-of-electronic-patient-records-be-independently-and-e
277. Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. Pharmacoepidemiol Drug Saf. 2009;18(8):704–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19455565/
278. Rait G, Walters K, Griffin M, Buszewicz M, Petersen I, Nazareth I. Recent trends in the incidence of recorded depression in primary care. The British Journal of Psychiatry. 2009;195(6):520–4. Available from: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/recent-trends-in-the-incidence-of-recorded-depression-in-primary-care/61902688F4ACE12657342BD8B33A58B2
279. Dowrick C, Frances A. Medicalising unhappiness: new classification of depression risks more patients being put on drug treatment from which they will not benefit. BMJ. 2013 Dec 9;347. Available from: https://www.bmj.com/content/347/bmj.f7140

280. Kendrick T, Stuart B, Newell C, Geraghty AWA, Moore M. Changes in rates of recorded depression in English primary care 2003–2013: Time trend analyses of effects of the economic recession, and the GP contract quality outcomes framework (QOF). J Affect Disord. 2015 Jul 15;180:68–78.
281. Eastwood S v., Mathur R, Atkinson M, Brophy S, Sudlow C, Flaig R, et al. Algorithms for the Capture and Adjudication of Prevalent and Incident Diabetes in UK Biobank. PLoS One. 2016 Sep 1;11(9):e0162388. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162388
282. Mathur R, Bhaskaran K, Edwards E, Lee H, Chaturvedi N, Smeeth L, et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: A cohort study in the Clinical Practice Research Datalink 2004-2014. BMJ Open. 2017 Feb 1;7(2).
283. Chan EW, Lau WCY, Leung WK, Mok MTC, He Y, Tong TSM, et al. Prevention of Dabigatran-Related Gastrointestinal Bleeding With Gastroprotective Agents: A Population-Based Study. Gastroenterology. 2015 Sep 1;149(3):586e3-595.e3. Available from: https://pubmed.ncbi.nlm.nih.gov/25960019/
284. Santella C, Yin H, Hicks BM, Yu OHY, Bouganim N, Azoulay L. Weight-lowering Effects of Glucagon-like Peptide-1 Receptor Agonists and Detection of Breast Cancer Among Obese Women with Diabetes. Epidemiology. 2020 Jul 1;31(4):559–66. Available from: https://pubmed.ncbi.nlm.nih.gov/32282437/
285. Rouette J, Yin H, Yu OHY, Bouganim N, Platt RW, Azoulay L. Incretin-based drugs and risk of lung cancer among individuals with type 2 diabetes. Diabetic Medicine. 2020 May 1;37(5):868–75. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.14287
286. Douros A, Abrahami D, Yin H, Yun Yu OH, Renoux C, Hudson M, et al. Use of Dipeptidyl Peptidase-4 Inhibitors and New-onset Rheumatoid Arthritis in Patients with Type 2 Diabetes. Epidemiology. 2018 Nov 1;29(6):904–12. Available from: https://europepmc.org/article/med/30028343
287. Metcalfe D, Masters J, Delmestri A, Judge A, Perry D, Zogg C, et al. Coding algorithms for defining Charlson and Elixhauser co-morbidities in Read-coded databases. BMC Med Res Methodol. 2019 Jun 6;19(1):1–9. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-019-0753-5
288. University College London. CALIBER. [Internet] [cited on 2022 October 14]. Available from: https://www.caliberresearch.org/portal/codelists

289. National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. [Internet] [cited on 2022 October 14]. Available from: https://www.nice.org.uk/guidance/ng17
290. Tsang C, Majeed A, Banarsee R, Gnani S, Aylin P. Recording of adverse events in English general practice: analysis of data from electronic patient records. Inform Prim Care. 2010;18(2):117–24. Available from: https://pubmed.ncbi.nlm.nih.gov/21078234/
291. Group TDC and CTR. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. https://doi.org/101056/NEJM199309303291401. 1993 Sep 30;329(14):977–86. Available from: https://www.nejm.org/doi/10.1056/NEJM199309303291401
292. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. Br J Clin Pharmacol. 1999;48(5):643. Available from: /pmc/articles/PMC2014359/
293. Essebag V, Platt RW, Abrahamowicz M, Pilote L. Comparison of nested case-control and survival analysis methodologies for analysis of time-dependent exposure. BMC Med Res Methodol. 2005 Jan 25;5.
294. Suissa S. Novel Approaches to Pharmacoepidemiology Study Design and Statistical Analysis. Textbook of Pharmacoepidemiology. 2013 May 31;383–95.
295. Breslow N, Day N, Heseltine E. Statistical methods in cancer research. [Internet] 1980 [cited on 2022 October 14].; Available from: http://publications.iarc.fr/_publications/media/download/3469/3be6599f0227fbc06d00d91a99aa5ce007090018.pdf
296. DAGitty v3.0. [Internet] [cited on 2022 October 14]. Available from: http://www.dagitty.net/dags.html#
297. van den Anker J, Reed MD, Allegaert K, Kearns GL. Developmental Changes in Pharmacokinetics and Pharmacodynamics. J Clin Pharmacol. 2018 Oct 1;58 Suppl 10:S10–25. Available from: https://pubmed.ncbi.nlm.nih.gov/30248190/
298. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018 Dec 2;17(12):1185–96. Available from: https://pubmed.ncbi.nlm.nih.gov/30540223/

299. Royal College of Psychiatrists. Depression in older adults. [Internet] [cited on 2022 October 14]. Available from: https://www.rcpsych.ac.uk/mental-health/problems-disorders/depression-in-older-adults
300. Wagner S, Wollschläger D, Dreimüller N, Engelmann J, Herzog DP, Roll SC, et al. Effects of age on depressive symptomatology and response to antidepressant treatment in patients with major depressive disorder aged 18 to 65 years. Compr Psychiatry. 2020 May 1;99:152170.
301. Orlando V, Mucherino S, Guarino I, Guerriero F, Trama U, Menditto E. Gender Differences in Medication Use: A Drug Utilization Study Based on Real World Data. Int J Environ Res Public Health. 2020 Jun 1;17(11). Available from: /pmc/articles/PMC7312791/
302. Loikas D, Wettermark B, von Euler M, Bergman U, Schenck-Gustafsson K. Differences in drug utilisation between men and women: a cross-sectional analysis of all dispensed drugs in Sweden. BMJ Open. 2013 Jan 1;3(5):e002378. Available from: https://bmjopen.bmj.com/content/3/5/e002378
303. Orlando V, Mucherino S, Guarino I, Guerriero F, Trama U, Menditto E. Gender Differences in Medication Use: A Drug Utilization Study Based on Real World Data. International Journal of Environmental Research and Public Health 2020, Vol 17, Page 3926. 2020 Jun 1;17(11):3926. Available from: https://www.mdpi.com/1660-4601/17/11/3926/htm
304. Piccinelli M, Wilkinson G. Gender differences in depression: Critical review. The British Journal of Psychiatry. 2000;177(6):486–92. Available from: https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/gender-differences-in-depression/0770B51752F17A5A081F9878B0952608
305. Kautzky-Willer A, Harreiter J, Pacini G. Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus. Endocr Rev. 2016 Jun 1;37(3):278. Available from: /pmc/articles/PMC4890267/
306. HM Government. Common mental disorders - GOV.UK Ethnicity facts and figures. [Internet] [cited on 2022 October 14]. Available from: https://www.ethnicity-facts-figures.service.gov.uk/health/mental-health/adults-experiencing-common-mental-disorders/latest
307. The King's Fund. The health of people from ethnic minority groups in England. [Internet] [cited on 2022 October 14]. Available from:

https://www.kingsfund.org.uk/publications/health-people-ethnic-minority-groups-england
308. Institute of Health Equity. [Internet] [cited on 2022 October 14]. Available from: https://www.instituteofhealthequity.org/
309. Dykxhoorn J, Fischer L, Bayliss B, Brayne C, Crosby L, Galvin B, et al. Conceptualising public mental health: development of a conceptual framework for public mental health. BMC Public Health 2022 22:1. 2022 Jul 23;22(1):1–15. Available from: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-022-13775-9
310. Cox DR. Regression Models and Life-Tables. [Internet] [cited on 2022 October 14]. Available from: https://about.jstor.org/terms
311. Biometrics JC, 1982 undefined. The efficiency of the proportions test and the logrank test for censored survival data. JSTOR. 1982;38(4):1033–9. Available from: https://www.jstor.org/stable/2529884
312. Annesi I, Moreau T, Lellouch J. Efficiency of the logistic regression and cox proportional hazards models in longitudinal studies. Stat Med. 1989 Dec 1;8(12):1515–21. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/sim.4780081211
313. Green M. A comparison of the logistic risk function and the proportional hazards model in prospective epidemiologic studies. MSJ of chronic diseases. Elsevier. 1983. Available from: https://www.sciencedirect.com/science/article/pii/0021968183901650
314. de Boor C. A Practical Guide to Splines - Revised Edition. Springer-Verlag, New York. 2001;366.
315. Malloy EJ, Kapellusch JM, Garg A. Estimating and Interpreting Effects from Nonlinear Exposure-Response Curves in Occupational Cohorts Using Truncated Power Basis Expansions and Penalized Splines. Comput Math Methods Med. 2017;2017.
316. McFadden D. Conditional logit analysis of qualitative choice behaviour. In University of California at Berkeley; 1973. p. 105–42. Available from: https://eml.berkeley.edu/reprints/mcfadden/zarembka.pdf
317. Denee T, Kerr C, Ming T, Wood R, Tritton T, Middleton-Dalby C, et al. Current treatments used in clinical practice for major depressive disorder and treatment resistant depression in England: A retrospective database study. J Psychiatr Res. 2021 Jul 1;139:172–8.

318. Mars B, Heron J, Gunnell D, Martin RM, Thomas KH, Kessler D. Prevalence and patterns of antidepressant switching amongst primary care patients in the UK. Journal of Psychopharmacology. 2017 May 1;31(5):553–60.
319. De Crescenzo F, Garriga C, Tomlinson A, Coupland C, Efthimiou O, Fazel S, et al. Real-world effect of antidepressants for depressive disorder in primary care: protocol of a population-based cohort study. Evid Based Ment Health. 2020 Aug 1;23(3):122–6.
320. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, Minhas R, Sheikh A, et al. Predicting cardiovascular risk in England and Wales: prospective derivation and validation of QRISK2. BMJ. 2008 Jun 28;336(7659):1475–82. Available from: https://pubmed.ncbi.nlm.nih.gov/18573856/
321. Raum E, Krämer HU, Rüter G, Rothenbacher D, Rosemann T, Szecsenyi J, et al. Medication non-adherence and poor glycaemic control in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2012 Sep;97(3):377–84.
322. Horii T, Momo K, Yasu T, Kabeya Y, Atsuda K. Determination of factors affecting medication adherence in type 2 diabetes mellitus patients using a nationwide claim-based database in Japan. PLoS One. 2019 Oct 1;14(10). Available from: /pmc/articles/PMC6782087/
323. Jensen ML, Jørgensen ME, Hansen EH, Aagaard L, Carstensen B. Long-term patterns of adherence to medication therapy among patients with type 2 diabetes mellitus in Denmark: The importance of initiation. PLoS One. 2017 Jun 1;12(6).
324. Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and Medication Adherence in Patients With Type 2 Diabetes. Diabetes Care. 2003 May 1;26(5):1408–12. Available from: https://diabetesjournals.org/care/article/26/5/1408/24445/Polypharmacy-and-Medication-Adherence-in-Patients
325. Krass I, Schieback P, Dhippayom T. Adherence to diabetes medication: a systematic review. Diabetic Medicine. 2015 Jun 1;32(6):725–37. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.12651
326. de Munter L, Polinder S, Haagsma JA, Kruithof N, van de Ree CLP, Steyerberg EW, et al. Prevalence and Prognostic Factors for Psychological Distress After Trauma. Arch Phys Med Rehabil. 2020 May 1;101(5):877–84.
327. Vincent HK, Horodyski MB, Vincent KR, Brisbane ST, Sadasivan KK. Psychological Distress After Orthopedic Trauma: Prevalence in Patients and Implications for

Rehabilitation. PM&R. 2015 Sep 1;7(9):978–89. Available from: https://onlinelibrary.wiley.com/doi/full/10.1016/j.pmrj.2015.03.007

328. Medicines Agency E. Draft reflection paper on the pharmaceutical development of medicines for use in the older population.; Available from: www.ema.europa.eu/contact
329. McIsaac DI, Wong CA, Bryson GL, van Walraven C. Association of Polypharmacy with Survival, Complications, and Healthcare Resource Use after Elective Noncardiac SurgeryA Population-based Cohort Study. Anesthesiology. 2018 Jun 1;128(6):1140–50. Available from: https://pubs.asahq.org/anesthesiology/article/128/6/1140/19931/Association-of-Polypharmacy-with-Survival
330. Henssler J, Heinz A, Brandt L, Bschor T. Antidepressant Withdrawal and Rebound Phenomena. Dtsch Arztebl Int. 2019 May;116(20):355–61. Available from: https://pubmed.ncbi.nlm.nih.gov/31288917/
331. Lewis G, Marston L, Duffy L, Freemantle N, Gilbody S, Hunter R, et al. Maintenance or Discontinuation of Antidepressants in Primary Care. N Engl J Med. 2021 Sep 30;385(14):1257–67. Available from: https://pubmed.ncbi.nlm.nih.gov/34587384/
332. mhGAP Intervention Guide Mental Health Gap Action Programme Version 2.0 for mental, neurological and substance use disorders in non-specialized health settings. World Health Organisation. 2016;(2.0). Available from: http://www.who.int
333. Nierenberg AA, Petersen TJ, Alpert JE. Prevention of Relapse and Recurrence in Depression: The Role of Long-Term Pharmacotherapy and Psychotherapy. 2003;
334. Baumeister H, Balke K, Härter M. Psychiatric and somatic comorbidities are negatively associated with quality of life in physically ill patients. J Clin Epidemiol. 2005;58(11):1090–100. Available from: https://pubmed.ncbi.nlm.nih.gov/16223651/
335. Walker AJ, Croker R, Curtis HJ, MacKenna B, Goldacre B. Trends in antidepressant prescribing in England. Lancet Psychiatry. 2021 Apr 1;8(4):278–9.
336. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care. 1998;36(1):8–27. Available from: https://pubmed.ncbi.nlm.nih.gov/9431328/
337. Diabetes UK. Chapter 5 - Psychological barriers to insulin use. [Internet] [cited on 2022 October 13]. Available from: https://www.diabetes.org.uk/professionals/resources/shared-practice/psychological-care/emotional-health-professionals-guide/chapter-5-fear-insulin

338. van Dooren FEP, Nefs G, Schram MT, Verhey FRJ, Denollet J, Pouwer F. Depression and Risk of Mortality in People with Diabetes Mellitus: A Systematic Review and Meta-Analysis. PLoS One. 2013 Mar 5;8(3):e57058. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0057058
339. National Institute for Health and Care Excellence. BNF: Drug: Citalopram. [Internet] [cited on 2022 October 13]. Available from: https://bnf.nice.org.uk/drugs/citalopram/
340. Trevino K, Mcclintock SM, Vora A, Husain MM. Defining treatment-resistant depression: A comprehensive review of the literature. Annals of Clinical Psychiatry. 2014;26(3):222–32. Available from: https://www.researchgate.net/publication/265135713
341. Snoek FJ, Bremmer MA, Hermanns N. Constructs of depression and distress in diabetes: time for an appraisal. Lancet Diabetes Endocrinol. 2015 Jun 1;3(6):450–60. Available from: https://pubmed.ncbi.nlm.nih.gov/25995123/
342. Berry E, Lockhart S, Davies M, Lindsay JR, Dempster M. Diabetes distress: understanding the hidden struggles of living with diabetes and exploring intervention strategies. Postgrad Med J. 2015 May 1;91(1075):278–83. Available from: https://pmj.bmj.com/content/91/1075/278
343. Westley K v, August KJ, Alger MR, Markey CH. Main and interactive effects of diabetes distress and stress from life events on overall psychological distress. J Health Psychol. 2018 Oct 17;1359105318804865. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30326741
344. Stone M, Laughren T, Jones ML, Levenson M, Holland PC, Hughes A, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ. 2009 Aug 11;339(7718):431–4. Available from: https://www.bmj.com/content/339/bmj.b2880
345. Bogowicz P, Curtis HJ, Walker AJ, Cowen P, Geddes J, Goldacre B. Trends and variation in antidepressant prescribing in English primary care: a retrospective longitudinal study. BJGP Open. 2021 Aug 1;5(4):1–12. Available from: https://bjgpopen.org/content/5/4/BJGPO.2021.0020
346. Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ. 2009 Feb 3;180(3):291–7. Available from: https://pubmed.ncbi.nlm.nih.gov/19188627/

347. SØndergØrd L, Lopez AG, Andersen PK, Kessing LV. Continued antidepressant treatment and suicide in patients with depressive disorder. Arch Suicide Res. 2007 Apr;11(2):163–75. Available from: https://pubmed.ncbi.nlm.nih.gov/17453694/
348. Coupland C, Hill T, Morriss R, Arthur A, Moore M, Hippisley-Cox J. Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database. BMJ. 2015 Feb 18;350. Available from: https://www.bmj.com/content/350/bmj.h517
349. Madsen KB, Plana-Ripoll O, Musliner KL, Debost JCP, Petersen LV, Munk-Olsen T. Cause-specific life years lost in individuals with treatment-resistant depression: A Danish nationwide register-based cohort study. J Affect Disord. 2021 Feb 1;280:250–7.
350. Cipriani A, Barbui C, Geddes JR. Suicide, depression, and antidepressants. BMJ. 2005 Feb 17;330(7488):373–4. Available from: https://www.bmj.com/content/330/7488/373
351. Rockett A, Smith GS. Suicide Misclassification in an International Context. [Internet] [cited on 2022 October 13]. Available from: http://www.suicidology-online.com/pdf/SOL-2011-2-48-61.pdf
352. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-Risk-Increasing Drugs: A Systematic Review and Meta-Analysis: II. Psychotropics. J Am Med Dir Assoc. 2018 Apr 1;19(4):371.e11-371.e17. Available from: https://pubmed.ncbi.nlm.nih.gov/29402652/
353. Handley SA, Flanagan RJ. Drugs and other chemicals involved in fatal poisoning in England and Wales during 2000 – 2011. Clin Toxicol (Phila). 2014 Jan;52(1):1–12. Available from: https://pubmed.ncbi.nlm.nih.gov/24397714/
354. Gummin DD, Mowry JB, Beuhler MC, Spyker DA, Brooks DE, Dibert KW, et al. 2019 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 37th Annual Report. Clin Toxicol (Phila). 2020 Dec 1;58(12):1360–541. Available from: https://pubmed.ncbi.nlm.nih.gov/33305966/
355. Cameron DH, Rapoport MJ. Antidepressants and Driving in Older Adults: A Systematic Review. Can J Aging. 2016 Jun 1;35 Suppl 1(S1):7–14. Available from: https://pubmed.ncbi.nlm.nih.gov/27091414/
356. Umpierrez G, Korytkowski M. Diabetic emergencies - ketoacidosis, hyperglycaemic hyperosmolar state and hypoglycaemia. Nat Rev Endocrinol. 2016 Apr 1;12(4):222–32. Available from: https://pubmed.ncbi.nlm.nih.gov/26893262/

357. Hoogendoorn CJ, Shapira A, Roy JF, Walker EA, Cohen HW, Gonzalez JS. Depressive symptom dimensions and medication non-adherence in suboptimally controlled type 2 diabetes. J Diabetes Complications. 2019 Mar;33(3):217–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30598369
358. Bradford AL, Crider CC, Xu X, Naqvi SH. Predictors of Recurrent Hospital Admission for Patients Presenting With Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. J Clin Med Res. 2017;9(1):35–9. Available from: https://pubmed.ncbi.nlm.nih.gov/27924173/
359. Kong APS, Chan JCN. Hypoglycemia and Comorbidities in Type 2 Diabetes. Curr Diab Rep. 2015 Oct 7;15(10):1–7. Available from: https://link.springer.com/article/10.1007/s11892-015-0646-x
360. National Health Service. What are the health risks of smoking? [Internet] [cited 2022 Oct 12]. Available from: https://www.nhs.uk/common-health-questions/lifestyle/what-are-the-health-risks-of-smoking/
361. Camidge DR, Wood RJ, Bateman DN. The epidemiology of self-poisoning in the UK. Br J Clin Pharmacol. 2003 Dec;56(6):613. Available from: /pmc/articles/PMC1884308/
362. World Health Organisation. ICD-10 Version:2019. ? [Internet] [cited 2022 Oct 12]. Available from: https://icd.who.int/browse10/2019/en#/E10-E14
363. Nouwen A, Adriaanse MC, van Dam K, Iversen MM, Viechtbauer W, Peyrot M, et al. Longitudinal associations between depression and diabetes complications: a systematic review and meta-analysis. Diabet Med. 2019 Dec 1;36(12):1562–72. Available from: https://pubmed.ncbi.nlm.nih.gov/31215077/
364. Gosmanov AR, Gosmanova EO, Kitabchi AE. Hyperglycemic Crises: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. Acute Endocrinology. 2021 May 9;119–47. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279052/
365. Heller SR, Peyrot M, Oates SK, Taylor AD. Hypoglycemia in patient with type 2 diabetes treated with insulin: it can happen. BMJ Open Diabetes Res Care. 2020 Jun 1;8(1):e001194. Available from: https://drc.bmj.com/content/8/1/e001194
366. Diabetes UK. Diabetes Life Expectancy - Type 1 and Type 2 Life Expectancy. [Internet] [cited 2022 Oct 12]. Available from: https://www.diabetes.co.uk/diabetes-life-expectancy.html

367. Haneuse S, Daniels M. A General Framework for Considering Selection Bias in EHR-Based Studies: What Data Are Observed and Why? EGEMS (Wash DC). 2016 Aug 31;4(1):16. Available from: https://pubmed.ncbi.nlm.nih.gov/27668265/
368. Kukafka R, Ancker JS, Chan C, Chelico J, Khan S, Mortoti S, et al. Redesigning electronic health record systems to support public health. J Biomed Inform. 2007 Aug;40(4):398–409. Available from: https://pubmed.ncbi.nlm.nih.gov/17632039/
369. McGrath N, O Neill K, McHugh SM, Toomey E, Kearney PM. Epidemiology of undiagnosed depression in people with diabetes mellitus: a comparative analysis of Ireland, England and the USA. BMJ Open. 2021 Oct 13;11(10). Available from: https://pubmed.ncbi.nlm.nih.gov/34645663/
370. Stromberg R, Wernering E, Aberg-Wistedt A, Furhoff AK, Johansson SE, Backlund LG. Screening and diagnosing depression in women visiting GPs' drop in clinic in Primary Health Care. BMC Fam Pract. 2008;9.
371. Prior L, Wood F, Lewis G, Pill R. Stigma revisited, disclosure of emotional problems in primary care consultations in Wales. Soc Sci Med. 2003 May;56(10):2191–200.
372. Cape J, McCulloch Y. Patients' reasons for not presenting emotional problems in general practice consultations. British Journal of General Practice. 1999;49(448):875–9.
373. Carreira H, Williams R, Strongman H, Bhaskaran K. Identification of mental health and quality of life outcomes in primary care databases in the UK: a systematic review. BMJ Open. 2019 Jul 1; 9(7). Available from: /pmc/articles/PMC6609128/
374. Martín-Merino E, Ruigómez A, Johansson S, Wallander MA, García-Rodriguez LA. Study of a Cohort of Patients Newly Diagnosed With Depression in General Practice: Prevalence, Incidence, Comorbidity, and Treatment Patterns. Prim Care Companion CNS Disord. 2010 Feb 18;12(1):26885. Available from: https://www.psychiatrist.com/pcc/depression/study-cohort-patients-newly-diagnosed-depression-general
375. Bansal N, Hudda M, Payne RA, Smith DJ, Kessler D, Wiles N. Antidepressant use and risk of adverse outcomes: population-based cohort study. BJPsych Open . 2022 Sep;8(5):e164. Available from: https://www.cambridge.org/core/journals/bjpsych-open/article/antidepressant-use-and-risk-of-adverse-outcomes-populationbased-cohort-study/6AAA6943E55F8B08DD9E25155E72931F
376. Freemantle N, Marston L, Walters K, Wood J, Reynolds MR, Petersen I. Making inferences on treatment effects from real world data: propensity scores, confounding

by indication, and other perils for the unwary in observational research. BMJ. 2013 Nov 11;347. Available from: https://www.bmj.com/content/347/bmj.f6409

377. Spence R, Roberts A, Ariti C, Bardsley M. Focus On: Antidepressant prescribing Trends in the prescribing of antidepressants in primary care. 2014. [Internet] [cited 2022 Oct 12] Available from: www.qualitywatch.org.uk
378. Mosley-Johnson E, Walker RJ, Thakkar M, Campbell JA, Hawks L, Pyzyk S, et al. Relationship between housing insecurity, diabetes processes of care, and self-care behaviors. BMC Health Serv Res. 2022 Dec;22(1):1–8. Available from: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-022-07468-7
379. Vijayaraghavan M, Jacobs EA, Seligman H, Fernandez A. The association between housing instability, food insecurity, and diabetes self-efficacy in low-income adults. J Health Care Poor Underserved. 2011;22(4):1279–91. Available from: https://pubmed.ncbi.nlm.nih.gov/22080709/
380. Berkowitz SA, Kalkhoran S, Edwards ST, Essien UR, Baggett TP. Unstable Housing and Diabetes-Related Emergency Department Visits and Hospitalization: A Nationally Representative Study of Safety-Net Clinic Patients. Diabetes Care. 2018 May 1;41(5):933–9. Available from: https://pubmed.ncbi.nlm.nih.gov/29301822/
381. Chambers EC, McAuliff KE, Heller CG, Fiori K, Hollingsworth N. Toward Understanding Social Needs Among Primary Care Patients With Uncontrolled Diabetes. J Prim Care Community Health. 2021;12. Available from: https://pubmed.ncbi.nlm.nih.gov/33467953/
382. Varanka-Ruuska T, Rautio N, Lehtiniemi H, Miettunen J, Keinänen-Kiukaanniemi S, Sebert S, et al. The association of unemployment with glucose metabolism: a systematic review and meta-analysis. Int J Public Health. 2018 May 1;63(4):435–46. Available from: https://pubmed.ncbi.nlm.nih.gov/29170882/
383. Roelfs DJ, Shor E, Davidson KW, Schwartz JE. Losing life and livelihood: A systematic review and meta-analysis of unemployment and all-cause mortality. Soc Sci Med. 2011 Mar 1;72(6):840–54.
384. Lundin A, Falkstedt D, Lundberg I, Hemmingsson T. Unemployment and coronary heart disease among middle-aged men in Sweden: 39 243 men followed for 8 years. Occup Environ Med. 2014 Mar 1;71(3):183–8. Available from: https://oem.bmj.com/content/71/3/183

385. Vaalavuo M. Deterioration in health: What is the role of unemployment and poverty? Scand J Public Health. 2016 Jun 1;44(4):347–53. Available from: https://journals.sagepub.com/doi/10.1177/1403494815623654
386. Public Health England. Wider Determinants of Health - OHID. [Internet] [cited 2022 Oct 12]. Available from: https://fingertips.phe.org.uk/profile/wider-determinants
387. Marston L, Carpenter JR, Walters KR, Morris RW, Nazareth I, White IR, et al. Smoker, ex-smoker or non-smoker? The validity of routinely recorded smoking status in UK primary care: a cross-sectional study. BMJ Open. 2014 [cited 2022 Sep 6];4(4). Available from: https://pubmed.ncbi.nlm.nih.gov/24760355/
388. Labrecque JA, Swanson SA. Target trial emulation: teaching epidemiology and beyond. Eur J Epidemiol. 2017 Jun 1;32(6):473. Available from: /pmc/articles/PMC5550532/
389. Biondi-Zoccai G, Romagnoli E, Agostoni P, Capodanno D, Castagno D, D'Ascenzo F, et al. Are propensity scores really superior to standard multivariable analysis? Contemp Clin Trials. 2011 Sep 1;32(5):731–40.
390. Pokropek A. Introduction to instrumental variables and their application to large-scale assessment data. Large Scale Assess Educ. 2016 Dec 1;4(1):1–20. Available from: https://largescaleassessmentsineducation.springeropen.com/articles/10.1186/s40536-016-0018-2
391. Swanson SA. Instrumental Variable Analyses in Pharmacoepidemiology: What Target Trials Do We Emulate? Curr Epidemiol Rep. 2017 Dec;4(4):281. Available from: /pmc/articles/PMC5711965/
392. Wiles N, Taylor A, Turner N, Barnes M, Campbell J, Lewis G, et al. Management of treatment-resistant depression in primary care: a mixed-methods study. British Journal of General Practice. 2018 Oct 1;68(675):e673–81. Available from: https://bjgp.org/content/68/675/e673
393. Solmi M, Miola A, Croatto G, Pigato G, Favaro A, Fornaro M, et al. How can we improve antidepressant adherence in the management of depression? A targeted review and 10 clinical recommendations. Brazilian Journal of Psychiatry. 2021 Mar 1;43(2):189. Available from: /pmc/articles/PMC8023158/
394. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: Systematic review and meta-analysis. Prev Med (Baltim). 2017 Jun 1;99:269–76.

395. Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. The Lancet. 2003 Feb 22;361(9358):653–61.
396. AADE. AADE7 Self-Care Behaviors. Diabetes Educ. 2008 May;34(3):445–9. Available from: https://pubmed.ncbi.nlm.nih.gov/18535317/
397. Egede LE, Ellis C. The Effects of Depression on Diabetes Knowledge, Diabetes Self-Management, and Perceived Control in Indigent Patients with Type 2 Diabetes. https://home.liebertpub.com/dia. 2008 May;10(3):213–9. Available from: https://www.liebertpub.com/doi/10.1089/dia.2007.0278
398. Public Health England. Physical Activity - Data - OHID. [Internet] [cited 2022 Oct 12]. Available from: https://fingertips.phe.org.uk/profile/physical-activity/data#page/1
399. HM Government. Social prescribing: applying All Our Health - GOV.UK. [Internet] [cited 2022 Oct 12]. Available from: https://www.gov.uk/government/publications/social-prescribing-applying-all-our-health/social-prescribing-applying-all-our-health
400. Pilkington K, Loef M, Polley M. Searching for Real-World Effectiveness of Health Care Innovations: Scoping Study of Social Prescribing for Diabetes. J Med Internet Res. 2017 Feb 1;19(2). Available from: https://pubmed.ncbi.nlm.nih.gov/28153817/
401. Carek PJ, Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med. 2011 Jan 1;41(1):15–28. Available from: https://journals.sagepub.com/doi/10.2190/PM.41.1.c?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed
402. Public Health England. Public health profiles - Fruit. [[Internet] [cited 2022 Oct 12]. Available from: https://fingertips.phe.org.uk/search/fruit
403. Povey RC, Clark-Carter D. Diabetes and healthy eating: a systematic review of the literature. Diabetes Educ. 2007 Nov;33(6):931–59. Available from: https://pubmed.ncbi.nlm.nih.gov/18057263/
404. Litchman ML, Oser TK, Hodgson L, Heyman M, Walker HR, Deroze P, et al. In-Person and Technology-Mediated Peer Support in Diabetes Care: A Systematic Review of Reviews and Gap Analysis. Diabetes Educ. 2020 Jun 1;46(3):230–41. Available from: https://pubmed.ncbi.nlm.nih.gov/32321370/
405. Ahola AJ, Groop PH. Barriers to self-management of diabetes. Diabet Med. 2013 Apr 1;30(4):413–20. Available from: https://pubmed.ncbi.nlm.nih.gov/23278342/

406. Diabetes UK. Flash glucose monitors (Freestyle Libre) and continuous glucose monitors (CGM). [Internet] [cited 2022 Oct 12].. Available from: https://www.diabetes.org.uk/guide-to-diabetes/diabetes-technology/flash-glucose-monitors-and-continuous-glucose-monitors
407. Simon GE, Katon WJ, Lin EHB, Rutter C, Manning WG, von Korff M, et al. Cost-effectiveness of Systematic Depression Treatment Among People With Diabetes Mellitus. Arch Gen Psychiatry. 2007 Jan 1 [;64(1):65–72. Available from: https://jamanetwork.com/journals/jamapsychiatry/fullarticle/209967
408. Ell K, Katon W, Xie B, Lee PJ, Kapetanovic S, Guterman J, et al. Collaborative care management of major depression among low-income, predominantly Hispanic subjects with diabetes: a randomized controlled trial. Diabetes Care. 2010 Apr;33(4):706–13. Available from: https://pubmed.ncbi.nlm.nih.gov/20097780/
409. Boren SA, Gunlock TL, Schaefer J, Albright A. Reducing Risks in Diabetes Self-management; A Systematic Review of the Literature. Diabetes Educ. 2007 Nov 1;33(6):1053–78. Available from: https://go.gale.com/ps/i.do?p=AONE&sw=w&issn=01457217&v=2.1&it=r&id=GALE%7CA171941201&sid=googleScholar&linkaccess=fulltext
410. Weinberger AH, Kashan RS, Shpigel DM, Esan H, Taha F, Lee CJ, et al. Depression and cigarette smoking behavior: A critical review of population-based studies. Am J Drug Alcohol Abuse. 2017 Jul 4;43(4):416–31. Available from: https://pubmed.ncbi.nlm.nih.gov/27286288/
411. Meneghini KFD, Hood CF, Menezes LO de, Mendoza-Sassi RA, Dumith SC. Influenza vaccination coverage in elderly and high-risk adults: characterization of associated factors. Einstein. 2021 [cited 2022 Sep 3];19:eAO5830. Available from: /pmc/articles/PMC8244927/
412. Pereira MG, Pedras S, Ferreira G. Self-reported adherence to foot care in type 2 diabetes patients: do illness representations and distress matter? Prim Health Care Res Dev. 2018;20. Available from: https://pubmed.ncbi.nlm.nih.gov/30095065/
413. Egede LE, Osborn CY. Role of motivation in the relationship between depression, self-care, and glycemic control in adults with type 2 diabetes. Diabetes Educator. 2010 Feb 23;36(2):276–83. Available from: https://journals.sagepub.com/doi/10.1177/0145721710361389?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed

414. Hernandez R, Ruggiero L, Prohaska TR, Chavez N, Boughton SW, Peacock N, et al. A Cross-sectional Study of Depressive Symptoms and Diabetes Self-care in African Americans and Hispanics/Latinos With Diabetes: The Role of Self-efficacy. Diabetes Educ. 2016 Aug 1;42(4):452–61. Available from: https://pubmed.ncbi.nlm.nih.gov/27324747/
415. Gonzalez JS, Peyrot M, McCarl LA, Collins EM, Serpa L, Mimiaga MJ, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care. 2008 Dec;31(12):2398–403. Available from: https://pubmed.ncbi.nlm.nih.gov/19033420/
416. Nouwen A. Depression and diabetes distress. Diabetic Medicine. 2015 Oct 1;32(10):1261–3. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/dme.12863
417. McGuigan K, Hill A, Coates V, O'Kane M, Thompson DR, Ski CF, et al. Moderating the relationship between diabetes distress and mastery: the role of depression and empowerment. Psychol Health Med. 2022;27(4):838–47. Available from: https://pubmed.ncbi.nlm.nih.gov/33641545/
418. Mukherjee N, Chaturvedi SK. Depressive symptoms and disorders in type 2 diabetes mellitus. Curr Opin Psychiatry. 2019 Sep 1;32(5):416–21. Available from: https://pubmed.ncbi.nlm.nih.gov/31135489/
419. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a Brief Depression Severity Measure. J Gen Intern Med.;16(9):606. Available from: /pmc/articles/PMC1495268/
420. National Health Service. Social care and support guide. [Internet] [cited 2022 Oct 12]. Available from: https://www.nhs.uk/conditions/social-care-and-support-guide/
421. Dwyer P, Scullion L, Jones K, McNeill J, Stewart ABR. Work, welfare, and wellbeing: The impacts of welfare conditionality on people with mental health impairments in the UK. Soc Policy Adm. 2020 Mar 1;54(2):311–26.
422. National Institute for Health and Care Excellence. Standards and Indicators. [Internet] [cited 2022 Oct 12]. Available from: https://www.nice.org.uk/standards-and-indicators/indicators
423. Diabetes UK. Diabetes education courses. [Internet] [cited 2022 Oct 12]. Available from: https://www.diabetes.org.uk/guide-to-diabetes/managing-your-diabetes/education

424. Roy M, Sengupta N, Sahana PK, Das C, Talukdar P, Baidya A, et al. Type 2 diabetes and influence of diabetes-specific distress on depression. Diabetes Res Clin Pract. 2018 Sep;143:194–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30009934
425. Gutierrez AP, Fortmann AL, Savin K, Clark TL, Gallo LC. Effectiveness of Diabetes Self-Management Education Programs for US Latinos at Improving Emotional Distress: A Systematic Review. Diabetes Educ. 2019;45(1):13–33. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30569831
426. Chew BH, Vos RC, Fernandez A, Shariff Ghazali S, Shamsuddin NH, Ismail M, et al. The effectiveness of an emotion-focused educational programme in reducing diabetes distress in adults with type 2 diabetes mellitus at 12-month follow-up: a cluster randomized controlled trial. Ther Adv Endocrinol Metab. 2019;10:2042018819853761. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31210922
427. Salisbury H, Oxford GP. Helen Salisbury: The 10 minute appointment. BMJ. 2019 Jun 4;365. Available from: https://www.bmj.com/content/365/bmj.l2389
428. National Health Service. NHS Long Term Plan » Chapter 5: Digitally-enabled care will go mainstream across the NHS. [Internet] [cited 2022 Oct 12]. Available from: https://www.longtermplan.nhs.uk/online-version/chapter-5-digitally-enabled-care-will-go-mainstream-across-the-nhs/
429. Lewis G, Hayes J. Common mental disorders: falling through the gap. Lancet Psychiatry. 2019 Aug 1;6(8):636–7. Available from: http://www.thelancet.com/article/S2215036619302524/fulltext
430. Pal K, Sharma M, Mukadam NM, Petersen I. Initiation of antidepressant medication in people with type 2 diabetes living in the United Kingdom —A retrospective cohort study . Pharmacoepidemiol Drug Saf. 2022 Aug 10;
431. Miranda-Moreno LF, Heydari S, Lord D, Fu L. Bayesian road safety analysis: incorporation of past evidence and effect of hyper-prior choice. J Safety Res. 2013;46:31–40. Available from: https://pubmed.ncbi.nlm.nih.gov/23932683/
432. McCarthy MA, Masters P. Profiting from prior information in Bayesian analyses of ecological data. Journal of Applied Ecology. 2005 Dec 1;42(6):1012–9. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2664.2005.01101.x
433. Moser CB, Gupta M, Archer BN, White LF. The Impact of Prior Information on Estimates of Disease Transmissibility Using Bayesian Tools. PLoS One. 2015 Mar

20;10(3):e0118762. Available from:
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0118762

Appendices

Appendix A – Systematic review search terms (included example from Medline database)

1. exp Diabetes Mellitus, Type 2/
2. (DMT2 or NIDDM or T2D* or "non?insulin* depend*").mp.
3. (("typ? 2" or "typ? II" or "typ?2" or "typ?II") adj3 diabet*).mp.
4. (((late or adult* or matur* or slow or stabl*) adj3 onset) and diabet*).mp.
5. 1 or 2 or 3 or 4
6. exp Mood Disorders/
7. ("depressi* symptom*" or dysthymi* or melancholi* or depress*).mp.
8. ((depressi* or mood or affectiv*) adj3 disorder*).mp.
9. exp Depression/ or exp Depressive Disorder/ or exp Depressive Disorder, Major/
10. 6 or 7 or 8 or 9
11. exp Antidepressive Agents, Second-Generation/ or exp Antidepressive Agents/ or exp Antidepressive Agents, Tricyclic/
12. exp Serotonin Uptake Inhibitors/
13. exp Neurotransmitter Uptake Inhibitors/
14. exp Monoamine Oxidase Inhibitors/
15. (antidepress* or anti-depress* or "anti depress").mp.
16. (MAOI* or RIMA* or SSRI* or SNRI* or NARI* or SARI* or NDRI* or TCA*).mp.
17. "monoamine oxidase inhibitor*".mp.
18. (tricyclic or heterocyclic or thymoanaleptic* or thymoleptic*).mp.
19. (noradrenerg* or antiadrenerg* or "anti adrenerg*" or anti-adrenerg*).mp.

20. ((serotonin or "nor epinephrine" or norepinephrine or noradrenaline or "nor adrenaline" or neurotransmitter* or dopamin*) adj3 (uptake or re-uptake or reuptake or "re uptake")).mp.

21. (Agomelatin* or Melitor or Thymanax or Valdoxan).mp.

22. (Amineptin* or Survector).mp.

23. (Amitr?pt?li* or Adepril or ADT or amineurin or amioxid or amirol or amitec or amit or amitone or amitor or amitrip or amitryn or amrea or amypres or amytril or amyzol or anapsique or conmitrip or crypton or deprelio or elatrol* or elavil or eliwel or endep or equilibrin or fiorda or gentrip or kamitrin or laroxyl or latilin or levate or maxivalet or mitryp-10 or neurotrypt or noriline or novo-triptyn or odep or polytanol or protanol or qualitriptine or redomex or sarote* or stelminal or syneudon or teperin or thymontil or trepiline or tripta or tripsyline or tript?lin* or tr?ptizol or tripsol or tryptal* or tryptanol or tryptin* or tryptomer or uxen).mp.

24. (Amoxapin* or amolife or asendin or defanyl or demolox or oxamine or oxcap or amoksapi*).mp.

25. (Buproprion* or Amfebutamone or aplenzin or budeprion or bup or bupep or bupisure or budeprion or buproban or butrew or buxon or clorprax or elontril or ession or fortivo or "le fu ting" or lung or nicotex or odranal or prexaton or quomen or voxtra or wellbutrin or "yue ting" or zetron or zyban or zyntabac).mp.

26. (butriptylin* or evadene).mp.

27. (Citalo* or Actipram or Adco-Talomil or Alcytam or Atopran or Calton or Celapram or Celexa or Celica or Ciazil or Cilate or Cilift or Ciloram or Cimal or Cipram* or "Cita Sandoz" or Citaforin or Citagran or Citalvir or Citaprass or Citara or Citol or Citolap or Citrex or Citta or Claropram or Copsam or Cortran or CTP or Denyl or "Duo Po" or Eostar* or Eslopram or Finap* or Frisdal or Genprol* or Humorap or Laira or Maxapran or Opra or Pasilopram or Pram or Pramcil or Prisma or Prodmax or Psiconor or Ran-Citalo or Relapaz or Relaxol or Sedopram or Ser?pram or Seregra or Setronil or Sintab or Siozam or Somact or Talam or Talohexal* or "Te Lin Na" or Temperax or Tensiopax or Vodelax or Zebrak or Zentius or Zoxipan or Zydtapran).mp.

28. (Clomipram* or anafranil or atenual or ausentron or Chlomipram* or clo or clofranil or clom or clomidep or clomine or clomip or klomipram* or clomistar or clomizil

or clonil or clopram or clopress or denapranil or depnil or deprelin or equinorm or fenatil or hydiphen or mario or maronil or novo-clopamine or ocifril or placil or zoiral).mp.

29. (Demexiptilin* or deparon or tinoran).mp.

30. (Desiprami* or deziprami* or Desiparamin* or desipram or distonal or norpramin or nortimil or pertofran* or petylyl or desmethylimiprami* or desmetiliprami*).mp.

31. (Desvenlafaxin* or pristiq).mp.

32. (Dibenz?pin* or noveril).mp.

33. (Dimetacrin* or acripramine or dimethacrine or iston?l or linostil or miroistonil).mp.

34. (Dos?ulepi* or depropin or dopress or dothcin or dothep or dot?iepin* or dothip or espin or othtric or prepadine or prothiaden or qualiaden or thaden or vick-thiaden).mp.

35. (Doxepin* or Anten or Antimax or aponal or Deptran or doksepi* or Doneurin or Doxal or Doxe or doxedep or doxetar or doxin or doxyril or Gilex or "Li Ke Ning" or Mareen or noctaderm or Prudoxin or Qualiquan or Quitaxon or sagalon or Silenor or Sinepin or Sin?quan* or Spectra or xepin or zonalon).mp.

36. (Duloxetin* or "ao si ping" or ariclaim or c-pact or cymbalta or delok or duceten or dulife or dumore or duvanta or duxet or duxetin or duzela or lervitan or lexapro or nitexol or nudep or tioxetine or xeristar or yentreve).mp.

37. (Escitalopram* or alivate-e or aloce or alwel or ambulax-ad or anxila or Aramix or articalm or avertyn or Axiomat or Beaplen or c-pram-s or celtium or cilentra or cipralex or Citalex or cita-s or citalop-s or citel or citofast or citoles or citraz or depart or deplam-s or deptune or depralin or depresinal or deprigen or deprilept or despra or eciprax or ecitalop or ecitrix or ectiban or elcit or elicea or emdes or entact or escertal or escilan or escimylan or escin or escinapram or esciprex or esciprox or escirdec or escita* or esciterokam or escitil or escitomar or escitotab or escitrac or escitralex or esdep or esertia or esfan?y or esipra? or esitalo or esitonic or esitor or esjoy or eslorex or esmax or esopram or esoprex or espar or espax or espram or esprolan or esram or essobel or esto or estomine or etalopro or exodus or ex3 or feliz-s or firsito or heipram or ipran or isozyloram or itakem or jolivel or jopram or jovia or lenuxin or lexam or lexamil or lexapro or lextor or lideropram or lorepram or losiram or loxalate or meridian

or monopram or mozarin or mylopram or neopresol or neozentius or nestilo or nexipram or nexito or "novo humorap" or pramatis or premalex or rasec or recita or reconter or reposil or s-citadep or s-citalopram* or sades or scippa or scipral or secita or selectra or seroplex or sipralexa or solatcit or tacipram or talogen or talomam or talpram or ticofarma or tiopram or zecidec or zendor or zenvas or zepaz or zocital or zytomil).mp.

38. (Fluox* or Actan or Actisac or A?dep or Adepssir or Adofen or Affex or Afzot or Alental or Alentol or Alivate or Andepin or Animex-On or Anisimol or Aniup or Anoxen or Ansi or Antipres* or Anzac or Anzolden or "Ao Mai Lun" or Apo-Fluoxetine or Aprinol or Auroken or Auscap or Axtin or Azur or Barozac or Bellzac or Bioxetin or Biozac or Captaton or Clexiclor or Clinium or Cloriflox or Courage or CP-Fluoxet or Curix or Daforin or Dagrilan or Dawnex or Defluox or Depreks or Depress or Depr?x* or Depr?za? or Depro?in or Depset or Depten or Depzac or Diesan or Digassim or Dinalexin or Docfluoxetine or Dominium or Eburnate or Elizac or Equilibrane or Eufor or Exostrept or Faa or Faboxetina or Fadep or Farmaxetina or Faxtin or Felicium or Felixina or F-Exina or Fibrotina or Floccin or Flocet* or Flonital or Florak or Florexal or Flotina or Flox* or Fluchem or Fluctin* or Fludac or Fludawn or Fludep or Flugen or Flulox or flumed or Flumusa-20 or Flunat or Fluneurin or flunil or Flunisan or Fluocalm or Fluocim or Fluohexal or Fluopiram or Fluovex or Fluralex or Fluran or Fluriv or Flusac or Flustad or Flutin* or Flutop or Flutr?c or fluval or FluWinox or Flux* or Fluz? or Fokeston or Fondur* or Fontex or Foransi or Foxeteva or Fox?tin or Framex or Fulsac or Fulx or Fusum or FXT or F-ZAC or Gerozac or Griloc or Hapilux or HT or Indozul or Ipsumor or "Jin Kai Ke" or "Kai Ke" or Kalxetin or Ladose or Lapsus or Lebensart or Lecimar or Lodep or Loftil or Loksetin or Lorien or Lovan or Loxetine or Luramon or Magrilan or Mitilase or Molux or Motivest or Mutan or Nazuk or Nedep or Nerbet or Nervosal or Neupax or "Neuro Laz" or Neuxetin or Noc or Nopres or Nortec or Norzac or Noxetine or Nuzac or Nuzak or Orthon or Ovisen or Oxedep or Oxetine or Oxipres or Oxsac or Pisaurit or Platin or Plinzene or Plumed or Portal or Positivum or Pragmaten or Prizma or Prodep or Prodin or Proflusak or ProHexal or Prosimed or Proz* or Psipax or Psiquial or Qualisac or Quanilene or Ranflocs or Regultron or Reneuron or Rezak or Salipax or Sarafem or Sartuzin or Saurat or Selectus or Selfemra or Seromex or Seronil or Sinzac or Siquial or Sofelin or Sostac or Stephadilat-S or Stressless or Teczac or Thiramil or Trizac or Tuneluz or Ulmely or

Ultiflox or Unprozy or Verotina or Xeredien or Xetin or Xetiran or Youke or Za?tin or ZAC or Zedprex or Zezac or Zinovat or Zyfloxin).mp.

39. (Fluvoxamin* or deprivox or desiflu or dumirox or dumyrox or favarin or favoxil or fevarin or floxyfral or flox-ex or fluvamteva or fluvator or fluvoksami* or fluvohexal or fluvosol or fluvoxadura or fluvoxin or foxa or luvox or maveral or movox or myroxine or revoxin or riva-fluvox or ruibile or sorest or uvox or voxam or voxamine or vuminix).mp.

40. (Imiprami* or antidep or antipres or celamine or depik or depramin* or depranil or depsol or depsonil or diamin or elamin or eldep or elepsin or ethipramine or fixon or imidobenzyle or imipra or imiprex or imizin or impril or imprine or inpramine or janimine or melipramin* or mepramin or microdep or mipra?in* or novo-pramine or praminan or primonil or pryleugan or talpramin or tofranil or tolerade or "uni imiprax" or venefon).mp.

41. (Iproniazid* or marsilid).mp.

42. (Isocarboxazid* or isokarboksatsid* or isokarboxazid* or marplan).mp.

43. (Levomilnacipran* or fetzima).mp.

44. (Lofepramin* or emdalen or gam?nil or lomont).mp.

45. (Maprotili* or aprotilin or deprilept or dibencycladine or klimastress or ludiomil or ludios or lunaline or maprolu or mapromil or maprotibene or maprotil or melodil or mirpan or psymion or retinyl or sandepril or tilsan).mp.

46. (Melitracen* or ambulax-fm or anfree or danxipress or deanxit or delewal or denxol or flupen-m or forcalm or franxit or fycida-m or melicen-fp or meliyos or melthix or metflu or quali-xit).mp.

47. (Metapramin* or prodastene or timaxel).mp.

48. (Mianseri?n* or ath?mil or bolvidon or bonserin or depnon or deprexolet or lantanon or lerivon or lumin or mealin or miabene or miagen or mianeurin or miansec or miansegen or miansemerck or miaser or miaxan or norserin or prevalina or servin or tolimed or tolmin or tolvon).mp.

49. (Milnacipra* or dalcipran or ixel or midalcipran or milborn or milnace or misulvan or savella or toledomin).mp.

50. (Mirtazapi* or Adco-Mirteron or Afloyan or Amirel or Arintapin or Avanza or Axit or Azapin or Azatrim or Beron or Bexmirt or BexZis* or Bilanz or Calixta or Comenter or Ciblex or Combar or Comenter or Depreram or Divaril or Esprital or Kompazin or Matiz or Maz or Menelat or Merdaten or "Mi Er Ning" or Minelza or Mira or Miramerck or Miramind or Mirap or Mirasol or Miraz or Mirazep or Mirnite or Miro or Mirpax or Mirpik or Mirpine or Mirrador or Mirstar or Mirt or Mirta* or Mirtel or Mirtin or Mirtor or Mirzalux or Mirzasna or Mirzaten or Mirzest or Mitabor or Mitaxind or Mitocent or Mizapin or Motofen or Mytra or Nassa or Norset or Noxibel or Nutaz or Paidisheng or Promyrtil or Psidep or Razapina or Redepra or Remergil or remer?on* or Remirta or Rexer or Saxib or Tazamel or Tetrazic or Trimazimyl or Valdren or Vastat or Velorin or Yarocen or Zapatabs or Zapex or Zestat or Zismirt or zispin or Zuleptan or azamianserin or mepirzepine or mirtatsapi*).mp.

51. (Mo?lobimid* or amira or apo-moclob or arima or auror?x or "bei su" or clobemix or clorix or demobal or depnil or feraken or "hai bei lin" or inpront or langtian or manerix or maorex or maosig or mobemid* or moclamine or moclix or moclo* or mocrim or mohexal or molar or morex or lobem or rimarex or rimoc or "tian tai" or "ya zheng" or zorix).mp.

52. (Nefaz?don* or nefadon or nefirel).mp.

53. (Nitroxazepine or sintamil).mp.

54. (Nortript?lin* or Allegron or aventyl or desitriptyline or desmethylamitriptylin or norfenazin or noritren or norline or norpress or norterol or nortrilen or nortrip or nortylin* or norventyl or n-trip or ortrip or pamelor or paxtibi or sens?val).mp.

55. (Noxipt?lin* or agedal or dibenzoxine or elronon or nogedal).mp.

56. (Opripramol* or deprenil or insidon or insomin or inzeton or opipra* or opridon or oprimol or pramolan or sympramol).mp.

57. (Oxitriptan or "5 HTP" or 5?Hydroxytryptophan or 5HTP or 5-Hydroxytryptophan or Cincofarm or Levotonine or Trip-OH or 5-HTP).mp.

58. (Quinupramin* or kinupril).mp.

59. (Parox* or Actaparoxetine or Adepress or Afenexil or Allenopar or Apodepi or Apo-Oxpar or Apo-Parox or Arapaxel or Arketis or Aropax or Arotin or Aroxat or Bectam or Benepax or Brisdelle or Casbol or Cebrilin or Cinpar-CR or Dapagut or

Daparox or Datevan or Denerval or Deparoc or Depaxan or Deprox or Deprozel or Deroxat or Divarius or Dropax* or Ennos or Euplix or Eutimil or Extine or Faroe or Frosinor or Ixicrol or "Le You" or Leparox or Loxamine or Meloxat or Meplar or Moratus or Motivan or Neurotrox or Nokturn or Noprilex or Olane or Ontracel or Optipar or Oropaxin or Ox?tine or Pamax or Pamoxet or Panex or Paradise or Paratonina or Parax or Par?tin or Par?xat or Pari or paroc or Parocetan or parokseti* or Parogen or Parole* or ParoLich* or Paromerck or Paronex or Parosat or Paroser or Paroteva or Pasorex or Paxan or Paxera* or Pax or Paxetil or Paxil or Paxinol or Paxotin or Paxpar or Paxt or Paxtin* or Paxtrat or Paxxet or Pexeva or Plisil or Pondera or Posivyl or Prexat or Psicoasten or Remood or R?xetin or Ritlemi or Roxepar or Sedarin or Serestill or Seretran or Sereupin or Serorex or Seroxat or Seroxetabs or Serrapress or Sertero or Sicopax or Sicotral or Solben or Sostel or Stiliden or Taberil or Tagonis or Tamcere or Tiarix or Traviata or Voltak or Xet or Xetanor or Xetin or Xetroran or Xilanic or Zanoxina or Zoxapar or Zuria or Zyparox).mp.

60. (Phenelzin* or fenelzin* or margyl or nardelzine or nardil or phenethylhydrazine).mp.

61. (Pipofezin* or azaphen).mp.

62. (Pirlindol* or Implementor or normazidol or p?razidol).mp.

63. (Propizepine or depressin or vagran).mp.

64. (Protriptylin* or vivactil).mp.

65. (Reboxetin* or davedax or edronax or irenor or n?rebox or prolift or solvex or yeluoshu or zuolexin).mp.

66. (S?elegilin* or Amboneural or Antiparkin or Apo-Seleg or Apo-Selin or Atapryl or Brintenal or Calaquin or Carbex or Cognitiv or Cosmopril or Depren?l or Deprilan or Egibren or eldepryl or Elegelin or Elepril or emsam or Ermolax or Feliselin or "FP Tab" or "Fu An" or g?lin* or "Jin Si Ping" or Julab or Jum?x* or Jutagilin or Krautin or Legil or Mexil or Moverdin or Movergan or Niar or Niponeurin or Otrasel or Parkexin or Parkilyne or Plurimen or Procythol or Resostyl or Sefmex or Segan or Seldepar or Selecom or Seledat or Selegos or Selepark or Selerin or Selg?n* or Selgimed or Selgres or szelegilin* or Xilopar or zelapar).mp.

67. (Sertra* or Acortral or Actiser or Adco-Zertra or Aderta or Adjuvin or Aleval or Altisben or altruline or Aluprex or Anexin or Anilar or Antideprimal or Antipres or Apo-Sertral or Apresia or aremis or Aserin or Aserta or Asertin or Assert or Atenix or "Bei Yu" or besitran or Bicromil or Camidlin or Cefelic or Celonfex or Censir or Certorun or Concorz or Conexine or Cratular or Daxid or Dazolin or Deplin or deprax or Deprecalm or Deprefolt or Depreger or Deprilix or Depsert or Deptral or Dieloft or Diticone or Eleva* or Emergen or Enidap or Enore or Epilyd or Episod or Equivac or Eterim or Exulten or Fatral or Fridep or Gerlina or Gerotralin or gladem or Iglodep or Implicane or Inosert or Insertec or Irradial or JinDeSi or "Kuai Wu You" or Leyuan or Lindep or Line or Lowfin or Lusedan or Lusert or Lustec or Lustragen or lustral or Lustramerck or Luxeta or Luzina or Medisert or Mentolift or Miravil or Misol or Mycinil or Neurosedine or Novativ or Nudep or Obzin or Oralin or "Pi Mai Le" or Positiva or Prosertin or Psicotil or Resteral or Satil or sealdin or Sedoran or Selectra or Seralin or Serdep or Sered or Serena?a or Seretral or Serimel or Serivo or Serlain or Serlan or Serlif* or Serlin* or Serlo or Serlof or Serlosane or Sermax or Sernade or Serolux or Seronex or Seronip or Serot?p or Serpax or Serta* or Serteva or Sertex or Sertivan or Sertri? or Sertron? or Sertwin or Sertzol or Servantax or Setaloft or Setaratio or Setrof or Setrona or Somidal or Starin or Stimuloton or Tatig or Teuloft or Tialin or Tolrest or Torin or Tralin* or Trali?se? or Tralix or Tresleen or Vunot or "Wei Ta Ting" or "Xi Tong Jing" or "Xinya Quling" or Xsert or Xydep or "Yi Suo Ming" or "Ying Si Tiao" or "Yu Lang" or "Yu Luo Xin" or Zeelinax or Zeenix or Zeleft or Zerlin or Zolid or Zolodin or Zoloft or Zolotrin or Zoltralina or Zorta* or Zosert or Zotaline or Zotral or Zoxx or Zylin or Zysertin).mp.

68. (Setiptilin* or Teciptilin* or Tecipul).mp.

69. ("Saint John's Wort" or Alacre or Amenicil or Animic or Anxium or Apatinac or Arkocapsulas Hiperico or Bettermood or Cesradyston or Ciperico or Depasin or Depgard or Deprim or Deprivita or Doppelherz Nervotonik or Duchy Herbals Hyperi-Lift or Equilibrium or Esbericum or Euphypertuis or Felis or Felisio or Fiotan or Fitovital or Helarium or Herbal Mood Relief or Herbion Hypericum or Hewepsychon uno or Hipax or Hipcedan or Hiperex or Hipericin or Hiperico or Hiperikan or Hiperinat or Hipersac or HRI Good Mood or Hyneurin or Hypercaps or Hyperforat or Hyperherba or Hyperi-Calm or Hypericon or Hyperidrine or Hyperiforce or Hyperiforte or Hyperigreen or HyperiMed or Hyperiplant or Hypermin or Hyperosedat or Hyperval or

Iperisan or Jarsin or Johanicum or John*W or Jovin or J-Wort or Karma or Karmamood or Kira or Laif or Livren or Lucilium or "Mandal 425" or Mediflor or Mildac or Milperinol or Modigen or Mood Boost or Moodeze or Motiven or Myrall or Nat Trezalky or Negrustin or Nervaxon or Neukan or Neurokan or Neuroplant or Neuropret or Neurovegetalin or Novo-Passit or Perhip or Perika* or Prazen or Preso or Procalmil or Proserem or Prosoft or Psychotonin or Quetzal or Quiens or ReBalance or Remotiv or Remotive or saintjohn*w or Sanalum or "Shuganjieyu Jiaonang" or Silenil or Solevita or Spilan or StJohn* or stjohn*w or Stress-Relax or Texx or Tonizin or "Trezalka v Nalevovych Sacchich" or Trezalkov* or Triativ or Ucalm or Velzina or Vitalium or Zibrine).mp.

70. (Tianeptin* or stablon or coaxil or tatinol).mp.

71. (Tran?lc?promin* or jatrosom or parnate or transamine).mp.

72. (Traz?don* or azona or deprax or des?rel or diapresan or donaren or molipaxin or mesyrel or nestrolan or oleptro or "shu xu" or sideril or "su yu" or taxagon or thombran or trant or tranzelm or trazo or trazolan or trazone or trazorel or triticum or trittico or tronsalan or zameg or zodonrel or zorel).mp.

73. (Trim?pramin* or apo-trimip or herphonal or novo-tripramine or rhotrimine or sapilent or stangyl or strattera or surmontil or trimeprimin* or trimidura or trimine or trimineurin or trimip or trimipramiini or tripramine or tripress or tydamine).mp.

74. (Tryptophan* or ardeydorm or ardeytropin or kalma or lyphan or naturruhe or optimax or triptofan* or trophan or trofan or tryptacin or tryptan).mp.

75. (Venlafaxin* or afax or alenthus or alfaxin or alventa or arafaxina or argofan or arixen or arvifax or axone or axyven or benolaxe or bexalov or blossom or conervin or convalemin or dalium or depant or depefex or deprevix or depurol or desinax or dislaven or dobupal or ef*ex or efaxin or efectin or efegen or efetrin or efevelon or efevelon* or efexor or effectin or effexor or elafax or elaxine or elbfaxin or elify or envelaf or falven or faxigen or faxine or faxiprol or faxiven or faxolet or flavix or flaxlis or fobiven or foraven or ganavax or genexin or hafaxin or idoxen or illovex or ireven or jarvis or kofaxin or lafactin or lafax?n or lafaxven or lavenax or melocin or memomax-s or mezine or mollome or nervix or nisaxin or nopekar or norafexine or norezor or norpilen or novidat or odven sbk or olwexya or oriven or panofen or politid or pracet or pramina or prefaxine or quilarex or ranfaxiran or senexon or sentidol or serosmine or

sesaren or subelan or sunvex or symfaxin or tifaxin or tonpular or trevilor or tubenax or tudor or valosine or vedixal or velafax or velax or velaxatin or velaxin or velept or velexor or velift or velpine or venaxibene or venaxol or venaxx or vendep or venex or ven-fax or venfecto or venforin or veniba or venifax or venla or venla* or venlabaccher or venlaburg or venlacross or venladem or venladima or venladoz or venlafab or venlafex or venlagamma or venlakato or venlalic or venlamed or venlamyl or venlanofi or venlapete or venlapol or venlaraf or venlaran or venlasan or venlasand or venlathen or venlatif or venlatio or venlaxgen or venlaxin or venlaxor or venlectine or venlexor or venlifax or venlift or venlix or venlofex or venlor or vennaxa or vensir or ventadepress or venxin or venxor or vexor or viepax or voxafen or Wenlafaksyny or winfex or xadevil or xapnev or zacalen or zarelis or zarelix).mp.

76. (Vilazodon* or viibyrd).mp.

77. (Vortioxetin* or brintillex).mp.

78. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77

79. 5 and 10 and 78

80. exp Epidemiology/ or exp Epidemiologic Studies/ or epidemiolog*.mp. or exp Epidemiological Monitoring/

81. exp Risk Factors/ or exp Case-Control Studies/

82. (" risk factor*" or "case control" or case-control).mp.

83. exp Cohort Studies/

84. cohort.mp.

85. exp Cross-Sectional Studies/

86. ("cross section*" or cross-section*).mp.

87. exp Follow-Up Studies/

88. ("follow up" or follow-up).mp.

89. exp Prospective Studies/ or prospective.mp.

90. exp Longitudinal Studies/ or longitudinal.mp.

91. exp Retrospective Studies/ or retrospective.mp.

92. observational.mp. or exp Observational Study/

93. exp "Drug-Related Side Effects and Adverse Reactions"/ or adverse.mp. or exp Adverse Drug Reaction Reporting Systems/ or exp Long Term Adverse Effects/

94. (correlation* or "time series" or time-series or case-series or "case series" or "case-referent study" or "case referent study" or "case stud*" or case-stud* or descriptive).mp.

95. Electronic Health Records/ or Medical Records Systems, Computerized/ or Medical Records/

96. ("health* record*" or "patient record*" or "medical record*" or "personal record" or "routinely collected" or registr* or "hospital record*" or insurance or claims).mp.

97. 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96

98. 79 and 97

Appendix B – Adapted Newcastle-Ottawa Scale for risk of bias assessment

Studies scored stars (*) based on the following criteria:

Selection score (out of 4*):

- Case definition (* for independent evaluation or secure record; not for self-report)
- Representativeness (* for fully or somewhat representative of general population of adults with comorbid depression and T2DM)
- Non-respondent rates, description and action (* for satisfactory response rate and established comparability between respondents and non-respondents)
- Ascertainment of exposures (* for secure record or structured interview; not for self-report)

Comparability score (out of 2*):

- Controls for most important factor (* to control for depression severity)
- Controls for any other factor (*)

Outcome score (out of 1*):

- Ascertainment of outcome (* for independent evaluation or secure record; not self-report)

Appendix C - Independent Scientific Advisory Committee of CPRD approval for protocol no. 21_001648

Dear Dr Joseph Hayes,

Your study 21_001648 – “Antidepressant treatment and outcomes in the context of polypharmacy in adults with comorbid depression and type 2 diabetes ” has been approved by CPRD. You can view any additional feedback by logging on to eRAP at https://www.erap.cprd.com/.

If your study requires CPRD to extract the study dataset, please contact CPRD via enquiries@cprd.com to initiate a single-study licence agreement and discuss the data specification.

If your amended study will access CPRD data via an Institutional multi-study licence and you require linked data, you will need to make a request for the linked data.
• If you require linked data to identify the study cohort, please complete the Linkage Request Form, available on eRAP, and return this to enquiries@cprd.com with the code lists (in the form of a tab delimited text file) as soon as possible.
• If/when you require linked data for a cohort you have already defined, please complete the Linkage Request Form, available on eRAP, and return this to enquiries@cprd.com with your patient identifiers (in the form of a tab delimited text file).

Linked data will be provided, by secure transfer, within 10 working days of receipt of a valid request.

Should you require any advice regarding the implementation of your approved amendment please don't hesitate to contact us at enquiries@cprd.com.

Kind Regards,
CPRD

NIHR | National Institute for Health and Care Research

Appendix D – Depression clinical code list for CPRD

medcodeid	term	originalreadcode	cleansedreadcode	snomedctconceptid	snomedctdescriptionid
251629019	H/O: depression	1465	1465.00	161469008	251629019
407066012	C/O - feeling unhappy	1B17-2	1B17.12	272024005	407066012
1488626018	Symptoms of depression	1B1U	1B1U.00	394924000	1488626018
1494612017	Depressive symptoms	1B1U-1	1B1U.11	394924000	1494612017
369915018	Loss of interest	1BP	1BP..00	247753000	369915018

2548573012	Loss of interest in previously enjoyable activity	1BP0	1BP0.00	417523004	2548573012
369972011	Loss of capacity for enjoyment	1BQ	1BQ..00	247796005	369972011
490537016	Depressed mood	1BT	1BT..00	366979004	490537016
490537016	Low mood	1BT-1	1BT..11	366979004	490537016
490537016	Sad mood	1BT-2	1BT..12	366979004	490537016
450255017	Loss of hope for the future	1BU	1BU..00	307077003	450255017
2956111010	Suspected depression	1JJ	1JJ..00	473126001	2956111010
51590017	Dysphoric mood	1S40	1S40.00	30819006	51590017
2946210000000118	Depression resolved	212S	212S.00	196381000000100	294621000000118
1231868010	Puerperal depression	62T1	62T1.00	58703003	1231868010
1773563015	Depression management programme	8BK0	8BK0.00	401174001	1773563015
2533375017	Patient given advice about	8CAa	8CAa.00	415044007	2533375017

	management of depression				
300711000000119	Referral for guided self-help for depression	8HHq	8HHq.00	199111000000100	300711000000119
237006100000111	Referral for depression self-help video	8HHq0	8HHq000	923921000000104	237006100000111
239154100000115	Referral for guided self-help for depression declined	8IH52	8IH5200	933441000000101	239154100000115
2534096013	Depression annual review	9H90	9H90.00	413972000	2534096013
2534092010	Depression medication review	9H91	9H91.00	413974004	2534092010
2534091015	Depression interim review	9H92	9H92.00	413973005	2534091015
2474715017	On depression register	9HA0	9HA0.00	413169006	2474715017
406881000000111	Depression monitoring administration	9Ov	9Ov..00	713831000000108	156507100000118
408521000000112	Depression monitoring first letter	9Ov0	9Ov0.00	717211000000107	156975100000114

408541000000117	Depression monitoring second letter	9Ov1	9Ov1.00	716681000000100	1569231000000114
408561000000116	Depression monitoring third letter	9Ov2	9Ov2.00	716961000000102	1569511000000115
408581000000113	Depression monitoring verbal invite	9Ov3	9Ov3.00	717261000000109	1569801000000119
408601000000116	Depression monitoring telephone invite	9Ov4	9Ov4.00	716421000000103	1568971000000112
294081000000110	Exception reporting: depression quality indicators	9hC	9hC..00	716111000000102	1568671000000117
999901000006113	Excepted from depression quality indicators: Patient unsuita	9hC0	9hC0.00	716831000000103	1569381000000116
999911000006111	Excepted from depression quality indicators: Informed dissen	9hC1	9hC1.00	715831000000109	1568391000000112
226411000000110	Depression - enhanced services administration	9k4	9k4..00	166291000000108	1154541000000116

226581000000119	Depression - enhanced service completed	9k40	9k40.00	166481000000107	1154701000000110
1680571000006118	On full dose long term treatment depression - enh serv admin	9kQ	9kQ..00	361761000000106	681801000000113
681801000000113	On full dose long term treatment for depression	9kQ-1	9kQ..11	361761000000106	681801000000113
613791000006115	Depressive psychoses	E11-2	E11..12	35489007	59212011
401766011	Single major depressive episode	E112	E112.00	36923009	61590015
474171000006112	Agitated depression	E112-1	E112.11	83458005	138421012
642461000006116	Endogenous depression first episode	E112-2	E112.12	231499006	346972018
346972018	Endogenous depression first episode	E112-3	E112.13	231499006	346972018
441826016	Endogenous depression	E112-4	E112.14	300706003	441826016
294824018	Single major depressive	E1120	E112000	36923009	61590015

	episode, unspecified				
294825017	Single major depressive episode, mild	E1121	E112100	79298009	131561018
294826016	Single major depressive episode, moderate	E1122	E112200	15639000	26507014
142541000006115	Single major depressive episode, severe, without psychosis	E1123	E112300	251000119105	2916281014
294828015	Single major depressive episode, severe, with psychosis	E1124	E112400	191604000	294828015
142521000006110	Single major depressive episode, partial or unspec remission	E1125	E112500	70747007	117520015
294831019	Single major depressive episode, in full remission	E1126	E112600	19527009	3304522019
294832014	Single major depressive episode NOS	E112z	E112z00	36923009	61590015

182721000006111	Recurrent major depressive episode	E113	E113.00	268621008	401767019
410861011	Endogenous depression - recurrent	E113-1	E113.11	274948002	410861011
294836012	Recurrent major depressive episodes, unspecified	E1130	E113000	268621008	401767019
294837015	Recurrent major depressive episodes, mild	E1131	E113100	191610000	294837015
294838013	Recurrent major depressive episodes, moderate	E1132	E113200	191611001	294838013
182771000006112	Recurrent major depressive episodes, severe, no psychosis	E1133	E113300	764611000000100	1696221000000111
294840015	Recurrent major depressive episodes, severe, with psychosis	E1134	E113400	191613003	294840015
182801000006114	Recurrent major depressive	E1135	E113500	764691000000109	1696381000000115

	episodes,partial/unspec remission				
294843018	Recurrent major depressive episodes, in full remission	E1136	E113600	191615005	294843018
294844012	Recurrent depression	E1137	E113700	191616006	294844012
294845013	Recurrent major depressive episode NOS	E113z	E113z00	268621008	401767019
369982012	Seasonal affective disorder	E118	E118.00	247803002	369982012
294894013	Atypical depressive disorder	E11y2	E11y200	191659001	294894013
346973011	Masked depression	E11z2	E11z200	231500002	346973011
294917018	Reactive depressive psychosis	E130	E130.00	191676002	294917018
294918011	Psychotic reactive depression	E130-1	E130.11	191676002	294918011
138421012	Agitated depression	E135	E135.00	83458005	138421012

488211000006112	Anxiety with depression	E2003	E200300	231504006	346979010
675861000006113	Neurotic depression reactive type	E204	E204.00	87414006	144929012
882401000006115	Reactive (neurotic) depression	E204-99	E204.99	87414006	882401000006115
613781000006118	Depressive personality disorder	E2112	E211200	78667006	130532011
882421000006113	Depressive personality	E2112-99	E211299	78667006	882421000006113
525921000006119	Brief depressive reaction	E290	E290.00	192046006	295490019
295494011	Brief depressive reaction NOS	E290z	E290z00	192046006	295490019
202561000006114	Prolonged depressive reaction	E291	E291.00	192049004	295495012
295535012	Depressive disorder NEC	E2B	E2B..00	35489007	59212011
882671000006112	Depression	E2B-98	E2B..98	609311000000100	882671000006112
882681000006110	Depression NOS	E2B-99	E2B..99	609311000000100	882681000006110

295536013	Postviral depression	E2B0	E2B0.00	192079006	295536013
295537016	Chronic depression	E2B1	E2B1.00	192080009	295537016
959761000006118	Loss of interest/involvement in activities/self-care	EMISCLO3		959761000006102	959761000006118
959741000006117	Sadness/hopelessness/decreased self-esteem	EMISCSA2		959741000006101	959741000006117
197598100006114	Mild depressive episode, without somatic syndrome	EMISICD10|F3200		197598100006105	197598100006114
197599100006112	Mild depressive episode, with somatic syndrome	EMISICD10|F3201		197599100006108	197599100006112
197602100006115	Moderate depressive episode, without somatic syndrome	EMISICD10|F3210		197602100006104	197602100006115
197605100006112	Moderate depressive episode, with	EMISICD10|F3211		197605100006108	197605100006112

	somatic syndrome				
1976211000006116	Recurrent depressive disorder, current episode mild, without somatic syndrome	EMISICD10|F3300		1976211000006100	1976211000006116
1976231000006110	Recurrent depressive disorder, current episode mild, with somatic syndrome	EMISICD10|F3301		1976231000006106	1976231000006110
1976251000006115	Recurrent depressive disorder, current episode moderate, without somatic syndrome	EMISICD10|F3310		1976251000006104	1976251000006115
1976271000006113	Recurrent depressive disorder, current episode moderate, with somatic syndrome	EMISICD10|F3311		1976271000006109	1976271000006113
1976411000006115	Other recurrent mood affective	EMISICD10|F3810		1976411000006104	1976411000006115

	disorders, recurrent brief depressive disorder				
1976491000006113	Mixed anxiety and depressive reaction	EMISICD10|F4322		1976491000006109	1976491000006113
7345610000006117	Loss of interest	EMISLO1		7345610000006101	7345610000006117
1806431000006113	Adjustment disorder with depressed mood	EMISNQAD51		57194009	95129017
1823881000006110	Depression confirmed	EMISNQDE36		1823881000006106	1823881000006110
9155410000006117	Geriatric depression scale - 8 points	EMISNQGE10		9155410000006101	9155410000006117
9155510000006115	Geriatric depression scale - 9 points	EMISNQGE11		9155510000006104	9155510000006115
9155610000006118	Geriatric depression scale - 10 points	EMISNQGE12		9155610000006102	9155610000006118
9155710000006113	Geriatric depression scale - 11 points	EMISNQGE13		9155710000006109	9155710000006113

915581000006111	Geriatric depression scale - 12 points	EMISNQGE14		915581000006107	915581000006111
915591000006114	Geriatric depression scale - 13 points	EMISNQGE15		915591000006105	915591000006114
915601000006118	Geriatric depression scale - 14 points	EMISNQGE16		915601000006102	915601000006118
915611000006115	Geriatric depression scale - 15 points	EMISNQGE17		915611000006104	915611000006115
915521000006112	Geriatric depression scale - 6 points	EMISNQGE8		915521000006108	915521000006112
915531000006110	Geriatric depression scale - 7 points	EMISNQGE9		915531000006106	915531000006110
199501100006112	HoNOS (Health of the Nation Outcome Scales) for working age adults rating scale 7 - problems with depressed mood	EMISNQHO152		979581000000105	249120100000111
182131100006112	Hopelessness	EMISNQHO52		307077003	1821311000006112

1956431000006111	Keele ENHANCE trial - anxiety/depression	EMISNQKE196		1956431000006107	19564310006111
1956441000006118	Keele ENHANCE trial - anxiety/depression advice	EMISNQKE197		1956441000006102	19564410006118
1956481000006112	Keele ENHANCE trial - anxiety/depression verbal advice - alcohol	EMISNQKE200		1956481000006108	19564810006112
1956491000006110	Keele ENHANCE trial- anxiety/depresn verbal advice- managing mood	EMISNQKE201		1956491000006106	19564910006110
1956501000006119	Keele ENHANCE trial- anxiety/depression verbal advice- sleep habit	EMISNQKE202		1956501000006103	19565010006119
1956531000006110	Keele ENHANCE trial- anxiety/depression written advice - alcohol	EMISNQKE205		1956531000006106	19565310006110

1956541000006117	Keele ENHANCE trial- anxiety/depresn written advice- managing mood	EMISNQKE206		1956541000006101	1956541000006117
1956561000006118	Keele ENHANCE trial - anxiety/depression - no f/up appt needed	EMISNQKE208		1956561000006102	1956561000006118
1956571000006113	Keele ENHANCE trial- anxiety/depression- f/up nurse appt advised	EMISNQKE209		1956571000006109	1956571000006113
1956581000006111	Keele ENHANCE trial- anxiety/depression - f/up nurse appt booked	EMISNQKE210		1956581000006107	1956581000006111
1956591000006114	Keele ENHANCE trial - anxiety/depression - f/up GP appt advised	EMISNQKE211		1956591000006105	1956591000006114
1956601000006118	Keele ENHANCE trial - anxiety/depression - f/up GP appt booked	EMISNQKE212		1956601000006102	1956601000006118

1956621000006111	Keele ENHANCE trial- anxiety/depression- immediate advice from GP	EMISNQKE213		1956621000006107	1956621000006111
2017961000006113	Keele INCLUDE study - anxiety/depression	EMISNQKE301		2017961000006109	2017961000006113
2019001000006116	Keele STarT MSK score - anxious or low mood because of pain	EMISNQKE306		2019001000006100	2019001000006116
1839551000006116	PHQ9 total score 5-9 (mild depression)	EMISNQPH33		1839551000006100	1839551000006116
1839561000006119	PHQ9 total score 10-14 (moderate depression)	EMISNQPH34		1839561000006103	1839561000006119
1839571000006114	PHQ9 total score 15-19 (moderately severe depression)	EMISNQPH35		1839571000006105	1839571000006114
1839581000006112	PHQ9 total score 20-27 (severe depression)	EMISNQPH36		1839581000006108	1839581000006112

1008821000006112	PHQ9 score - feeling down or depressed or hopeless	EMISNQPH8		1008821000006108	1008821000006112
2659601000000116	Signposting to depression self-help group	ESCTSI25		1057351000000106	2659601000000116
376721000006114	[X]Depressive episode	Eu32	Eu32.00	35489007	486185019
426911000006111	[X]Single episode of depressive reaction	Eu32-1	Eu32.11	87414006	2951871015
426941000006110	[X]Single episode of psychogenic depression	Eu32-2	Eu32.12	87414006	2951871015
426971000006119	[X]Single episode of reactive depression	Eu32-3	Eu32.13	87414006	2951871015
296137015	[X]Mild depressive episode	Eu320	Eu32000	310495003	454082014
882811000006119	Mild depression	Eu320-99	Eu32099	430421000000104	882811000006119
296138013	[X]Moderate depressive episode	Eu321	Eu32100	310496002	454083016

882821000006110	Moderate depression	Eu321-99	Eu32199	4654410000000108	882821000006110
401866015	[X]Severe depressive episode without psychotic symptoms	Eu322	Eu32200	310497006	454084010
223741000000112	[X]Single episode major depression w'out psychotic symptoms	Eu322-2	Eu32212	310497006	454084010
426991000006118	[X]Single episode vital depression w'out psychotic symptoms	Eu322-3	Eu32213	310497006	454084010
882831000006113	Severe depression	Eu322-99	Eu32299	397701000000102	882831000006113
401869010	[X]Severe depressive episode with psychotic symptoms	Eu323	Eu32300	191604000	294828015
426921000006115	[X]Single episode of major depression and psychotic symptoms	Eu323-1	Eu32311	191604000	294828015

426951000006112	[X]Single episode of psychogenic depressive psychosis	Eu323-2	Eu32312	191676002	294917018
426961000006114	[X]Single episode of psychotic depression	Eu323-3	Eu32313	191604000	294828015
426981000006116	[X]Single episode of reactive depressive psychosis	Eu323-4	Eu32314	191676002	294917018
213641000000111	[X]Mild depression	Eu324	Eu32400	310495003	213641000000111
171577100006112	[X]Major depression, mild	Eu325	Eu32500	87512008	145089017
171518100006114	[X]Major depression, moderately severe	Eu326	Eu32600	832007	2451016
171578100006110	[X]Major depression, severe without psychotic symptoms	Eu327	Eu32700	75084000	124707013
171519100006112	[X]Major depression, severe with	Eu328	Eu32800	73867007	122670017

	psychotic symptoms				
1755901000006112	Single major depressive episode, severe, with psychosis, psychosis in remission	Eu329	Eu32900	755321000000106	1667601000000117
1755911000006110	Recurrent major depressive episodes, severe, with psychosis, psychosis in remission	Eu32A	Eu32A00	755331000000108	1667611000000115
401871010	[X]Other depressive episodes	Eu32y	Eu32y00	35489007	59212011
366561000006119	[X]Atypical depression	Eu32y-1	Eu32y11	191659001	294894013
426931000006117	[X]Single episode of masked depression NOS	Eu32y-2	Eu32y12	231500002	346973011
401872015	[X]Depressive episode, unspecified	Eu32z	Eu32z00	35489007	486185019
376691000006116	[X]Depression NOS	Eu32z-1	Eu32z11	35489007	486184015

376711000006118	[X]Depressive disorder NOS	Eu32z-2	Eu32z12	35489007	486185019
423611000006111	[X]Prolonged single episode of reactive depression	Eu32z-3	Eu32z13	87414006	2951871015
359121000006116	[X] Reactive depression NOS	Eu32z-4	Eu32z14	87414006	2951871015
401873013	[X]Recurrent depressive disorder	Eu33	Eu33.00	191616006	294844012
424631000006119	[X]Recurrent episodes of depressive reaction	Eu33-1	Eu33.11	191616006	294844012
424641000006112	[X]Recurrent episodes of psychogenic depression	Eu33-2	Eu33.12	191616006	294844012
424651000006114	[X]Recurrent episodes of reactive depression	Eu33-3	Eu33.13	191616006	294844012
425751000006115	[X]Seasonal depressive disorder	Eu33-4	Eu33.14	247803002	369982012

425411000006110	[X]SAD - Seasonal affective disorder	Eu33-5	Eu33.15	247803002	369983019
296180012	[X]Recurrent depressive disorder, current episode mild	Eu330	Eu33000	310495003	454082014
296181011	[X]Recurrent depressive disorder, current episode moderate	Eu331	Eu33100	310496002	454083016
379781000006118	[X]Endogenous depression without psychotic symptoms	Eu332-1	Eu33211	300706003	441826016
396081000006116	[X]Major depression, recurrent without psychotic symptoms	Eu332-2	Eu33212	268621008	401767019
432511000006119	[X]Vital depression, recurrent without psychotic symptoms	Eu332-4	Eu33214	310497006	454084010
379771000006116	[X]Endogenous depression with psychotic symptoms	Eu333-1	Eu33311	73867007	122670017

424541000006111	[X]Recurr severe episodes/major depression+psychotic symptom	Eu333-3	Eu33313	28475009	47670016
424551000006113	[X]Recurr severe episodes/psychogenic depressive psychosis	Eu333-4	Eu33314	191613003	294840015
424671000006116	[X]Recurrent severe episodes of psychotic depression	Eu333-5	Eu33315	191613003	294840015
424681000006118	[X]Recurrent severe episodes/reactive depressive psychosis	Eu333-6	Eu33316	1086471000000103	2721771000000114
296198011	[X]Recurrent depressive disorder, currently in remission	Eu334	Eu33400	698957003	2981573016
296199015	[X]Other recurrent depressive disorders	Eu33y	Eu33y00	191616006	294844012
401876017	[X]Recurrent depressive disorder, unspecified	Eu33z	Eu33z00	191616006	294844012

398841000006119	[X]Monopolar depression NOS	Eu33z-1	Eu33z11	35489007	59212011
376741000006119	[X]Depressive neurosis	Eu341-1	Eu34111	78667006	130534012
376751000006117	[X]Depressive personality disorder	Eu341-2	Eu34112	1084061000000106	2716551000000112
399961000006118	[X]Neurotic depression	Eu341-3	Eu34113	78667006	130534012
419841000006116	[X]Persistant anxiety depression	Eu341-4	Eu34114	231504006	346979010
424561000006110	[X]Recurrent brief depressive episodes	Eu3y1-1	Eu3y111	40568001	67653019
398561000006117	[X]Mixed anxiety and depressive disorder	Eu412	Eu41200	231504006	346979010
398351000006110	[X]Mild anxiety depression	Eu412-1	Eu41211	231504006	346979010
376701000006116	[X]Depressive conduct disorder	Eu920	Eu92000	231542000	347030014
909681000006110	[RFC] Depression	HNGNQRF13		909681000006106	909681000006110
1820771000006113	PCL-C - Loss of interest in activities you	JHCPC42		1820771000006109	1820771000006113

	used to enjoy: A little bit				
1820781000006111	PCL-C - Loss of interest in activities you used to enjoy: Moderately	JHCPC43		1820781000006107	1820781000006111
1820791000006114	PCL-C - Loss of interest in activities you used to enjoy: Quite a bit	JHCPC44		1820791000006105	1820791000006114
1820801000006110	PCL-C - Loss of interest in activities you used to enjoy: Extremely	JHCPC45		1820801000006106	1820801000006110
1222477019	[D]Postoperative depression	R007z-3	R007z13	82218004	136373018

Appendix E – Type 2 diabetes clinical code list for CPRD

medcode G	medcodeA	readcode	other code	readterm
7563		66A3.00		Diabetic on diet only
29979		C109900		Non-insulin-dependent diabetes mellitus without complication
8403		C109700		Non-insulin dependent diabetes mellitus - poor control
5884		C109.11		NIDDM - Non-insulin dependent diabetes mellitus
1684		66A4.00		Diabetic on oral treatment
43785		C109D00		Non-insulin dependent diabetes mellitus with hypoglyca coma
4513		C109.00		Non-insulin dependent diabetes mellitus
50609		L180600		Pre-existing diabetes mellitus, non-insulin-dependent
34912		C109400		Non-insulin dependent diabetes mellitus with ulcer
50429		C109100		Non-insulin-dependent diabetes mellitus with ophthalm comps

45467		C109B00		Non-insulin dependent diabetes mellitus with polyneuropathy
54212		C109F00		Non-insulin-dependent d m with peripheral angiopath
40962		C109H00		Non-insulin dependent d m with neuropathic arthropathy
55842		C109200		Non-insulin-dependent diabetes mellitus with neuro comps
40401		C109500		Non-insulin dependent diabetes mellitus with gangrene
72320		C109A00		Non-insulin dependent diabetes mellitus with mononeuropathy
62146		C109300		Non-insulin-dependent diabetes mellitus with multiple comps
59365		C109C00		Non-insulin dependent diabetes mellitus with nephropathy
69278		C109E00		Non-insulin depend diabetes mellitus with diabetic cataract
52303		C109000		Non-insulin-dependent diabetes mellitus with renal comps
24693		C109G00		Non-insulin dependent diabetes mellitus with arthropathy
56803		C107400		NIDDM with peripheral circulatory disorder

17262		C109600		Non-insulin-dependent diabetes mellitus with retinopathy
		C109E00		Non-insulin depend diabetes mellitus with diabetic cataract
		C109H00		Non-insulin dependent d m with neuropathic arthropathy
		C109A00		Non-insulin dependent diabetes mellitus with mononeuropathy
		C109C00		Non-insulin dependent diabetes mellitus with nephropathy
		C109B00		Non-insulin dependent diabetes mellitus with polyneuropathy
		C109200		Non-insulin-dependent diabetes mellitus with neuro comps
		C109100		Non-insulin-dependent diabetes mellitus with ophthalm comps
		C109000		Non-insulin-dependent diabetes mellitus with renal comps
		C109600		Non-insulin-dependent diabetes mellitus with retinopathy
51756		C10FP00		Type 2 diabetes mellitus with ketoacidotic coma
758		C10F.00		Type 2 diabetes mellitus

36695		C10D.00		Diabetes mellitus autosomal dominant type 2
34450		C10FK00		Hyperosmolar non-ketotic state in type 2 diabetes mellitus
45913		C109712		Type 2 diabetes mellitus - poor control
83532		66Ao.00		Diabetes type 2 review
46624		C10C.11		Maturity onset diabetes in youth
47315		C10F711		Type II diabetes mellitus - poor control
46917		C10FD00		Type 2 diabetes mellitus with hypoglycaemic coma
32627		C10FN00		Type 2 diabetes mellitus with ketoacidosis
1407		C10FJ00		Insulin treated Type 2 diabetes mellitus
25627		C10F700		Type 2 diabetes mellitus - poor control
18219		C109.13		Type II diabetes mellitus
24458		C109711		Type II diabetes mellitus - poor control

37648		C109J11		Insulin treated non-insulin dependent diabetes mellitus
22884		C10F.11		Type II diabetes mellitus
47954		C10F900		Type 2 diabetes mellitus without complication
56268		C109D11		Type II diabetes mellitus with hypoglycaemic coma
53392		C10F911		Type II diabetes mellitus without complication
64668		C10FJ11		Insulin treated Type II diabetes mellitus
98723		C10FD11		Type II diabetes mellitus with hypoglycaemic coma
17859		C109.12		Type 2 diabetes mellitus
18264		C109J12		Insulin treated Type II diabetes mellitus
59991		C10D.11		Maturity onset diabetes in youth type 2
18278		C109J00		Insulin treated Type 2 diabetes mellitus
36633		C109K00		Hyperosmolar non-ketotic state in type 2 diabetes mellitus

61071		C109D12		Type 2 diabetes mellitus with hypoglycaemic coma
25041		ZC2CA00		Dietary advice for type II diabetes
18777		C10F000		Type 2 diabetes mellitus with renal complications
49869		C109G12		Type 2 diabetes mellitus with arthropathy
18425		C10FB00		Type 2 diabetes mellitus with polyneuropathy
12736		C10F500		Type 2 diabetes mellitus with gangrene
47816		C109H11		Type II diabetes mellitus with neuropathic arthropathy
18143		C109G11		Type II diabetes mellitus with arthropathy
65704		C109412		Type 2 diabetes mellitus with ulcer
67905		C109211		Type II diabetes mellitus with neurological complications
18209		C109012		Type 2 diabetes mellitus with renal complications
25591		C10FQ00		Type 2 diabetes mellitus with exudative maculopathy

42762		C109612		Type 2 diabetes mellitus with retinopathy
47321		C10F100		Type 2 diabetes mellitus with ophthalmic complications
70316		C109112		Type 2 diabetes mellitus with ophthalmic complications
91646		C10F411		Type II diabetes mellitus with ulcer
48192		C109E11		Type II diabetes mellitus with diabetic cataract
24836		C109C12		Type 2 diabetes mellitus with nephropathy
34268		C10F200		Type 2 diabetes mellitus with neurological complications
63690		C10FR00		Type 2 diabetes mellitus with gastroparesis
49074		C10F400		Type 2 diabetes mellitus with ulcer
62107		C109511		Type II diabetes mellitus with gangrene
62674		C10FA00		Type 2 diabetes mellitus with mononeuropathy
59725		C109111		Type II diabetes mellitus with ophthalmic complications

50813		C109A 11		Type II diabetes mellitus with mononeuropathy
35385		C10FH 00		Type 2 diabetes mellitus with neuropathic arthropathy
47409		C109B 11		Type II diabetes mellitus with polyneuropathy
95351		C10FA 11		Type II diabetes mellitus with mononeuropathy
55075		C1094 11		Type II diabetes mellitus with ulcer
93727		C10FE 11		Type II diabetes mellitus with diabetic cataract
85991		C10F M11		Type II diabetes mellitus with persistent microalbuminuria
12640		C10FC 00		Type 2 diabetes mellitus with nephropathy
18496		C10F6 00		Type 2 diabetes mellitus with retinopathy
50225		C1090 11		Type II diabetes mellitus with renal complications
44779		C109E 12		Type 2 diabetes mellitus with diabetic cataract
44982		C10FE 00		Type 2 diabetes mellitus with diabetic cataract

39317		C106100		Diabetes mellitus, adult onset, + neurological manifestation
49655		C10F611		Type II diabetes mellitus with retinopathy
43227		C10F311		Type II diabetes mellitus with multiple complications
64571		C109C11		Type II diabetes mellitus with nephropathy
57278		C10F011		Type II diabetes mellitus with renal complications
98616		C10F211		Type II diabetes mellitus with neurological complications
46150		C109512		Type 2 diabetes mellitus with gangrene
18390		C10FM00		Type 2 diabetes mellitus with persistent microalbuminuria
66965		C109H12		Type 2 diabetes mellitus with neuropathic arthropathy
65267		C10F300		Type 2 diabetes mellitus with multiple complications
59253		C10FG00		Type 2 diabetes mellitus with arthropathy
60699		C109F12		Type 2 diabetes mellitus with peripheral angiopathy

37806		C10FF00		Type 2 diabetes mellitus with peripheral angiopathy
26054		C10FL00		Type 2 diabetes mellitus with persistent proteinuria
58604		C109611		Type II diabetes mellitus with retinopathy
54899		C109F11		Type II diabetes mellitus with peripheral angiopathy
50527		C10FB11		Type II diabetes mellitus with polyneuropathy
60796		C10FL11		Type II diabetes mellitus with persistent proteinuria
		C109K00		Hyperosmolar non-ketotic state in type 2 diabetes mellitus
		C10FK00		Hyperosmolar non-ketotic state in type 2 diabetes mellitus
		C109J00		Insulin treated Type 2 diabetes mellitus
		C10FJ00		Insulin treated Type 2 diabetes mellitus
		C109J12		Insulin treated Type II diabetes mellitus
		C10FJ11		Insulin treated Type II diabetes mellitus

		C109.12		Type 2 diabetes mellitus
		C10F.00		Type 2 diabetes mellitus
		C109712		Type 2 diabetes mellitus - poor control
		C10F700		Type 2 diabetes mellitus - poor control
		C109G12		Type 2 diabetes mellitus with arthropathy
		C10FG00		Type 2 diabetes mellitus with arthropathy
		C109E12		Type 2 diabetes mellitus with diabetic cataract
		C10FE00		Type 2 diabetes mellitus with diabetic cataract
		C109E12		Type 2 diabetes mellitus with diabetic cataract
		C10FE00		Type 2 diabetes mellitus with diabetic cataract
		C10FQ00		Type 2 diabetes mellitus with exudative maculopathy
		C10FQ00		Type 2 diabetes mellitus with exudative maculopathy

		C109512		Type 2 diabetes mellitus with gangrene
		C10F500		Type 2 diabetes mellitus with gangrene
		C10FR00		Type 2 diabetes mellitus with gastroparesis
		C10FR00		Type 2 diabetes mellitus with gastroparesis
		C109D12		Type 2 diabetes mellitus with hypoglycaemic coma
		C10FD00		Type 2 diabetes mellitus with hypoglycaemic coma
		C10FN00		Type 2 diabetes mellitus with ketoacidosis
		C10FP00		Type 2 diabetes mellitus with ketoacidotic coma
		C10FA00		Type 2 diabetes mellitus with mononeuropathy
		C10FA00		Type 2 diabetes mellitus with mononeuropathy
		C10F300		Type 2 diabetes mellitus with multiple complications
		C109C12		Type 2 diabetes mellitus with nephropathy

		C10FC00		Type 2 diabetes mellitus with nephropathy
		C109C12		Type 2 diabetes mellitus with nephropathy
		C10FC00		Type 2 diabetes mellitus with nephropathy
		C109212		Type 2 diabetes mellitus with neurological complications
		C10F200		Type 2 diabetes mellitus with neurological complications
		C109212		Type 2 diabetes mellitus with neurological complications
		C10F200		Type 2 diabetes mellitus with neurological complications
		C109H12		Type 2 diabetes mellitus with neuropathic arthropathy
		C10FH00		Type 2 diabetes mellitus with neuropathic arthropathy
		C109H12		Type 2 diabetes mellitus with neuropathic arthropathy
		C10FH00		Type 2 diabetes mellitus with neuropathic arthropathy
		C109112		Type 2 diabetes mellitus with ophthalmic complications

		C10F100		Type 2 diabetes mellitus with ophthalmic complications
		C109112		Type 2 diabetes mellitus with ophthalmic complications
		C10F100		Type 2 diabetes mellitus with ophthalmic complications
		C109F12		Type 2 diabetes mellitus with peripheral angiopathy
		C10FF00		Type 2 diabetes mellitus with peripheral angiopathy
		C10FM00		Type 2 diabetes mellitus with persistent microalbuminuria
		C10FM00		Type 2 diabetes mellitus with persistent microalbuminuria
		C10FL00		Type 2 diabetes mellitus with persistent proteinuria
		C10FL00		Type 2 diabetes mellitus with persistent proteinuria
		C10FB00		Type 2 diabetes mellitus with polyneuropathy
		C10FB00		Type 2 diabetes mellitus with polyneuropathy
		C109012		Type 2 diabetes mellitus with renal complications

		C10F000		Type 2 diabetes mellitus with renal complications
		C109012		Type 2 diabetes mellitus with renal complications
		C10F000		Type 2 diabetes mellitus with renal complications
		C109612		Type 2 diabetes mellitus with retinopathy
		C10F600		Type 2 diabetes mellitus with retinopathy
		C109612		Type 2 diabetes mellitus with retinopathy
		C10F600		Type 2 diabetes mellitus with retinopathy
		C109412		Type 2 diabetes mellitus with ulcer
		C10F400		Type 2 diabetes mellitus with ulcer
		C10F900		Type 2 diabetes mellitus without complication
		C108.13		Type I diabetes mellitus
		C109.13		Type II diabetes mellitus

		C10F.11		Type II diabetes mellitus
		C109711		Type II diabetes mellitus - poor control
		C10F711		Type II diabetes mellitus - poor control
		C109G11		Type II diabetes mellitus with arthropathy
		C109E11		Type II diabetes mellitus with diabetic cataract
		C10FE11		Type II diabetes mellitus with diabetic cataract
		C109E11		Type II diabetes mellitus with diabetic cataract
		C10FE11		Type II diabetes mellitus with diabetic cataract
		C109511		Type II diabetes mellitus with gangrene
		C109D11		Type II diabetes mellitus with hypoglycaemic coma
		C10FD11		Type II diabetes mellitus with hypoglycaemic coma
		C109A11		Type II diabetes mellitus with mononeuropathy

		C10FA11		Type II diabetes mellitus with mononeuropathy
		C109A11		Type II diabetes mellitus with mononeuropathy
		C10FA11		Type II diabetes mellitus with mononeuropathy
		C10F311		Type II diabetes mellitus with multiple complications
		C109C11		Type II diabetes mellitus with nephropathy
		C109C11		Type II diabetes mellitus with nephropathy
		C109211		Type II diabetes mellitus with neurological complications
		C10F211		Type II diabetes mellitus with neurological complications
		C109211		Type II diabetes mellitus with neurological complications
		C10F211		Type II diabetes mellitus with neurological complications
		C109H11		Type II diabetes mellitus with neuropathic arthropathy
		C109H11		Type II diabetes mellitus with neuropathic arthropathy

		C109111		Type II diabetes mellitus with ophthalmic complications
		C109111		Type II diabetes mellitus with ophthalmic complications
		C109F11		Type II diabetes mellitus with peripheral angiopathy
		C10FM11		Type II diabetes mellitus with persistent microalbuminuria
		C10FM11		Type II diabetes mellitus with persistent microalbuminuria
		C10FL11		Type II diabetes mellitus with persistent proteinuria
		C10FL11		Type II diabetes mellitus with persistent proteinuria
		C109B11		Type II diabetes mellitus with polyneuropathy
		C10FB11		Type II diabetes mellitus with polyneuropathy
		C109B11		Type II diabetes mellitus with polyneuropathy
		C10FB11		Type II diabetes mellitus with polyneuropathy
		C109011		Type II diabetes mellitus with renal complications

		C10F011		Type II diabetes mellitus with renal complications
		C109011		Type II diabetes mellitus with renal complications
		C10F011		Type II diabetes mellitus with renal complications
		C109611		Type II diabetes mellitus with retinopathy
		C10F611		Type II diabetes mellitus with retinopathy
		C109611		Type II diabetes mellitus with retinopathy
		C10F611		Type II diabetes mellitus with retinopathy
		C109411		Type II diabetes mellitus with ulcer
		C10F411		Type II diabetes mellitus with ulcer
		C10F911		Type II diabetes mellitus without complication
109103		C109911		Type II diabetes mellitus without complication
105784		C109912		Type 2 diabetes mellitus without complication

101801		66At100		Type II diabetic dietary review
107701		C10FK11		Hyperosmolar non-ketotic state in type II diabetes mellitus
102611		66At111		Type 2 diabetic dietary review
106061		C10FP11		Type II diabetes mellitus with ketoacidotic coma
303250		250 A		SUGAR DIABETES
107824		C10P100		Type II diabetes mellitus in remission
106528		C10FN11		Type II diabetes mellitus with ketoacidosis
103902		C10FG11		Type II diabetes mellitus with arthropathy
104639		C10FF11		Type II diabetes mellitus with peripheral angiopathy
100964		C10F111		Type II diabetes mellitus with ophthalmic complications
102201		C10FC11		Type II diabetes mellitus with nephropathy
104323		C10F511		Type II diabetes mellitus with gangrene

108005		C109312		Type 2 diabetes mellitus with multiple complications
109197		C10FH11		Type II diabetes mellitus with neuropathic arthropathy
	7966931000006114		^ESCTAN796693	Angina associated with type 2 diabetes mellitus
	7966941000006116		^ESCTAN796694	Angina associated with type II diabetes mellitus
	7966951000006119		^ESCTDI796695	Diabetic angina pectoris associated with type 2 diabetes mellitus
	2288071000000116	C10P111	C10P1-1	Type 2 diabetes mellitus in remission
	8453100000 6118	C109A12	C109A-2	Type 2 diabetes mellitus with mononeuropathy
	8460100000 6110	C109B12	C109B-2	Type 2 diabetes mellitus with polyneuropathy
	9383310000 06118	C10FQ11	C10FQ-1	Type II diabetes mellitus with exudative maculopathy
	1667921000000117	C10FR11	C10FR-1	Type II diabetes mellitus with gastroparesis
	8491100000 6119	C109311	C1093-1	Type II diabetes mellitus with multiple complications

Appendix F – Antidiabetic medications code list for CPRD

drugsubstance	code DB
Semaglutide	128762410000331 11 A
Semaglutide	128765410000331 13 A
Semaglutide	128766410000331 14 A
Semaglutide	128763410000331 18 A
Semaglutide	128761410000331 16 A
Semaglutide	128764410000331 12 A
Albiglutide	109523410000331 19 A
Albiglutide	109510410000331 14 A
Albiglutide	109511410000331 13 A
Albiglutide	109530410000331 13 A
Chlorpropamide	249441000033114 A

Chlorpropamide	249541000033110 A
Acarbose	645341000033115 A
Acarbose	11541000033110 A
Acarbose	11441000033114 A
Acarbose	645241000033113 A
Metformin hydrochloride	896941000033112 A
Metformin hydrochloride	644941000033117 A
Metformin hydrochloride	645041000033117 A
Metformin hydrochloride	897041000033113 A
Metformin hydrochloride	787494100003311 0 A
Metformin hydrochloride	639104100003311 7 A
Metformin hydrochloride	923064100003311 3 A
Metformin hydrochloride	123265410000331 10 A

Metformin hydrochloride	125931410000331 15 A
Metformin hydrochloride	126644410000331 15 A
Metformin hydrochloride	322824100003311 2 A
Metformin hydrochloride	322814100003311 7 A
Metformin hydrochloride	495774100003311 8 A
Metformin hydrochloride	602984100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	319134100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	299514100003311 0 A
Metformin hydrochloride/ Rosiglitazone maleate	299524100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	319144100003311 4 A
Metformin hydrochloride/ Rosiglitazone maleate	320054100003311 6 A
Metformin hydrochloride/ Rosiglitazone maleate	320074100003311 2 A

Metformin hydrochloride/ Rosiglitazone maleate	320084100003311 9 A
Metformin hydrochloride/ Rosiglitazone maleate	320064100003311 5 A
Metformin hydrochloride	599704100003311 5 A
Metformin hydrochloride	105988410000331 13 A
Metformin hydrochloride	125932410000331 10 A
Metformin hydrochloride	123266410000331 11 A
Metformin hydrochloride	454914100003311 8 A
Metformin hydrochloride	454924100003311 3 A
Metformin hydrochloride	627974100003311 7 A
Metformin hydrochloride	834894100003311 3 A
Metformin hydrochloride	923084100003311 4 A
Metformin hydrochloride	105989410000331 17 A

Metformin hydrochloride	123267410000331 19 A
Metformin hydrochloride	125933410000331 17 A
Metformin hydrochloride	494524100003311 7 A
Metformin hydrochloride	494534100003311 0 A
Metformin hydrochloride/ Pioglitazone hydrochloride	398394100003311 5 A
Metformin hydrochloride/ Pioglitazone hydrochloride	398424100003311 4 A
Metformin hydrochloride	262024100003311 9 A
Metformin hydrochloride	398234100003311 0 A
Metformin hydrochloride	398244100003311 6 A
Metformin hydrochloride/ Vildagliptin	445244100003311 3 A
Metformin hydrochloride/ Vildagliptin	445254100003311 4 A
Metformin hydrochloride/ Vildagliptin	445264100003311 0 A

Metformin hydrochloride/ Vildagliptin	445234100003311 9 A
Metformin hydrochloride	500774100003311 1 A
Metformin hydrochloride	500794100003311 4 A
Metformin hydrochloride	500764100003311 9 A
Metformin hydrochloride	500784100003311 8 A
Metformin hydrochloride/ Sitagliptin phosphate	513224100003311 6 A
Metformin hydrochloride/ Sitagliptin phosphate	557604100003311 5 A
Linagliptin/ Metformin hydrochloride	811594100003311 6 A
Linagliptin/ Metformin hydrochloride	811574100003311 9 A
Linagliptin/ Metformin hydrochloride	811584100003311 2 A
Linagliptin/ Metformin hydrochloride	811604100003311 4 A
Metformin hydrochloride/ Saxagliptin hydrochloride	824264100003311 3 A

Metformin hydrochloride/ Saxagliptin hydrochloride	824284100003311 4 A
Metformin hydrochloride/ Saxagliptin hydrochloride	824254100003311 2 A
Metformin hydrochloride/ Saxagliptin hydrochloride	824274100003311 6 A
Alogliptin benzoate/ Metformin hydrochloride	895994100003311 0 A
Alogliptin benzoate/ Metformin hydrochloride	895984100003311 9 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910624100003311 9 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910604100003311 0 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910614100003311 4 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910634100003311 2 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985154100003311 4 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985184100003311 1 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985164100003311 0 A

Canagliflozin hemihydrate/ Metformin hydrochloride	985174100003311 8 A
Empagliflozin/ Metformin hydrochloride	106144410000331 12 A
Empagliflozin/ Metformin hydrochloride	106148410000331 10 A
Empagliflozin/ Metformin hydrochloride	106143410000331 18 A
Empagliflozin/ Metformin hydrochloride	106147410000331 17 A
Empagliflozin/ Metformin hydrochloride	106146410000331 14 A
Empagliflozin/ Metformin hydrochloride	106142410000331 11 A
Empagliflozin/ Metformin hydrochloride	106141410000331 16 A
Empagliflozin/ Metformin hydrochloride	106145410000331 13 A
Metformin hydrochloride	117813410000331 17 A
Metformin hydrochloride	117814410000331 11 A
Insulin glargine	106006410000331 18 A

Insulin glargine	278084100003311 8 A
Insulin glargine	386934100003311 4 A
Insulin glargine	279894100003311 1 A
Insulin glargine	106007410000331 10 A
Insulin glargine	126866410000331 12 A
Insulin glargine	425854100003311 1 A
Insulin glargine	278094100003311 4 A
Insulin glargine	279904100003311 9 A
Insulin aspart	121866410000331 13 A
Insulin aspart	186204100003311 3 A
Insulin aspart	186234100003311 0 A
Insulin aspart	645644100003311 9 A

Insulin aspart	121865410000331 12 A
Insulin aspart	186244100003311 6 A
Insulin aspart	279664100003311 5 A
Insulin aspart	327774100003311 8 A
Insulin aspart/ Insulin aspart protamine	272474100003311 1 A
Insulin aspart/ Insulin aspart protamine	272484100003311 8 A
Insulin isophane human/ Insulin soluble human	181814100003311 0 A
Insulin isophane human/ Insulin soluble human	295354100003311 2 A
Insulin isophane human/ Insulin soluble human	295344100003311 1 A
Insulin isophane human/ Insulin soluble human	215854100003311 7 A
Insulin isophane human/ Insulin soluble human	226704100003311 8 A
Insulin isophane human/ Insulin soluble human	215844100003311 8 A

Insulin isophane human/ Insulin soluble human	181824100003311 5 A
Insulin isophane human/ Insulin soluble human	295374100003311 6 A
Insulin isophane human/ Insulin soluble human	161624100003311 1 A
Insulin isophane human/ Insulin soluble human	295364100003311 3 A
Insulin isophane human/ Insulin soluble human	203564100003311 5 A
Insulin isophane human/ Insulin soluble human	226714100003311 9 A
Insulin isophane human/ Insulin soluble human	601184100003311 2 A
Insulin isophane human/ Insulin soluble human	203554100003311 6 A
Insulin isophane human/ Insulin soluble human	181834100003311 3 A
Insulin isophane human/ Insulin soluble human	725341000033110 A
Insulin isophane human/ Insulin soluble human	295394100003311 8 A
Insulin isophane human/ Insulin soluble human	295404100003311 6 A

Insulin isophane human/ Insulin soluble human	161634100003311 8 A
Insulin isophane human/ Insulin soluble human	727341000033117 A
Insulin isophane human/ Insulin soluble human	264474100003311 6 A
Insulin isophane human/ Insulin soluble human	295384100003311 4 A
Insulin isophane human/ Insulin soluble human	333384100003311 3 A
Insulin isophane human/ Insulin soluble human	591074100003311 7 A
Insulin isophane human/ Insulin soluble human	181844100003311 9 A
Insulin isophane human/ Insulin soluble human	295424100003311 2 A
Insulin isophane human/ Insulin soluble human	295414100003311 7 A
Insulin isophane human/ Insulin soluble human	181854100003311 8 A
Insulin isophane human/ Insulin soluble human	722841000033112 A
Insulin isophane human/ Insulin soluble human	215874100003311 3 A

Insulin isophane human/ Insulin soluble human	295454100003311 4 A
Insulin isophane human/ Insulin soluble human	226724100003311 4 A
Insulin isophane human/ Insulin soluble human	295434100003311 9 A
Insulin isophane human/ Insulin soluble human	215864100003311 6 A
Insulin isophane porcine/ Insulin soluble porcine	201894100003311 2 A
Insulin isophane porcine/ Insulin soluble porcine	201884100003311 6 A
Insulin isophane porcine/ Insulin soluble porcine	915641000033117 A
Insulin isophane bovine	735841000033116 A
Insulin isophane bovine	182164100003311 9 A
Insulin isophane human	171404100003311 6 A
Insulin isophane human	724041000033112 A
Insulin isophane human	295324100003311 0 A

Insulin isophane human	779141000033111 A
Insulin isophane human	203524100003311 8 A
Insulin isophane porcine	182144100003311 6 A
Insulin isophane porcine	734941000033111 A
Insulin isophane porcine	763341000033116 A
Insulin lispro/ Insulin lispro protamine	173704100003311 7 A
Insulin lispro/ Insulin lispro protamine	460864100003311 9 A
Insulin lispro/ Insulin lispro protamine	460874100003311 1 A
Insulin lispro/ Insulin lispro protamine	218214100003311 7 A
Insulin lispro/ Insulin lispro protamine	173694100003311 8 A
Insulin zinc suspension mixed bovine	735941000033112 A
Insulin isophane porcine/ Insulin soluble porcine	291734100003311 6 A

Insulin isophane bovine	291704100003311 8 A
Insulin isophane bovine	182174100003311 1 A
Insulin soluble bovine	291694100003311 9 A
Insulin isophane porcine	182154100003311 5 A
Insulin isophane porcine	291724100003311 4 A
Insulin soluble porcine	291714100003311 9 A
Insulin detemir	313724100003311 1 A
Insulin detemir	313694100003311 6 A
Insulin detemir	412654100003311 0 A
Insulin detemir	313704100003311 5 A
Insulin detemir	313714100003311 6 A
Insulin glulisine	334574100003311 7 A

Insulin glulisine	334594100003311 9 A
Insulin glulisine	396394100003311 7 A
Insulin glulisine	391424100003311 2 A
Insulin glulisine	391434100003311 9 A
Insulin glulisine	425864100003311 2 A
Insulin lispro/ Insulin lispro protamine	392264100003311 1 A
Insulin human	394514100003311 4 A
Insulin human	394524100003311 9 A
Insulin human	106739410000331 10 A
Insulin human	106741410000331 11 A
Insulin human	442304100003311 4 A
Insulin lispro/ Insulin lispro protamine	540354100003311 8 A

Insulin human	106740410000331 12 A
Insulin human	106743410000331 14 A
Insulin degludec	826434100003311 8 A
Insulin degludec	826444100003311 2 A
Insulin degludec	826414100003311 6 A
Insulin degludec	826394100003311 7 A
Insulin degludec	826404100003311 5 A
Insulin degludec	826424100003311 1 A
Insulin aspart	967704100003311 6 A
Insulin aspart	967714100003311 7 A
Insulin degludec/ Liraglutide	100445410000331 13 A
Insulin degludec/ Liraglutide	100446410000331 14 A

Insulin lispro	102526410000331 11 A
Insulin lispro	102527410000331 19 A
Insulin glargine	104942410000331 10 A
Insulin glargine	104944410000331 11 A
Insulin human	124816410000331 15 A
Insulin aspart	186194100003311 9 A
Insulin aspart	121864410000331 11 A
Insulin aspart	186224100003311 7 A
Insulin glargine	279884100003311 5 A
Insulin glargine	278074100003311 1 A
Insulin glulisine	334564100003311 4 A
Insulin glulisine	334584100003311 0 A

Insulin isophane human	203544100003311 7 A
Insulin isophane human	161594100003311 3 A
Insulin isophane human	295334100003311 7 A
Insulin isophane human	638964100003311 1 A
Insulin isophane human	295314100003311 5 A
Insulin isophane human	264464100003311 3 A
Insulin isophane human	279674100003311 2 A
Insulin isophane human	226684100003311 0 A
Insulin isophane human	218244100003311 3 A
Insulin isophane human	591154100003311 9 A
Insulin lispro	757641000033112 A
Insulin lispro	720541000033111 A

Insulin lispro	762441000033118 A
Insulin lispro	126007410000331 16 A
Insulin lispro	723241000033118 A
Insulin lispro	126008410000331 14 A
Insulin lispro	173994100003311 0 A
Insulin lispro	173684100003311 4 A
Insulin lispro	218224100003311 2 A
Insulin lispro	126009410000331 18 A
Insulin lispro	124862410000331 11 A
Insulin lispro	218234100003311 9 A
Insulin lispro	460854100003311 5 A
Insulin protamine zinc bovine	111974100003311 4 A

Insulin protamine zinc bovine	736141000033115 A
Insulin soluble bovine	736041000033119 A
Insulin soluble human	721041000033110 A
Insulin soluble human	295284100003311 6 A
Insulin soluble human	295464100003311 0 A
Insulin soluble human	724341000033114 A
Insulin soluble human	295304100003311 9 A
Insulin soluble human	161604100003311 5 A
Insulin soluble human	203464100003311 9 A
Insulin soluble human	727041000033119 A
Insulin soluble human	226694100003311 9 A
Insulin soluble human	295294100003311 2 A

Insulin soluble human	203444100003311 6 A
Insulin soluble porcine	126242410000331 11 A
Insulin soluble porcine	735441000033119 A
Insulin soluble porcine	174944100003311 6 A
Insulin zinc suspension crystalline human	295484100003311 1 A
Insulin zinc suspension crystalline human	724541000033119 A
Insulin zinc suspension mixed human	295474100003311 8 A
Insulin zinc suspension mixed human	725841000033118 A
Nateglinide	228844100003311 3 A
Nateglinide	228874100003311 8 A
Nateglinide	228864100003311 0 A
Nateglinide	228834100003311 9 A

Nateglinide	228824100003311 2 A
Nateglinide	228854100003311 4 A
Repaglinide	639114100003311 8 A
Repaglinide	165994100003311 6 A
Repaglinide	167294100003311 0 A
Repaglinide	399394100003311 9 A
Repaglinide	639124100003311 3 A
Repaglinide	399404100003311 7 A
Repaglinide	167274100003311 2 A
Repaglinide	166004100003311 8 A
Repaglinide	639134100003311 5 A
Repaglinide	166014100003311 9 A

Repaglinide	167284100003311 9 A
Repaglinide	399414100003311 8 A
Pioglitazone hydrochloride	652604100003311 7 A
Pioglitazone hydrochloride	883934100003311 6 A
Pioglitazone hydrochloride	103370410000331 13 A
Pioglitazone hydrochloride	219084100003311 3 A
Pioglitazone hydrochloride	219104100003311 0 A
Pioglitazone hydrochloride	103369410000331 12 A
Pioglitazone hydrochloride	102513410000331 12 A
Pioglitazone hydrochloride	652594100003311 0 A
Pioglitazone hydrochloride	219094100003311 7 A
Pioglitazone hydrochloride	219074100003311 5 A

Pioglitazone hydrochloride	652614100003311 8 A
Pioglitazone hydrochloride	883944100003311 0 A
Pioglitazone hydrochloride	103371410000331 12 A
Pioglitazone hydrochloride	299604100003311 9 A
Pioglitazone hydrochloride	299594100003311 2 A
Metformin hydrochloride/ Pioglitazone hydrochloride	398394100003311 5 A
Metformin hydrochloride/ Pioglitazone hydrochloride	398424100003311 4 A
Alogliptin benzoate/ Metformin hydrochloride	895994100003311 0 A
Alogliptin benzoate/ Metformin hydrochloride	895984100003311 9 A
Alogliptin benzoate	895934100003311 1 A
Alogliptin benzoate	895964100003311 5 A
Alogliptin benzoate	895974100003311 2 A

Alogliptin benzoate	895944100003311 7 A
Alogliptin benzoate	895924100003311 8 A
Alogliptin benzoate	895954100003311 6 A
Linagliptin	644404100003311 7 A
Linagliptin	644414100003311 8 A
Linagliptin/ Metformin hydrochloride	811594100003311 6 A
Linagliptin/ Metformin hydrochloride	811574100003311 9 A
Linagliptin/ Metformin hydrochloride	811584100003311 2 A
Linagliptin/ Metformin hydrochloride	811604100003311 4 A
Sitagliptin phosphate	768754100003311 2 A
Sitagliptin phosphate	768744100003311 1 A
Sitagliptin phosphate	413334100003311 0 A

Sitagliptin phosphate	413324100003311 7 A
Sitagliptin phosphate	768734100003311 7 A
Sitagliptin phosphate	768724100003311 0 A
Metformin hydrochloride/ Sitagliptin phosphate	513224100003311 6 A
Metformin hydrochloride/ Sitagliptin phosphate	557604100003311 5 A
Vildagliptin	426994100003311 9 A
Vildagliptin	426974100003311 7 A
Metformin hydrochloride/ Vildagliptin	445244100003311 3 A
Metformin hydrochloride/ Vildagliptin	445254100003311 4 A
Metformin hydrochloride/ Vildagliptin	445264100003311 0 A
Metformin hydrochloride/ Vildagliptin	445234100003311 9 A
Dapagliflozin propanediol monohydrate	819954100003311 3 A

Dapagliflozin propanediol monohydrate	819934100003311 8 A
Dapagliflozin propanediol monohydrate	819964100003311 4 A
Dapagliflozin propanediol monohydrate	819944100003311 2 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910624100003311 9 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910604100003311 0 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910614100003311 4 A
Dapagliflozin propanediol monohydrate/ Metformin hydrochloride	910634100003311 2 A
Dapagliflozin propanediol monohydrate/ Saxagliptin hydrochloride	118980410000331 11 A
Dapagliflozin propanediol monohydrate/ Saxagliptin hydrochloride	118981410000331 10 A
Canagliflozin hemihydrate	911054100003311 7 A
Canagliflozin hemihydrate	911034100003311 2 A
Canagliflozin hemihydrate	911044100003311 8 A

Canagliflozin hemihydrate	911064100003311 6 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985154100003311 4 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985184100003311 1 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985164100003311 0 A
Canagliflozin hemihydrate/ Metformin hydrochloride	985174100003311 8 A
Empagliflozin	933714100003311 4 A
Empagliflozin	933664100003311 9 A
Empagliflozin	933684100003311 8 A
Empagliflozin	933724100003311 9 A
Empagliflozin/ Metformin hydrochloride	106144410000331 12 A
Empagliflozin/ Metformin hydrochloride	106148410000331 10 A
Empagliflozin/ Metformin hydrochloride	106143410000331 18 A

Empagliflozin/ Metformin hydrochloride	106147410000331 17 A
Empagliflozin/ Metformin hydrochloride	106146410000331 14 A
Empagliflozin/ Metformin hydrochloride	106142410000331 11 A
Empagliflozin/ Metformin hydrochloride	106141410000331 16 A
Empagliflozin/ Metformin hydrochloride	106145410000331 13 A
Dulaglutide	102078410000331 18 A
Dulaglutide	102080410000331 12 A
Dulaglutide	102081410000331 11 A
Dulaglutide	102079410000331 14 A
Exenatide	414944100003311 7 A
Exenatide	414964100003311 5 A
Exenatide	414954100003311 6 A

Exenatide	414934100003311 1 A
Exenatide	638824100003311 7 A
Exenatide	638834100003311 0 A
Exenatide	100425410000331 17 A
Exenatide	100426410000331 16 A
Liraglutide	119190410000331 13 A
Liraglutide	513134100003311 7 A
Liraglutide	513124100003311 0 A
Insulin degludec/ Liraglutide	100445410000331 13 A
Insulin degludec/ Liraglutide	100446410000331 14 A
Lixisenatide	826734100003311 0 A
Lixisenatide	826754100003311 5 A

Lixisenatide	826744100003311 6 A
Lixisenatide	826764100003311 9 A
Gliclazide	100433410000331 16 A
Gliclazide	107016410000331 16 A
Gliclazide	119189410000331 16 A
Gliclazide	228994100003311 3 A
Gliclazide	228944100003311 5 A
Gliclazide	613534100003311 7 A
Gliclazide	537814100003311 7 A
Gliclazide	581534100003311 5 A
Gliclazide	494124100003311 9 A
Gliclazide	646441000033117 A

Gliclazide	160294100003311 7 A
Gliclazide	463541000033118 A
Gliclazide	586924100003311 4 A
Gliclazide	395304100003311 3 A
Gliclazide	570974100003311 6 A
Gliclazide	570984100003311 4 A
Gliclazide	829824100003311 8 A
Gliclazide	829814100003311 3 A
Gliclazide	107017410000331 13 A
Gliclazide	100434410000331 10 A
Glimepiride	645841000033112 A
Glimepiride	58841000033113 A
Glimepiride	452214100003311 2 A

Glimepiride	452204100003311 3 A
Glimepiride	59541000033116 A
Glimepiride	645941000033116 A
Glimepiride	646041000033114 A
Glimepiride	59641000033115 A
Glimepiride	452224100003311 7 A
Glimepiride	452234100003311 0 A
Glimepiride	59741000033112 A
Glimepiride	646141000033113 A
Glimepiride	812524100003311 9 A
Glipizide	920241000033117 A
Glipizide	644741000033115 A
Glipizide	644841000033113 A
Glipizide	646541000033116 A

Glipizide	920141000033112 A
Gliquidone	646841000033119 A
Gliquidone	646941000033110 A
Rosiglitazone maleate	214764100003311 9 A
Rosiglitazone maleate	214784100003311 8 A
Rosiglitazone maleate	214774100003311 1 A
Rosiglitazone maleate	214754100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	319134100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	299514100003311 0 A
Metformin hydrochloride/ Rosiglitazone maleate	299524100003311 5 A
Metformin hydrochloride/ Rosiglitazone maleate	319144100003311 4 A
Metformin hydrochloride/ Rosiglitazone maleate	320054100003311 6 A

Metformin hydrochloride/ Rosiglitazone maleate	320074100003311 2 A
Metformin hydrochloride/ Rosiglitazone maleate	320084100003311 9 A
Metformin hydrochloride/ Rosiglitazone maleate	320064100003311 5 A
Tolbutamide	145094100003311 3 A
Glymidine Sodium	24848 G
Semaglutide	75397 G
Semaglutide	75740 G
Semaglutide	75938 G
Tolazamide	10427 G
Tolazamide	19336 G
Tolazamide	21489 G
Tolazamide	22145 G
Troglitazone	13628 G
Glibornuride	12245 G
Glibornuride	12259 G
Albiglutide	69947 G
Acetohexamide	22858 G
Acetohexamide	26118 G

Chlorpropamide	1253 G
Chlorpropamide	1847 G
Chlorpropamide	8034 G
Chlorpropamide	8168 G
Chlorpropamide	27969 G
Acarbose	479 G
Acarbose	5174 G
Acarbose	5621 G
Acarbose	9105 G
Acarbose	71020 G
Metformin hydrochloride	23 G
Metformin hydrochloride	93 G
Metformin Hydrochloride	735 G
Rosiglitazone maleate/Metformin hydrochloride	6855 G
Metformin hydrochloride	7048 G
Metformin hydrochloride	7166 G
Rosiglitazone maleate/Metformin hydrochloride	7325 G
Rosiglitazone maleate/Metformin hydrochloride	7375 G
Metformin hydrochloride	7610 G
Rosiglitazone maleate/Metformin hydrochloride	11601 G
Rosiglitazone maleate/Metformin hydrochloride	11604 G

Metformin Hydrochloride/Rosiglitazone Maleate	11609 G
Metformin Hydrochloride/Rosiglitazone Maleate	11610 G
Rosiglitazone maleate/Metformin hydrochloride	11717 G
Metformin Hydrochloride/Rosiglitazone Maleate	11737 G
Metformin Hydrochloride/Rosiglitazone Maleate	11760 G
Metformin hydrochloride	11990 G
Rosiglitazone maleate/Metformin hydrochloride	14164 G
Metformin hydrochloride	16044 G
Rosiglitazone maleate/Metformin hydrochloride	17580 G
Metformin hydrochloride/Pioglitazone hydrochloride	18220 G
Metformin hydrochloride	25678 G
Metformin hydrochloride	26258 G
Metformin hydrochloride	27501 G
Metformin/Pioglitazone	30316 G
Metformin hydrochloride/Pioglitazone hydrochloride	31077 G
Metformin hydrochloride	31146 G
Metformin hydrochloride	33087 G
Metformin hydrochloride	33674 G
Metformin hydrochloride	34004 G
Metformin hydrochloride	34020 G
Metformin hydrochloride	34135 G

Metformin hydrochloride	34323 G
Metformin hydrochloride	34504 G
Metformin hydrochloride	34598 G
Metformin hydrochloride	34697 G
Metformin hydrochloride	34742 G
Metformin hydrochloride	34836 G
Metformin hydrochloride	34917 G
Metformin hydrochloride/Vildagliptin	37874 G
Vildagliptin/Metformin hydrochloride	37902 G
Metformin hydrochloride	38355 G
Metformin hydrochloride	38400 G
Vildagliptin/Metformin hydrochloride	38551 G
Metformin hydrochloride/Vildagliptin	39203 G
Metformin hydrochloride	39560 G
Metformin hydrochloride	39598 G
Metformin hydrochloride	39729 G
Metformin hydrochloride	39988 G
Metformin hydrochloride	40007 G
Metformin hydrochloride	40110 G
Metformin hydrochloride	40233 G
Metformin hydrochloride	42161 G

Metformin hydrochloride	43270 G
Sitagliptin phosphate/Metformin hydrochloride	43619 G
Sitagliptin phosphate/Metformin hydrochloride	43684 G
Metformin hydrochloride	44250 G
Metformin hydrochloride	45581 G
Metformin hydrochloride	46989 G
Metformin hydrochloride	47939 G
Metformin hydrochloride	48149 G
Metformin hydrochloride	49502 G
Metformin hydrochloride	49738 G
Metformin hydrochloride	50570 G
Metformin hydrochloride/Linagliptin	50682 G
Metformin hydrochloride	50821 G
Metformin hydrochloride	50970 G
Metformin hydrochloride	51080 G
Metformin hydrochloride	51135 G
Metformin hydrochloride	51527 G
Metformin hydrochloride	52221 G
Metformin hydrochloride	52442 G
Metformin hydrochloride/Linagliptin	52445 G
Metformin hydrochloride/Linagliptin	52449 G

Metformin hydrochloride	52634 G
Metformin hydrochloride	53478 G
Metformin hydrochloride	53774 G
Metformin hydrochloride	53867 G
Metformin hydrochloride/Linagliptin	54150 G
Metformin Hydrochloride	54442 G
Metformin hydrochloride/Saxagliptin hydrochloride	54891 G
Metformin hydrochloride	54898 G
Saxagliptin hydrochloride/Metformin hydrochloride	54973 G
Metformin hydrochloride	55270 G
Metformin hydrochloride	55711 G
Metformin hydrochloride	55739 G
Metformin hydrochloride/Saxagliptin hydrochloride	56965 G
Metformin hydrochloride	57147 G
Metformin hydrochloride	57457 G
Metformin hydrochloride	58051 G
Metformin hydrochloride	58607 G
Saxagliptin hydrochloride/Metformin hydrochloride	58865 G
Metformin hydrochloride/Alogliptin benzoate	59385 G
Metformin hydrochloride	59620 G
Metformin hydrochloride/Dapagliflozin	60012 G

Metformin hydrochloride	60074 G
Metformin hydrochloride	60286 G
Metformin hydrochloride/Alogliptin benzoate	60497 G
Metformin hydrochloride/Dapagliflozin	60643 G
Metformin hydrochloride	60968 G
Metformin hydrochloride	61043 G
Metformin hydrochloride	61559 G
Metformin hydrochloride	62144 G
Metformin hydrochloride	62265 G
Metformin hydrochloride	62605 G
Metformin hydrochloride	62824 G
Metformin hydrochloride/Dapagliflozin	63031 G
Metformin hydrochloride	63045 G
Metformin hydrochloride	63307 G
Metformin hydrochloride/Canagliflozin hemihydrate	63929 G
Canagliflozin hemihydrate/Metformin hydrochloride	64743 G
Metformin hydrochloride	64939 G
Empagliflozin/Metformin hydrochloride	65057 G
Metformin hydrochloride/Dapagliflozin	65059 G
Metformin hydrochloride/Empagliflozin	65066 G
Empagliflozin/Metformin hydrochloride	65083 G

Empagliflozin/Metformin hydrochloride	65344 G
Metformin hydrochloride	65694 G
Metformin hydrochloride	65923 G
Metformin hydrochloride/Empagliflozin	66008 G
Metformin hydrochloride	66136 G
Metformin hydrochloride/Canagliflozin hemihydrate	66854 G
Empagliflozin/Metformin hydrochloride	66855 G
Metformin hydrochloride	68203 G
Metformin hydrochloride	68214 G
Metformin hydrochloride	68389 G
Metformin hydrochloride	68589 G
Metformin hydrochloride	68636 G
Metformin hydrochloride	69221 G
Empagliflozin/Metformin hydrochloride	69370 G
Empagliflozin/Metformin hydrochloride	70463 G
Metformin hydrochloride	70477 G
Metformin hydrochloride	70744 G
Metformin hydrochloride	71012 G
Metformin hydrochloride	71198 G
Metformin hydrochloride	71890 G
Metformin hydrochloride	72001 G

Metformin hydrochloride	72046 G
Metformin hydrochloride	72052 G
Metformin hydrochloride	72107 G
Metformin hydrochloride	72695 G
Metformin hydrochloride	73252 G
Metformin hydrochloride	73254 G
Metformin hydrochloride	73285 G
Metformin hydrochloride	73303 G
Metformin hydrochloride	73460 G
Metformin hydrochloride	73511 G
Metformin hydrochloride	73525 G
Metformin hydrochloride	73673 G
Metformin hydrochloride	73808 G
Metformin hydrochloride	73892 G
Metformin hydrochloride	74021 G
Metformin hydrochloride	74734 G
Metformin hydrochloride	75700 G
Metformin hydrochloride	75778 G
Insulin lispro	322 G
Insulin zinc suspension mixed human	1587 G
Insulin Soluble Human	1588 G

Insulin Soluble Human	1592 G
Insulin isophane human	1593 G
Insulin soluble human	1594 G
Insulin isophane human	1595 G
Insulin Soluble Human/Insulin Isophane Human	1649 G
Insulin Soluble Human/Insulin Isophane Human	1805 G
Insulin Soluble Human/Insulin Isophane Human	1806 G
Insulin Soluble Human	1840 G
Insulin soluble porcine	1842 G
Insulin isophane porcine	1843 G
Insulin zinc suspension crystalline human	1844 G
Insulin isophane human	1886 G
Insulin Soluble Human/Insulin Isophane Human	2220 G
Insulin soluble human/Insulin isophane human	2221 G
Insulin Soluble Human/Insulin Isophane Human	2454 G
Insulin soluble human/Insulin isophane human	2455 G
Insulin soluble human/Insulin isophane human	2456 G
Insulin soluble porcine/Insulin isophane porcine	2459 G
Insulin soluble human/Insulin isophane human	2812 G
Insulin Soluble Human/Insulin Isophane Human	2929 G
Insulin Soluble Human/Insulin Isophane Human	3396 G

Insulin Soluble Human/Insulin Isophane Human	3439 G
Insulin Soluble Human/Insulin Isophane Human	3550 G
Insulin Soluble Human/Insulin Isophane Human	3551 G
Insulin soluble human/Insulin isophane human	4093 G
Insulin soluble porcine	4129 G
Insulin/Insulin Soluble Porcine	4163 G
Insulin Soluble Human/Insulin Isophane Human	4198 G
Insulin Soluble Human/Insulin Isophane Human	4199 G
Insulin isophane porcine	4247 G
Insulin soluble human	4706 G
Insulin Lispro/Insulin Lispro Protamine	4715 G
Insulin Isophane Human	4760 G
Pork Insulin/Insulin Zinc Suspension Mixed Bovine	4784 G
Insulin soluble human/Insulin isophane human	4790 G
Insulin aspart	5021 G
Insulin lispro	5214 G
Insulin Lispro/Insulin Lispro Protamine	5250 G
Insulin Soluble Human/Insulin Isophane Human	5255 G
Insulin Isophane Human	5501 G
Insulin soluble human/Insulin isophane human	5845 G
Insulin isophane human	5891 G

Insulin aspart	5892 G
Insulin isophane human/Insulin soluble human	5933 G
Insulin Glargine	5953 G
Insulin Glargine	6057 G
Insulin Aspart/Insulin Aspart Protamine	6061 G
Insulin aspart	6209 G
Insulin Aspart	6447 G
Insulin detemir	6958 G
Insulin detemir	6965 G
Insulin aspart protamine/Insulin aspart	7228 G
Insulin soluble human/Insulin isophane human	7231 G
Insulin glargine	7237 G
Insulin glargine	7266 G
Insulin aspart/Insulin aspart protamine	7267 G
Insulin soluble human/Insulin isophane human	7300 G
Insulin lispro	7318 G
Insulin soluble human/Insulin isophane human	7319 G
Insulin soluble human	7349 G
Insulin isophane porcine	7350 G
Insulin glargine	7393 G
Insulin glargine	7400 G

Insulin glargine	7402 G
Insulin zinc suspension crystalline human	7537 G
Insulin isophane human	7771 G
Insulin isophane human	7772 G
Insulin soluble human/Insulin isophane human	7793 G
Insulin Isophane Human	8118 G
Insulin soluble human/Insulin isophane human	8203 G
Insulin Zinc Suspension Crystalline Human/Insulin Zinc Suspension Mixed Human	8322 G
Insulin soluble human/Insulin isophane human	8841 G
Insulin Isophane Porcine/Insulin Soluble Porcine	8895 G
Insulin Soluble Human/Insulin Isophane Human	9341 G
Insulin Zinc Suspension Crystalline Human	9376 G
Insulin protamine zinc bovine	9503 G
Insulin soluble porcine	9521 G
Insulin soluble human	9565 G
Insulin isophane porcine/Insulin soluble porcine	9618 G
Insulin isophane human	9737 G
Insulin lispro protamine/Insulin lispro	10001 G
Insulin Aspart/Insulin Aspart Protamine	10067 G
Insulin isophane human	10175 G

Insulin Detemir	10184 G
Insulin isophane human	10207 G
Insulin isophane human	10208 G
Insulin glargine	10225 G
Insulin isophane human	10229 G
Insulin lispro/Insulin lispro protamine	10243 G
Insulin soluble human/Insulin isophane human	10244 G
Insulin soluble human/Insulin isophane human	10245 G
Insulin glargine	10259 G
Insulin lispro	10264 G
Insulin soluble human/Insulin isophane human	10277 G
Insulin Soluble Human/Insulin Isophane Human	10484 G
Insulin zinc suspension mixed human	10547 G
Insulin Soluble Bovine	10572 G
Insulin Soluble Human/Insulin Isophane Human	10887 G
Insulin Soluble Human/Insulin Isophane Human	10910 G
Insulin Soluble Human/Insulin Isophane Human	10915 G
Insulin Soluble Human/Insulin Isophane Human	11055 G
Insulin Soluble Human/Insulin Isophane Human	11056 G
Insulin Isophane Human	11080 G
Insulin Soluble Human/Insulin Isophane Human	11107 G

Insulin aspart	11337 G
Insulin zinc suspension mixed bovine	12035 G
Insulin Soluble Bovine	12297 G
Pork Insulin	12299 G
Insulin Soluble Human	12638 G
Insulin Soluble Human	12654 G
Insulin soluble human/Insulin isophane human	12818 G
Insulin soluble human/Insulin isophane human	13277 G
Insulin/Insulin Soluble Porcine	13416 G
Insulin isophane bovine	13516 G
Insulin soluble porcine	13622 G
Insulin Isophane Human	13729 G
Insulin isophane porcine	13819 G
Insulin Soluble Human/Insulin Isophane Human	13837 G
Insulin lispro/Insulin lispro protamine	14270 G
Insulin isophane human	14290 G
Insulin glulisine	14299 G
Insulin detemir	14301 G
Insulin lispro	14313 G
Insulin detemir	14330 G
Insulin soluble bovine	14339 G

Insulin isophane bovine	14340 G
Insulin glulisine	14345 G
Insulin isophane human	14357 G
Insulin lispro	14362 G
Insulin protamine zinc bovine	14505 G
Insulin isophane porcine/Insulin soluble porcine	14619 G
Insulin Soluble Human/Insulin Isophane Human	14644 G
Insulin Soluble Human/Insulin Isophane Human	14649 G
Insulin isophane human	14918 G
Insulin Isophane Human	14925 G
Insulin isophane human	14928 G
Insulin soluble porcine	14930 G
Insulin isophane porcine	14933 G
Insulin Soluble Bovine	14938 G
Insulin soluble human	14944 G
Insulin Soluble Human/Insulin Isophane Human	15199 G
Insulin isophane bovine	15484 G
Insulin Soluble Human	15710 G
Insulin Isophane Human	15961 G
Insulin soluble human	16129 G
Insulin aspart	16142 G

Insulin soluble human/Insulin isophane human	16152 G
Insulin soluble human/Insulin isophane human	16160 G
Insulin zinc suspension mixed bovine	16682 G
Insulin Zinc Suspension Mixed Bovine	16700 G
Insulin Soluble Human	17336 G
Insulin zinc suspension mixed bovine	17712 G
Insulin soluble human/Insulin isophane human	17731 G
Insulin Soluble Human/Insulin Isophane Human	17809 G
Insulin lispro	18224 G
Insulin zinc suspension mixed human	18461 G
Insulin isophane bovine	18590 G
Insulin soluble bovine	18592 G
Insulin lispro protamine/Insulin lispro	18593 G
Insulin zinc suspension crystalline human	18931 G
Insulin glulisine	19491 G
Insulin soluble human/Insulin isophane human	19513 G
Insulin aspart	19877 G
Insulin soluble human/Insulin isophane human	19878 G
Insulin isophane human/Insulin soluble human	20422 G
Insulin soluble porcine/Insulin isophane porcine	20995 G
Insulin Soluble Human/Insulin Isophane Human	21110 G

Insulin soluble human/Insulin isophane human	21232 G
Insulin soluble human	21235 G
Insulin Soluble Human/Insulin Isophane Human	21347 G
Insulin Soluble Human/Insulin Isophane Human	21374 G
Insulin Soluble Human/Insulin Isophane Human	21395 G
Insulin soluble human/Insulin isophane human	21422 G
Insulin soluble human/Insulin isophane human	21554 G
Insulin glulisine	21583 G
Insulin glulisine	21590 G
Insulin Soluble Human/Insulin Isophane Human	22058 G
Insulin Soluble Human/Insulin Isophane Human	22155 G
Insulin soluble human/Insulin isophane human	22697 G
Insulin Soluble Human	22945 G
Insulin soluble human	22983 G
Insulin aspart protamine/Insulin aspart	23099 G
Insulin soluble bovine	23231 G
Insulin isophane human	23992 G
Insulin soluble human	23993 G
Insulin soluble human/Insulin isophane human	24002 G
Insulin Soluble Bovine	24593 G
Insulin aspart/Insulin aspart protamine	24795 G

Insulin soluble porcine/Insulin isophane porcine	24800 G
Insulin Soluble Human	24846 G
Insulin soluble human/Insulin isophane human	24993 G
Insulin soluble human/Insulin isophane human	25133 G
Insulin soluble porcine	25479 G
Insulin soluble human/Insulin isophane human	25735 G
Insulin soluble human/Insulin isophane human	25736 G
Insulin isophane human	25812 G
Insulin lispro	26060 G
Insulin soluble porcine	26098 G
Insulin Soluble Human/Insulin Isophane Human	26403 G
Pork Insulin/Insulin Zinc Suspension Mixed Bovine	26498 G
Insulin Soluble Human	26621 G
Insulin Lispro/Insulin Lispro Protamine	27177 G
Insulin soluble porcine/Insulin isophane porcine	27280 G
Insulin soluble porcine	27396 G
Insulin soluble human	27402 G
Insulin isophane human	27461 G
Insulin Soluble Human/Insulin Isophane Human	27614 G
Insulin soluble human/Insulin isophane human	28096 G
Insulin glulisine	28101 G

Insulin isophane porcine	28183 G
Insulin lispro/Insulin lispro protamine	28185 G
Insulin Glulisine	28442 G
Insulin isophane bovine	28588 G
Insulin aspart	29567 G
Insulin Soluble Human/Insulin Isophane Human	29837 G
Insulin glulisine	29953 G
Insulin soluble porcine	30209 G
Insulin Isophane Bovine	30236 G
Insulin isophane porcine	30686 G
Insulin soluble human/Insulin isophane human	30819 G
Insulin isophane human/Insulin soluble human	31205 G
Insulin lispro/Insulin lispro protamine	31258 G
Insulin human	31465 G
Insulin human	31467 G
Insulin Soluble Human/Insulin Isophane Human	33167 G
Insulin soluble human/Insulin isophane human	33232 G
Insulin Isophane Human	33966 G
Pork Insulin	34031 G
Insulin Soluble Human/Insulin Isophane Human	34097 G
Insulin soluble human/Insulin isophane human	35253 G

Insulin detemir	35260 G
Insulin isophane human	35468 G
Insulin lispro protamine/Insulin lispro	35701 G
Insulin soluble porcine/Insulin isophane porcine	36031 G
Insulin isophane bovine	36066 G
Insulin lispro protamine/Insulin lispro	36146 G
Insulin soluble human/Insulin isophane human	36194 G
Insulin human	36355 G
Insulin human	36356 G
Insulin soluble human	36430 G
Insulin soluble porcine	36513 G
Insulin glargine	36853 G
Insulin glulisine	36920 G
Insulin isophane bovine	38422 G
Insulin lispro	38986 G
Insulin lispro/Insulin lispro protamine	39006 G
Insulin lispro protamine/Insulin lispro	39086 G
Insulin isophane human/Insulin soluble human	41120 G
Insulin zinc suspension mixed bovine	41834 G
Insulin Soluble Human	41959 G
Insulin lispro/Insulin lispro protamine	42395 G

Insulin soluble human/Insulin isophane human	42954 G
Insulin isophane human	43950 G
Insulin lispro/Insulin lispro protamine	43953 G
Insulin soluble human/Insulin isophane human	43991 G
Pork Insulin	44251 G
Insulin soluble human/Insulin isophane human	44378 G
Insulin soluble human/Insulin isophane human	44480 G
Insulin soluble human/Insulin isophane human	45158 G
Insulin isophane human	46001 G
Insulin aspart	46666 G
Insulin Soluble Bovine	47360 G
Insulin isophane bovine	47856 G
Insulin aspart	49108 G
Insulin glargine	49831 G
Insulin glargine	50633 G
Insulin soluble human/Insulin isophane human	50691 G
Insulin aspart	51743 G
Insulin lispro protamine/Insulin lispro	52522 G
Insulin soluble human/Insulin isophane human	52722 G
Insulin isophane human	52748 G
Insulin aspart	53118 G

Insulin aspart	53251 G
Insulin human	53710 G
Insulin Soluble Human/Insulin Isophane Human	54462 G
Insulin degludec	55234 G
Insulin degludec	55462 G
Insulin isophane human	55517 G
Insulin lispro	55603 G
Insulin detemir	55618 G
Insulin degludec	55687 G
Insulin degludec	55907 G
Insulin degludec	55910 G
Insulin soluble human	56115 G
Insulin aspart/Insulin aspart protamine	56489 G
Insulin glargine	56495 G
Insulin soluble human	56502 G
Insulin degludec	56691 G
Insulin soluble human/Insulin isophane human	56857 G
Insulin lispro	57529 G
Insulin lispro	57564 G
Insulin soluble human/Insulin isophane human	57620 G
Insulin lispro protamine/Insulin lispro	57622 G

Insulin isophane human	59500 G
Insulin aspart	59533 G
Insulin soluble human/Insulin isophane human	60933 G
Insulin soluble human/Insulin isophane human	60938 G
Insulin human	60951 G
Insulin aspart	61845 G
Insulin aspart	62180 G
Insulin human	62276 G
Insulin degludec/Liraglutide	62899 G
Insulin lispro	63464 G
Insulin degludec/Liraglutide	63562 G
Insulin Soluble Bovine	63679 G
Insulin glargine	64354 G
Insulin glargine	64460 G
Insulin glargine	64723 G
Insulin glargine	64987 G
Insulin glargine	66316 G
Insulin Isophane Porcine/Insulin Soluble Porcine	66335 G
Insulin glargine	67230 G
Insulin aspart	67231 G
Insulin soluble human/Insulin isophane human	67266 G

Insulin soluble human/Insulin isophane human	67267 G
Insulin isophane porcine	67279 G
Insulin aspart	67313 G
Insulin soluble human/Insulin isophane human	67324 G
Insulin human	67429 G
Insulin lispro/Insulin lispro protamine	68031 G
Insulin lispro/Insulin lispro protamine	69583 G
Insulin aspart	69715 G
Insulin aspart	69823 G
Insulin aspart	70055 G
Insulin isophane human	71118 G
Insulin isophane bovine	71137 G
Insulin soluble human/Insulin isophane human	71340 G
Insulin glargine	71351 G
Insulin isophane human	71361 G
Insulin aspart protamine/Insulin aspart	71369 G
Insulin lispro/Insulin lispro protamine	71395 G
Insulin isophane human	71428 G
Insulin lispro/Insulin lispro protamine	71430 G
Insulin human	72479 G
Insulin isophane human	72559 G

Insulin lispro	73282 G
Insulin aspart/Insulin aspart protamine	74020 G
Insulin lispro/Insulin lispro protamine	74071 G
Insulin aspart	74179 G
Insulin lispro/Insulin lispro protamine	74388 G
Insulin lispro	74389 G
Insulin lispro/Insulin lispro protamine	74391 G
Insulin glulisine	74392 G
Insulin lispro	74479 G
Insulin aspart/Insulin aspart protamine	74680 G
Insulin soluble human	74824 G
Insulin soluble human/Insulin isophane human	74842 G
Insulin isophane human	74845 G
Insulin glargine	74862 G
Insulin Isophane Human	74970 G
Insulin lispro	75329 G
Insulin isophane human/Insulin soluble human	75550 G
Nateglinide	5678 G
Nateglinide	5989 G
Nateglinide	11483 G
Nateglinide	15955 G

Nateglinide	23945 G
Nateglinide	27125 G
Repaglinide	9707 G
Repaglinide	9748 G
Repaglinide	9865 G
Repaglinide	11316 G
Repaglinide	11321 G
Repaglinide	11366 G
Repaglinide	35561 G
Repaglinide	36774 G
Repaglinide	36948 G
Repaglinide	52203 G
Repaglinide	61925 G
Repaglinide	74860 G
Pioglitazone hydrochloride	548 G
Pioglitazone hydrochloride	9699 G
Pioglitazone hydrochloride	10051 G
Metformin hydrochloride/Pioglitazone hydrochloride	18220 G
Pioglitazone hydrochloride	19472 G
Pioglitazone hydrochloride	20287 G
Pioglitazone hydrochloride	20889 G

Metformin/Pioglitazone	30316 G
Metformin hydrochloride/Pioglitazone hydrochloride	31077 G
Pioglitazone hydrochloride	48139 G
Pioglitazone hydrochloride	56208 G
Pioglitazone hydrochloride	57659 G
Pioglitazone hydrochloride	62426 G
Pioglitazone hydrochloride	63046 G
Pioglitazone hydrochloride	63107 G
Pioglitazone hydrochloride	63421 G
Pioglitazone hydrochloride	64900 G
Pioglitazone hydrochloride	65562 G
Pioglitazone hydrochloride	65563 G
Pioglitazone hydrochloride	68934 G
Pioglitazone hydrochloride	69885 G
Pioglitazone hydrochloride	72163 G
Alogliptin benzoate	59177 G
Metformin hydrochloride/Alogliptin benzoate	59385 G
Alogliptin benzoate	59809 G
Alogliptin benzoate	60328 G
Metformin hydrochloride/Alogliptin benzoate	60497 G
Alogliptin benzoate	60681 G

Alogliptin benzoate	60682 G
Alogliptin benzoate	62326 G
Alogliptin benzoate	68258 G
Alogliptin benzoate	69459 G
Linagliptin	46665 G
Linagliptin	46716 G
Metformin hydrochloride/Linagliptin	50682 G
Metformin hydrochloride/Linagliptin	52445 G
Metformin hydrochloride/Linagliptin	52449 G
Metformin hydrochloride/Linagliptin	54150 G
Sitagliptin phosphate	35022 G
Sitagliptin phosphate	35462 G
Sitagliptin phosphate/Metformin hydrochloride	43619 G
Sitagliptin phosphate/Metformin hydrochloride	43684 G
Sitagliptin phosphate	48401 G
Sitagliptin phosphate	48533 G
Sitagliptin phosphate	50087 G
Sitagliptin phosphate	50124 G
Sitagliptin phosphate	72539 G
Sitagliptin phosphate	73150 G
Metformin hydrochloride/Vildagliptin	37874 G

Vildagliptin	37875 G
Vildagliptin/Metformin hydrochloride	37902 G
Vildagliptin/Metformin hydrochloride	38551 G
Vildagliptin	39149 G
Metformin hydrochloride/Vildagliptin	39203 G
Dapagliflozin	54182 G
Dapagliflozin	54203 G
Dapagliflozin	54265 G
Dapagliflozin	54480 G
Metformin hydrochloride/Dapagliflozin	60012 G
Metformin hydrochloride/Dapagliflozin	60643 G
Metformin hydrochloride/Dapagliflozin	63031 G
Dapagliflozin	63516 G
Metformin hydrochloride/Dapagliflozin	65059 G
Saxagliptin hydrochloride/Dapagliflozin propanediol monohydrate	69540 G
Saxagliptin hydrochloride/Dapagliflozin propanediol monohydrate	69654 G
Canagliflozin hemihydrate	60211 G
Canagliflozin hemihydrate	60379 G
Canagliflozin hemihydrate	60386 G

Canagliflozin hemihydrate	60430 G
Metformin hydrochloride/Canagliflozin hemihydrate	63929 G
Canagliflozin hemihydrate/Metformin hydrochloride	64743 G
Metformin hydrochloride/Canagliflozin hemihydrate	66854 G
Empagliflozin	61756 G
Empagliflozin	62172 G
Empagliflozin	62760 G
Empagliflozin	64217 G
Empagliflozin/Metformin hydrochloride	65057 G
Metformin hydrochloride/Empagliflozin	65066 G
Empagliflozin/Metformin hydrochloride	65083 G
Empagliflozin/Metformin hydrochloride	65344 G
Metformin hydrochloride/Empagliflozin	66008 G
Empagliflozin/Metformin hydrochloride	66855 G
Empagliflozin/Metformin hydrochloride	69370 G
Empagliflozin/Metformin hydrochloride	70463 G
Dulaglutide	63336 G
Dulaglutide	63401 G
Dulaglutide	63785 G
Dulaglutide	63823 G
Exenatide	35144 G

Exenatide	35149 G
Exenatide	35150 G
Exenatide	35251 G
Exenatide	46458 G
Exenatide	46469 G
Exenatide	62661 G
Exenatide	62904 G
Exenatide	64622 G
Liraglutide	40642 G
Liraglutide	40693 G
Insulin degludec/Liraglutide	62899 G
Insulin degludec/Liraglutide	63562 G
Liraglutide	69548 G
Lixisenatide	55413 G
Lixisenatide	55459 G
Lixisenatide	55728 G
Lixisenatide	55729 G
Glibornuride	12245 G
Glibornuride	12259 G
Gliclazide	32 G
Gliclazide	1964 G

Gliclazide	5627 G
Gliclazide	11695 G
Gliclazide	15374 G
Gliclazide	17343 G
Gliclazide	21564 G
Gliclazide	21892 G
Gliclazide	29939 G
Gliclazide	31212 G
Gliclazide	33562 G
Gliclazide	34399 G
Gliclazide	34932 G
Gliclazide	36856 G
Gliclazide	40425 G
Gliclazide	42790 G
Gliclazide	43065 G
Gliclazide	43465 G
Gliclazide	44473 G
Gliclazide	45215 G
Gliclazide	45831 G
Gliclazide	47074 G
Gliclazide	47894 G

Gliclazide	48056 G
Gliclazide	51955 G
Gliclazide	53288 G
Gliclazide	54764 G
Gliclazide	55862 G
Gliclazide	56008 G
Gliclazide	56437 G
Gliclazide	57830 G
Gliclazide	58882 G
Gliclazide	60495 G
Gliclazide	61957 G
Gliclazide	62034 G
Gliclazide	63048 G
Gliclazide	63131 G
Gliclazide	67781 G
Gliclazide	68415 G
Gliclazide	68819 G
Gliclazide	69669 G
Gliclazide	70432 G
Gliclazide	70490 G
Gliclazide	71781 G

Gliclazide	72852 G
Gliclazide	75823 G
Glimepiride	5276 G
Glimepiride	5316 G
Glimepiride	5353 G
Glimepiride	6337 G
Glimepiride	7284 G
Glimepiride	7332 G
Glimepiride	7409 G
Glimepiride	11284 G
Glimepiride	40365 G
Glimepiride	44738 G
Rosiglitazone Maleate/Glimepiride	56376 G
Glimepiride	61311 G
Glimepiride	62014 G
Glimepiride	66399 G
Glimepiride	67056 G
Glimepiride	68289 G
Glimepiride	68675 G
Glimepiride	71476 G
Glimepiride	71477 G

Glimepiride	71665 G
Glimepiride	71667 G
Glipizide	547 G
Glipizide	5636 G
Glipizide	12513 G
Glipizide	17698 G
Glipizide	17706 G
Glipizide	29326 G
Glipizide	34802 G
Gliquidone	8390 G
Gliquidone	19658 G
Rosiglitazone maleate	469 G
Rosiglitazone maleate	5227 G
Rosiglitazone maleate/Metformin hydrochloride	6855 G
Rosiglitazone maleate/Metformin hydrochloride	7325 G
Rosiglitazone maleate/Metformin hydrochloride	7375 G
Rosiglitazone maleate	9662 G
Rosiglitazone maleate/Metformin hydrochloride	11601 G
Rosiglitazone maleate/Metformin hydrochloride	11604 G
Metformin Hydrochloride/Rosiglitazone Maleate	11609 G
Metformin Hydrochloride/Rosiglitazone Maleate	11610 G

Rosiglitazone maleate/Metformin hydrochloride	11717 G
Metformin Hydrochloride/Rosiglitazone Maleate	11737 G
Metformin Hydrochloride/Rosiglitazone Maleate	11760 G
Rosiglitazone maleate/Metformin hydrochloride	14164 G
Rosiglitazone maleate	15232 G
Rosiglitazone maleate/Metformin hydrochloride	17580 G
Rosiglitazone Maleate	37617 G
Rosiglitazone Maleate	48120 G
Rosiglitazone Maleate/Glimepiride	56376 G
Tolbutamide	1965 G
Tolbutamide	11946 G
Tolbutamide	12455 G
Tolbutamide	33673 G
Tolbutamide	34957 G
Tolbutamide	44304 G
Tolbutamide	46927 G

Appendix G – Diabetes diagnostic tests code list for CPRD

MedCodeId	CleansedReadCode	Term	SnomedCTConceptId	SnomedCTDescriptionId
1665741000000117	44gA.00	180 minute plasma glucose level	1003121000000103	2561101000000114
259587012	44f1.00	Serum fasting glucose level	1003131000000101	2564071000000115
259598013	44g1.00	Plasma fasting glucose level	1003141000000105	2560571000000116
703610000006116	466..00	Urine test for glucose	1003181000000102	2585411000000116
404515015	4669.00	Urine dipstick for glucose	1003181000000102	2585411000000116
259800016	466Z.00	Urine glucose test NOS	1003181000000102	2585411000000116
457628015	44TE.00	30 minute blood glucose level	1003691000000108	2584801000000117
457384010	44TF.00	60 minute blood glucose level	1003701000000108	2585471000000114
457491012	44TG.00	90 minute blood glucose level	1003711000000105	2584811000000115
457490013	44TH.00	120 minute blood glucose level	1003721000000104	2579861000000112

457605016	44TI.00	150 minute blood glucose level	1003731000000102	2561191000000119
186131017	7P17200	Glucose tolerance test	1005711000000106	2585781000000117
803621000006115	44V..00	Glucose tolerance test	1005711000000106	2585781000000117
375613019	44V..11	Blood glucose tolerance	1005711000000106	2585781000000117
762431000006110	4I39.00	Fluid sample glucose	1010401000000107	2578501000000118
411749015	4I39.11	Glucose in sample	1010401000000107	2578501000000118
129841000000118	44f..00	Serum glucose level	1010611000000107	2578521000000110
457616011	44f3.00	30 minute serum glucose level	1010621000000101	2586481000000115
457617019	44f4.00	60 minute serum glucose level	1010631000000104	2562021000000111
457712015	44f5.00	90 minute serum glucose level	1010641000000108	2574281000000115
457620010	44f6.00	120 minute serum glucose level	1010651000000106	2574291000000118
457908016	44f7.00	150 minute serum glucose level	1010661000000109	2564981000000117

502060018	44TA.00	Plasma glucose	1010671000000102	2582401000000112
134471000000110	44g..00	Plasma glucose level	1010671000000102	2582401000000112
457608019	44g3.00	30 minute plasma glucose level	1010681000000100	2564991000000115
457609010	44g4.00	60 minute plasma glucose level	1010691000000103	2552411000000115
457711010	44g5.00	90 minute plasma glucose level	1010701000000103	2586491000000118
457612013	44g6.00	120 minute plasma glucose level	1010711000000101	2565001000000110
457613015	44g7.00	150 minute plasma glucose level	1012661000000105	2578791000000119
977341000006114	4Q80.00	Glucose level	1018851000000108	2575211000000111
259584017	44f0.00	Serum random glucose level	1028881000000105	2600091000000116
259588019	44f2.00	Serum 2-hr post-prandial glucose level	1028891000000107	2600101000000112
259601015	44g2.00	Plasma 2-hr post-prandial glucose level	1028901000000108	2600121000000115
433741000006118	44U7.00	2 hour post-prandial blood glucose level	1030551000000103	2599601000000116

259597015	44g0.00	Plasma random glucose level	1031331000000106	2600111000000114
259307010	44T..00	Blood glucose method	1031451000000106	2598861000000114
2634891000000112		210 minute plasma glucose concentration	1045471000000104	2634891000000112
259368019	44VZ.00	Glucose tolerance test NOS	113076002	186131017
259341019	44TZ.00	Blood glucose method NOS	166888009	259307010
259346012	44U1.00	Blood glucose 0-1.4 mmol/L	166914001	259346012
259347015	44U2.00	Blood glucose 1.5-2.4 mmol/L	166915000	259347015
259348013	44U3.00	Blood glucose 2.5-4.9 mmol/L	166916004	259348013
259349017	44U4.00	Blood glucose 5-6.9 mmol/L	166917008	259349017
259350017	44U5.00	Blood glucose 7-9.9 mmol/L	166918003	259350017
259351018	44U6.00	Blood glucose 10-13.9 mmol/L	166919006	259351018
259353015	44U8.00	Blood glucose normal	166921001	259353015

259356011	44U9.00	Blood glucose abnormal	166922008	259356011
412230017	R105700	[D]Glucose, blood level abnormal	166922008	259356011
259357019	44UZ.00	Blood glucose 14+ mmol/L	166923003	259357019
259363011	44V1.00	Glucose tolerance test normal	166926006	259363011
259364017	44V2.00	Glucose tol. test impaired	166927002	259364017
1222530014	R102.12	[D]Impaired glucose tolerance test	166927002	2818163011
259365016	44V3.00	Glucose tol. test diabetic	166928007	2817641015
259790016	4662.00	Urine glucose test negative	167261002	259790016
259791017	4663.00	Urine glucose test = trace	167262009	259791017
259794013	4664.00	Urine glucose test = +	167264005	259794013
259795014	4665.00	Urine glucose test = ++	167265006	259795014
259796010	4666.00	Urine glucose test = +++	167266007	259796010

259797018	4667.00	Urine glucose test = ++++	167267003	259797018
260209019	46S4.00	Urine glucose: chem. titre	167523004	260209019
803551000006111	46S4.11	Glucose - urine titre	167523004	260209019
180729100006110		Capillary random blood glucose level	180729100006106	180729100006110
180730100006111		Capillary fasting blood glucose level	180730100006107	180730100006111
700510000006115	68K1.00	Urine screen for glucose	268556000	401577015
317635013	R102.00	[D]Glucose tolerance test abnormal	274858002	410727018
180728100006112		Capillary blood glucose measurement	302789003	444676015
147491000006111	8A17.00	Self monitoring of blood glucose	308113006	451421013
147501000006115	8A18.00	Self monitoring of urine glucose	308114000	451422018
147481000006113	8A19.00	Self monitoring of blood and urine glucose	308115004	451423011
457053016	44j..00	Glucose load test	313194008	457053016

1824941000006112		Glucose monitoring at home	359772000	475099017
1812221000006112	8A1B.00	Ambulat contin glucose monitor of interstitial tissue fluid	439926003	2791248017
1787101000006114		Ambulatory continuous glucose monitoring of interstitial tissue fluid	439926003	2791248017
259358012	44Uz.00	Blood glucose raised NOS	444780001	2872829018
2476507015	R10D.00	[D]Elevated blood glucose level	444780001	2872829018
500531000006111		Average home blood glucose	500531000006107	500531000006111
500541000006118		Average post-breakfast blood glucose	500541000006102	500541000006118
500551000006116		Average post-dinner blood glucose	500551000006100	500551000006116
500561000006119		Average post-lunch blood glucose	500561000006103	500561000006119
500571000006114		Average pre-bed blood glucose	500571000006105	500571000006114
500591000006110		Average pre-breakfast blood glucose	500591000006106	500591000006110
500631000006110		Average pre-lunch blood glucose	500631000006106	500631000006110

500651000006115		Average pre-tea blood glucose	500651000006104	500651000006115
173999100000114	44TJ700	Overnight blood glucose range	773781000000106	1727751000000113
173941100000110	44TJ200	Bedtime blood glucose range	773931000000105	1728941000000113
172977100000114	44TJ000	Blood glucose range before breakfast	774331000000109	1729771000000114
172979100000113	44TJ400	Blood glucose range after lunch	774341000000100	1729791000000113
172981100000114	44TJ500	Blood glucose range before evening meal	774351000000102	1729811000000114
172983100000118	44TJ100	Blood glucose range after breakfast	774361000000104	1729831000000118
172985100000113	44TJ600	Blood glucose range after evening meal	774371000000106	1729851000000113
173108100000110	44TJ300	Blood glucose range before lunch	774921000000106	1731081000000110
777221000033118		Blood Glucose Monitoring	777221000033102	7772210000033118
803541000006114	C313000	Glucose galactose intolerance	802711000000101	1794601000000115
853071000006116		2 Hour post prandial glucose	853071000006100	8530710000006116

884221000033119		Blood Glucose Meter	884221000033103	884221000033119
2365491000000112	9lQ..00	Blood glucose self-monitoring record checked	921721000000101	2365491000000112
2378701000000111	44TJ800	Baseline blood glucose level	928041000000101	2378701000000111
2389131000000119	44TJ900	Blood glucose level after evening meal	932401000000106	2389131000000119
2389171000000117	44TJA00	Blood glucose level during night	932421000000102	2389171000000117
2474483019	44TM.00	Blood glucose series	994411000000106	2554951000000115
3995810000000114	44V6.00	Extended glucose tolerance test	996311000000105	2572531000000114
1123651000000116	4Q83.00	Estimated average glucose level	996491000000105	2581701000000113
1280910000000112	44TJ.00	Blood glucose level	997671000000106	2563461000000115
2241910000006110	44U..12	Plasma glucose level	997671000000106	2563461000000115
5177910000006115	44U..00	Blood glucose result	997671000000106	2563461000000115
405633013	44TK.00	Fasting blood glucose level	997681000000108	2572691000000111

635701000000114	44g8.00	240 minute plasma glucose level	998281000000106	2581901000000110
635711000000111	44g9.00	300 minute plasma glucose level	998291000000108	2581911000000112
457954013	42W4.00	HbA1c level (DCCT aligned)	1019431000000105	2566161000000115
457953019	42c3.00	HbA1 level (DCCT aligned)	1019551000000104	2583661000000115
1986181000006111		HbA1c level (diagnostic reference range) - IFCC standardised	1049301000000100	2643101000000114
1986191000006114		HbA1c level (monitoring ranges) - IFCC standardised	1049321000000109	2643141000000112
817471000006110	42c0.00	HbA1 < 7% - good control	165679005	2770693019
817491000006111	42c1.00	HbA1 7 - 10% - borderline control	165680008	2768430011
817481000006113	42c2.00	HbA1 > 10% - bad control	165681007	2767754019
1927791000006119		Raised HbA1c level	1927791000006103	1927791000006119
453910015	42c..00	HbA1 - diabetic control	365845005	1206639010
129761000000114	44TB.00	Haemoglobin A1c level	1003671000000109	2560611000000113

2397611000000111	44TB100	Haemoglobin A1c (monitoring ranges)	1010941000000103	2582421000000115
2397571000000119	44TB000	Haemoglobin A1c (diagnostic reference range)	1010951000000100	2557081000000116
457954013	42W4.00	HbA1c level (DCCT aligned)	1019431000000105	2566161000000115
1986181000006111		HbA1c level (diagnostic reference range) - IFCC standardised	1049301000000100	2643101000000114
1986191000006114		HbA1c level (monitoring ranges) - IFCC standardised	1049321000000109	2643141000000112
257619018	42W1.00	Hb. A1C < 7% - good control	165679005	257619018
257620012	42W2.00	Hb. A1C 7-10% - borderline	165680008	257620012
257621011	42W3.00	Hb. A1C > 10% - bad control	165681007	257621011
1927791000006119		Raised HbA1c level	1927791000006103	1927791000006119
404444016	42W..00	Hb. A1C - diabetic control	269823000	1206383011
257623014	42WZ.00	Hb. A1C - diabetic control NOS	269823000	404444016
2160141012	66Ae.00	HBA1c target	408591000	1739591000000117

1753211000006115	66Ae000	HbA1c target level - IFCC standardised	446074002	1725291000000118
1700711000006113	42W5.00	Haemoglobin A1c level - IFCC standardised	999791000000106	2572901000000113
2154205011	44TL.00	Total glycosylated haemoglobin level	1013511000000100	2574561000000110
8041210000006112	42W..11	Glycosylated Hb	269823000	1206383011
5179210000006115	44Uz.11	Blood hyperglycaemia NOS	444780001	2872829018
404444016	42W..00	Hb. A1C - diabetic control	269823000	1206383011
257623014	42WZ.00	Hb. A1C - diabetic control NOS	269823000	404444016
453910015	42c..00	HbA1 - diabetic control	365845005	1206639010
1194410000006118	466..11	Sugar - urine test	1003181000000102	2585411000000116
375614013	44V..12	Blood sugar tolerance	1005711000000106	2585781000000117
458235019	46a..00	Urine sugar chromatography	1023731000000108	2581061000000110
1194510000006116	46S..12	Sugars in urine	1023741000000104	2575881000000117

518531000006111	44T..11	Blood sugar method	1031451000000106	2598861000000114
621801000006111	44T4.00	Dip-stick blood sugar	104686004	281007011
216681000006119	44T3.11	Post prandial blood sugar	1083781000000102	2715921000000119
116631000006118	44T7.00	Supper time blood sugar	1083851000000100	2716081000000110
259310015	44T1000	Random blood sugar normal	166890005	259310015
259311016	44T1100	Random blood sugar low	166891009	259311016
259312011	44T1200	Random blood sugar raised	166892002	259312011
259320013	44T5.00	Laboratory blood sugar	166896004	259320013
259327011	44T9.00	Glucometer blood sugar	166900001	259327011
264699014	66AB.00	Urine sugar charts	170755004	264699014
264700010	66AC.00	Blood sugar charts	170756003	264700010
1780371000006119		Breakfast time blood sugar	1780371000006103	1780371000006119

70071000006113	68K1.11	Urine screen for sugar	268556000	401576012
19176100 0006112	44T1.00	Random blood sugar	271061004	405631010
50058100 0006112		Average pre-bed sugar	500581000006108	500581000006112
50060100 0006119		Average pre-breakfast sugar	500601000006103	500601000006119
50062100 0006112		Average pre-evening meal sugar	500621000006108	500621000006112
50064100 0006117		Average pre-lunch sugar	500641000006101	500641000006117
50445100 0006113	44T8.00	Bedtime blood sugar	873281000000104	225539100000118
73331100 0006111	44T6.00	Lunch time blood sugar	873311000000101	225548100000113
43375100 0006116	44T3.00	2 hours post food blood sugar	88856000	508248018
51854100 0006118	44U..11	Blood sugar result	997671000000106	256346100000115
66718100 0006113	44T2.00	Fasting blood sugar	997681000000108	257269100000111
1485484012	466A.00	Urine clinitest	1021391000000109	256996100000110

264676010	66A..00	Diabetic monitoring	170742000	264676010
264729012	66AZ.00	Diabetic monitoring NOS	170742000	264676010
1884591000006118	66o..00	Further diabetic monitoring	170742000	264676010
264677018	66A1.00	Initial diabetic assessment	170743005	264677018
264678011	66A2.00	Follow-up diabetic assessment	170744004	264678011
264728016	66AT.00	Annual diabetic blood test	170778005	264728016
616341000006117	6872.00	Diabetes mellitus screen	171183004	265249012
461270012	ZV77100	[V]Screening for diabetes mellitus	171183004	265249012
1227832019	ZV77111	[V]Screening for diabetes mellitus (DM)	171183004	265249012
987441000006113		Six month diabetic review	987441000006109	987441000006113
1488822019	46Z0.00	Urine screening test for diabetes	395123002	1488822019
1485448017	43aE.00	Serum anti-glutamic decarboxylase level	1004991000000100	2561371000000115

1485550010	43m8.00	Glutamic acid decarboxylase antibody level	1007741000000102	2561661000000116
2501821000000112	43m8000	Serum glutamic acid decarboxylase antibody concentration	1011031000000101	2557101000000110
42	466..00	Urine test for glucose		
55	44U..00	Blood glucose result		
98	44g..00	Plasma glucose level		
2274	44V..00	Glucose tolerance test		
3295	R102.12	[D]Impaired glucose tolerance test		
3505	C313500	Glucose intolerance		
5986	R105700	[D]Glucose, blood level abnormal		
8113	44TJ.00	Blood glucose level		
8793	44TK.00	Fasting blood glucose level		
10042	R10E.00	[D]Impaired glucose tolerance		
10289	44g1.00	Plasma fasting glucose level		
10921	C11y200	Impaired glucose tolerance		
11818	R102.00	[D]Glucose tolerance test abnormal		
13594	4666.00	Urine glucose test = +++		

13595	4664.00	Urine glucose test = +		
13601	4665.00	Urine glucose test = ++		
13625	44T..00	Blood glucose method		
13824	44TA.00	Plasma glucose		
13825	44f0.00	Serum random glucose level		
13826	44f..00	Serum glucose level		
13828	44g6.00	120 minute plasma glucose level		
13829	44U7.00	2 hour post-prandial blood glucose level		
13830	44f1.00	Serum fasting glucose level		
13831	44U..12	Plasma glucose level		
13832	44TH.00	120 minute blood glucose level		
13864	44V1.00	Glucose tolerance test normal		
13936	4669.00	Urine dipstick for glucose		
14088	4667.00	Urine glucose test = ++++		
17478	8A17.00	Self monitoring of blood glucose		
17541	68K1.00	Urine screen for glucose		
17846	8A18.00	Self monitoring of urine glucose		

19775	44U8.00	Blood glucose normal		
19776	44g0.00	Plasma random glucose level		
19781	44V2.00	Glucose tol. test impaired		
20985	44U9.00	Blood glucose abnormal		
22225	44U5.00	Blood glucose 7-9.9 mmol/L		
22531	D102000	Glucose-6-phosphate dehydrogenase deficiency anaemia		
23122	44U1.00	Blood glucose 0-1.4 mmol/L		
23123	44f6.00	120 minute serum glucose level		
23204	4I39.11	Glucose in sample		
23240	42G4.00	Glucose 6-phosphate dehydrog.		
25044	44UZ.00	Blood glucose 14+ mmol/L		
25446	R10D.00	[D]Elevated blood glucose level		
27039	44f2.00	Serum 2-hr post-prandial glucose level		
27573	44Uz.00	Blood glucose raised NOS		
29219	4I39.00	Fluid sample glucose		
31161	R10D011	[D]Impaired fasting glucose		
31283	44U4.00	Blood glucose 5-6.9 mmol/L		

31288	44V..11	Blood glucose tolerance		
32770	44V3.00	Glucose tol. test diabetic		
33274	44j..00	Glucose load test		
33288	44TF.00	60 minute blood glucose level		
33289	44U3.00	Blood glucose 2.5-4.9 mmol/L		
33290	44g4.00	60 minute plasma glucose level		
33302	466Z.00	Urine glucose test NOS		
35549	44TZ.00	Blood glucose method NOS		
35550	44TI.00	150 minute blood glucose level		
37239	46S4.00	Urine glucose: chem. titre		
38199	44g2.00	Plasma 2-hr post-prandial glucose level		
39204	44U2.00	Blood glucose 1.5-2.4 mmol/L		
39208	44VZ.00	Glucose tolerance test NOS		
39246	46S4.11	Glucose - urine titre		
40171	44f4.00	60 minute serum glucose level		
41434	44U6.00	Blood glucose 10-13.9 mmol/L		

42217	8A19.00	Self monitoring of blood and urine glucose		
47532	44TM.00	Blood glucose series		
48994	44g3.00	30 minute plasma glucose level		
48995	44g5.00	90 minute plasma glucose level		
48996	44g7.00	150 minute plasma glucose level		
58660	44TG.00	90 minute blood glucose level		
58661	44TE.00	30 minute blood glucose level		
59705	44f3.00	30 minute serum glucose level		
59706	44f5.00	90 minute serum glucose level		
59707	44f7.00	150 minute serum glucose level		
61767	7P17200	Glucose tolerance test		
67606	4Q80.00	Glucose level		
84142	44V6.00	Extended glucose tolerance test		
86419	4N2..00	Dialysis fluid glucose level		

98569	4Q83.00	Estimated average glucose level		
98973	44g8.00	240 minute plasma glucose level		
104668	44TJ100	Blood glucose range after breakfast		
105134	44TJ400	Blood glucose range after lunch		
105434	C11y400	Impaired glucose regulation		
105505	44TJ500	Blood glucose range before evening meal		
105565	44TJ000	Blood glucose range before breakfast		
105648	44gA.00	180 minute plasma glucose level		
105843	8A1B.00	Ambulat contin glucose monitor of interstitial tissue fluid		
105863	44TJ300	Blood glucose range before lunch		
109057	44TJA00	Blood glucose level during night		
109654	44g9.00	300 minute plasma glucose level		
109655	44TJ800	Baseline blood glucose level		

109742	9mX..00	Impaired glucose regulation monitoring invitation		
109764	9lQ..00	Blood glucose self-monitoring record checked		
109802	44TJ200	Bedtime blood glucose range		
110812	44TJ900	Blood glucose level after evening meal		
111442	44TJ600	Blood glucose range after evening meal		
14050	42c..00	HbA1 - diabetic control		
14053	42W4.00	HbA1c level (DCCT aligned)		
19807	42c3.00	HbA1 level (DCCT aligned)		
40463	42c1.00	HbA1 7 - 10% - borderline control		
42360	42c0.00	HbA1 < 7% - good control		
46079	42c2.00	HbA1 > 10% - bad control		
19435	466A.00	Urine clinitest		
608	66A2.00	Follow-up diabetic assessment		
3550	66A..00	Diabetic monitoring		
13067	66AZ.00	Diabetic monitoring NOS		
13070	66A1.00	Initial diabetic assessment		

107452	66o..00	Further diabetic monitoring		
1173	C321.00	Pure hyperglyceridaemia		
1789	R105712	[D]Hyperglycaemia		
9310	Ryu8A00	[X]Hyperglycaemia, unspecified		
10166	C307000	Hyperglycinaemia		
11050	44Uz.11	Blood hyperglycaemia NOS		
18167	66AT.00	Annual diabetic blood test		
5234	6872.00	Diabetes mellitus screen		
9958	42W..00	Hb. A1C - diabetic control		
13597	42W1.00	Hb. A1C < 7% - good control		
13604	42W3.00	Hb. A1C > 10% - bad control		
14049	42WZ.00	Hb. A1C - diabetic control NOS		
14051	44TB.00	Haemoglobin A1c level		
14053	42W4.00	HbA1c level (DCCT aligned)		
96968	42W5.00	Haemoglobin A1c level - IFCC standardised		
108943	44TB000	Haemoglobin A1c (diagnostic reference range)		
108963	44TB100	Haemoglobin A1c (monitoring ranges)		

3668	44T2.00	Fasting blood sugar		
6110	44U..11	Blood sugar result		
7887	44T..11	Blood sugar method		
12677	ZV77100	[V]Screening for diabetes mellitus		
13193	66AC.00	Blood sugar charts		
13599	44T1.00	Random blood sugar		
13605	44T4.00	Dip-stick blood sugar		
13827	44T1200	Random blood sugar raised		
13833	44T9.00	Glucometer blood sugar		
14090	466..11	Sugar - urine test		
16697	46S..12	Sugars in urine		
16971	ZV77111	[V]Screening for diabetes mellitus (DM)		
19774	44T3.00	2 hours post food blood sugar		
19777	44T1000	Random blood sugar normal		
20690	44T3.11	Post prandial blood sugar		
23251	47BZ.00	Faecal sugars - general NOS		
26510	66AB.00	Urine sugar charts		
27581	68K1.11	Urine screen for sugar		

35576	47B..00	Faecal sugars - general		
36563	8CA4911	Pt advised re sugar free diet		
38062	44T5.00	Laboratory blood sugar		
39603	44T8.00	Bedtime blood sugar		
40176	44V..12	Blood sugar tolerance		
48564	44T7.00	Supper time blood sugar		
49951	13BB.00	High sugar diet		
51827	44T6.00	Lunch time blood sugar		
65526	46a..00	Urine sugar chromatography		
38266	43m8.00	Glutamic acid decarboxylase antibody level		
43543	43aE.00	Serum anti-glutamic decarboxylase level		
44993	46Z0.00	Urine screening test for diabetes		
60322	44SU.00	Serum glutamic acid level		
71100	44kP.00	Plasma glutamic acid level		
110548	43m8000	Serum glutamic acid decarboxylase antibody concentration		

Appendix H – Antidepressants code list for CPRD

drugsubstance	strength	DID
Agomelatine	25.000mg	507714100003311 7 A
Agomelatine	25.000mg	507704100003311 6 A
Agomelatine	25mg	40295 G
Agomelatine	25mg	40494 G
Amitriptyline hydrochloride	50.000mg	60541000033115 A
Amitriptyline hydrochloride	50.000mg	45941000033110 A
Amitriptyline hydrochloride	50.000mg	819841000033110 A
Amitriptyline hydrochloride	10.000mg/1.000 ml	55541000033118 A
Amitriptyline hydrochloride	50mg	1888 G
Amitriptyline Hydrochloride	75mg	2525 G
Amitriptyline hydrochloride	50mg	2985 G
Amitriptyline hydrochloride	50mg	4682 G
Amitriptyline hydrochloride	10mg/1ml	4690 G
Amitriptyline hydrochloride	50mg	8332 G

Amitriptyline Hydrochloride	75mg	8831 G
Amitriptyline hydrochloride	50mg	27008 G
Amitriptyline hydrochloride	50mg	33624 G
Amitriptyline hydrochloride	50mg	34107 G
Amitriptyline hydrochloride	50mg	34182 G
Amitriptyline hydrochloride	10mg/1ml	34251 G
Amitriptyline hydrochloride	50mg	34274 G
Amitriptyline hydrochloride	50mg	34634 G
Amitriptyline hydrochloride	50mg	40396 G
Amitriptyline hydrochloride	50mg	46970 G
Amitriptyline Hydrochloride		48065 G
Amitriptyline hydrochloride	10mg/1ml	59820 G
Amitriptyline hydrochloride	1mg/1ml	64141 G
Amitriptyline hydrochloride	50mg	64330 G
Amitriptyline hydrochloride	50mg	69712 G
Amoxapine	50.000mg	60941000033114 A
Amoxapine	50.000mg	87941000033111 A
Amoxapine	100.000mg	87641000033116 A

Amoxapine	100.000mg	61041000033116 A
Amoxapine	50mg	3351 G
Amoxapine	100mg	3652 G
Amoxapine	150mg	4411 G
Amoxapine	50mg	14398 G
Amoxapine	25mg	15380 G
Amoxapine	25mg	17319 G
Amoxapine	100mg	21357 G
Amoxapine	150mg	24723 G
Amoxapine	50mg	55289 G
Citalopram hydrobromide	20.000mg	259141000033116 A
Citalopram hydrobromide	20.000mg	259241000033111 A
Citalopram hydrobromide	10.000mg	158334100003311 8 A
Citalopram hydrobromide	10.000mg	158324100003311 1 A
Citalopram hydrobromide	40.000mg	158304100003311 5 A
Citalopram hydrobromide	40.000mg	158314100003311 6 A

Citalopram hydrochloride	40.000mg/1.000 ml	190064100003311 2 A
Citalopram hydrochloride	40.000mg/1.000 ml	190074100003311 5 A
Escitalopram oxalate	10.000mg	274964100003311 5 A
Escitalopram oxalate	10.000mg	274954100003311 6 A
Escitalopram oxalate	20.000mg	295134100003311 6 A
Escitalopram oxalate	20.000mg	295144100003311 0 A
Escitalopram oxalate	5.000mg	303034100003311 0 A
Escitalopram oxalate	5.000mg	303054100003311 5 A
Escitalopram oxalate	10.000mg/1.000 ml	392894100003311 9 A
Escitalopram oxalate	10.000mg/1.000 ml	392884100003311 0 A
Escitalopram oxalate	20.000mg/1.000 ml	512864100003311 8 A
Escitalopram oxalate	20.000mg/1.000 ml	512854100003311 9 A
Citalopram hydrobromide	20mg	67 G

Citalopram hydrobromide	10mg	476 G
Citalopram hydrochloride	40mg/1ml	513 G
Escitalopram oxalate	10mg	603 G
Escitalopram oxalate	10mg	648 G
Escitalopram oxalate	5mg	785 G
Citalopram hydrochloride	40mg/1ml	815 G
Citalopram hydrobromide	20mg	1712 G
Citalopram hydrobromide	40mg	2408 G
Citalopram hydrobromide	10mg	3861 G
Citalopram hydrobromide	40mg	4770 G
Escitalopram oxalate	20mg	6218 G
Escitalopram oxalate	20mg	6360 G
Escitalopram oxalate	5mg	6405 G
Escitalopram oxalate	10mg/1ml	20152 G
Citalopram hydrobromide	20mg	26016 G
Escitalopram oxalate	10mg/1ml	26056 G
Citalopram hydrobromide	20mg	29756 G
Citalopram hydrobromide	10mg	32546 G
Citalopram hydrobromide	10mg	32848 G
Citalopram hydrobromide	10mg	33720 G
Citalopram hydrobromide	20mg	34356 G

Citalopram hydrobromide	10mg	34413 G
Citalopram hydrobromide	20mg	34415 G
Citalopram hydrobromide	10mg	34436 G
Citalopram hydrobromide	40mg	34466 G
Citalopram hydrobromide	10mg	34498 G
Citalopram hydrobromide	10mg	34499 G
Citalopram hydrobromide	10mg	34586 G
Citalopram hydrobromide	40mg	34603 G
Citalopram hydrobromide	20mg	34722 G
Citalopram hydrobromide	20mg	34822 G
Citalopram hydrobromide	20mg	34871 G
Citalopram hydrobromide	20mg	34966 G
Citalopram hydrobromide	20mg	34970 G
Citalopram hydrobromide	40mg	36746 G
Escitalopram oxalate	20mg/1ml	40726 G
Escitalopram oxalate	20mg/1ml	41062 G
Citalopram hydrobromide	10mg	41528 G
Citalopram hydrobromide	10mg	42660 G
Citalopram hydrobromide	40mg	43519 G
Citalopram hydrobromide	40mg	45223 G
Citalopram hydrobromide	10mg	45286 G

Citalopram hydrobromide	40mg	45304 G
Citalopram hydrobromide	40mg	46926 G
Citalopram hydrobromide	40mg	46977 G
Citalopram hydrobromide	20mg	48026 G
Citalopram hydrobromide	10mg	49165 G
Citalopram hydrobromide	10mg	52100 G
Citalopram hydrobromide	20mg	52354 G
Citalopram hydrobromide	10mg	52408 G
Citalopram hydrobromide	20mg	52607 G
Citalopram hydrobromide	10mg	52824 G
Citalopram hydrobromide	20mg	53394 G
Citalopram hydrobromide	10mg	53787 G
Citalopram hydrobromide	2mg/1ml	54827 G
Citalopram hydrobromide	40mg	55033 G
Citalopram hydrobromide	20mg	56009 G
Citalopram hydrochloride	40mg/1ml	56292 G
Citalopram hydrobromide	10mg	56355 G
Citalopram hydrochloride	40mg/1ml	57936 G
Citalopram hydrobromide	20mg	58476 G
Citalopram hydrobromide	10mg	59193 G
Citalopram hydrobromide	10mg	59650 G

Citalopram hydrobromide	20mg	60568 G
Citalopram hydrobromide	40mg	60839 G
Citalopram hydrobromide	10mg	60888 G
Citalopram hydrobromide	10mg	63441 G
Escitalopram oxalate	10mg	63916 G
Citalopram hydrobromide	20mg	63953 G
Citalopram hydrobromide	10mg	64423 G
Citalopram hydrobromide	20mg	67097 G
Citalopram hydrobromide	40mg	69571 G
Citalopram hydrobromide	40mg	70790 G
Citalopram hydrobromide	10mg	71005 G
Citalopram hydrobromide	4mg/1ml	71848 G
Citalopram hydrochloride	40mg/1ml	72124 G
Citalopram hydrobromide	20mg	72373 G
Escitalopram oxalate	20mg	72773 G
Citalopram hydrobromide	20mg	73417 G
Citalopram Hydrobromide		74753 G
Escitalopram oxalate	10mg	74785 G
Escitalopram oxalate	10mg	74858 G
Escitalopram oxalate	10mg	74993 G
Citalopram hydrobromide	40mg	75075 G

Citalopram hydrobromide	10mg	75697 G
Citalopram hydrobromide	40mg	75702 G
Clomipramine hydrochloride	10.000mg	262041000033115 A
Clomipramine hydrochloride	10.000mg	61941000033115 A
Clomipramine hydrochloride	25.000mg	62041000033114 A
Clomipramine hydrochloride	25.000mg	262141000033116 A
Clomipramine hydrochloride	50.000mg	262241000033111 A
Clomipramine hydrochloride	50.000mg	62141000033113 A
Clomipramine hydrochloride	5.000mg/1.000ml	284741000033110 A
Clomipramine hydrochloride	5.000mg/1.000ml	68641000033117 A
Clomipramine hydrochloride	10.000mg/1.000 ml	443154100003311 5 A
Clomipramine hydrochloride	75.000mg	285741000033111 A
Clomipramine hydrochloride	75.000mg	70241000033114 A
Clomipramine hydrochloride	10mg	3194 G

Clomipramine hydrochloride	25mg	3657 G
Clomipramine hydrochloride	25mg	3670 G
Clomipramine hydrochloride	50mg	3925 G
Clomipramine hydrochloride	10mg	7515 G
Clomipramine hydrochloride	50mg	7693 G
Clomipramine hydrochloride	75mg	7894 G
Clomipramine hydrochloride	75mg	8661 G
Clomipramine hydrochloride	5mg/1ml	8719 G
Clomipramine hydrochloride	5mg/1ml	8720 G
Clomipramine hydrochloride	12.5mg/1ml	26513 G
Clomipramine hydrochloride	12.5mg/1ml	30375 G
Clomipramine hydrochloride	25mg	34245 G
Clomipramine hydrochloride	10mg	34866 G
Clomipramine hydrochloride	10mg/1ml	38274 G
Clomipramine hydrochloride	25mg	41563 G
Clomipramine hydrochloride	50mg	41597 G
Clomipramine hydrochloride	10mg	41628 G
Clomipramine hydrochloride	10mg	43561 G
Clomipramine hydrochloride	50mg	45318 G
Clomipramine hydrochloride	25mg	45350 G
Clomipramine hydrochloride	10mg/1ml	53161 G

Clomipramine hydrochloride	50mg	53187 G
Clomipramine hydrochloride	10mg	62620 G
Clomipramine hydrochloride	5mg/1ml	64458 G
Clomipramine hydrochloride	25mg	65762 G
Clomipramine hydrochloride	50mg	65804 G
Clomipramine hydrochloride	10mg	68665 G
Dosulepin hydrochloride	25.000mg	472141000033110 A
Dosulepin hydrochloride	25.000mg	111154100003311 7 A
Dosulepin hydrochloride	25.000mg	111164100003311 6 A
Dosulepin hydrochloride	25.000mg	308894100003311 8 A
Dosulepin hydrochloride	75.000mg	308904100003311 0 A
Dosulepin hydrochloride	75.000mg	113594100003311 6 A
Dosulepin hydrochloride	75.000mg	113554100003311 0 A
Dosulepin hydrochloride	75.000mg	479641000033111 A
Dosulepin hydrochloride	15.000mg/1.000 ml	599224100003311 4 A

Dosulepin hydrochloride	15.000mg/1.000 ml	308924100003311 9 A
Dosulepin hydrochloride	5.000mg/1.000m l	589104100003311 6 A
Dosulepin hydrochloride	5.000mg/1.000m l	308914100003311 4 A
Dosulepin hydrochloride	75mg	74 G
Dosulepin hydrochloride	25mg	84 G
Dosulepin hydrochloride	25mg	1169 G
Dosulepin hydrochloride	25mg	1940 G
Dosulepin hydrochloride	75mg	2320 G
Dosulepin Hydrochloride	25mg/5ml	6054 G
Dosulepin Hydrochloride	75mg/5ml	10948 G
Dosulepin hydrochloride	75mg	15632 G
Dosulepin Hydrochloride	25mg/5ml	19168 G
Dosulepin hydrochloride	75mg	19186 G
Dosulepin hydrochloride	75mg	21157 G
Dosulepin hydrochloride	75mg	21819 G
Dosulepin hydrochloride	25mg	21820 G
Dosulepin hydrochloride	25mg	23426 G
Dosulepin hydrochloride	25mg	29875 G
Dosulepin hydrochloride	25mg	30376 G

Dosulepin hydrochloride	25mg	31824 G
Dosulepin hydrochloride	75mg	31826 G
Dosulepin hydrochloride	75mg	32121 G
Dosulepin hydrochloride	25mg	33164 G
Dosulepin hydrochloride	75mg	34058 G
Dosulepin hydrochloride	25mg	34223 G
Dosulepin hydrochloride	75mg	34525 G
Dosulepin hydrochloride	25mg	34641 G
Dosulepin hydrochloride	25mg	34643 G
Dosulepin hydrochloride	25mg	34745 G
Dosulepin hydrochloride	75mg	42734 G
Dosulepin hydrochloride	20mg/1ml	43024 G
Dosulepin hydrochloride	25mg	44853 G
Dosulepin Hydrochloride	25mg/5ml	45737 G
Dosulepin hydrochloride	5mg/1ml	50722 G
Dosulepin hydrochloride	25mg	51758 G
Dosulepin hydrochloride	15mg/1ml	57926 G
Dosulepin hydrochloride	75mg	62681 G
Dosulepin hydrochloride	75mg	67728 G
Dosulepin hydrochloride	25mg	67990 G
Dosulepin hydrochloride	5mg/1ml	70593 G

Dosulepin hydrochloride	25mg	70838 G
Dosulepin hydrochloride	5mg/1ml	71023 G
Dosulepin hydrochloride	75mg	71059 G
Doxepin hydrochloride	10.000mg	1294541000033115 A
Doxepin hydrochloride	10.000mg	473041000033119 A
Doxepin hydrochloride	25.000mg	473141000033115 A
Doxepin hydrochloride	25.000mg	1294641000033119 A
Doxepin hydrochloride	25.000mg	401044100033114 A
Doxepin hydrochloride	50.000mg	401054100033110 A
Doxepin hydrochloride	50.000mg	1294741000033111 A
Doxepin hydrochloride	50.000mg	473241000033110 A
Doxepin hydrochloride	75.000mg	473341000033117 A
Doxepin hydrochloride	75.000mg	1294841000033118 A
Doxepin hydrochloride	10.000mg/1.000 ml	495404100033114 A

Doxepin hydrochloride	25mg	3554 G
Doxepin hydrochloride	10mg	3842 G
Doxepin hydrochloride	50mg	5073 G
Doxepin hydrochloride	75mg	7059 G
Doxepin hydrochloride	10mg	10413 G
Doxepin hydrochloride	50mg	12125 G
Doxepin hydrochloride	25mg	12129 G
Doxepin hydrochloride	75mg	14519 G
Doxepin hydrochloride	25mg	35258 G
Doxepin hydrochloride	50mg	35493 G
Doxepin Hydrochloride	25mg/5ml	40777 G
Doxepin hydrochloride	10mg/1ml	73363 G
Duloxetine hydrochloride	60.000mg	107019410000331 11 A
Duloxetine hydrochloride	60.000mg	124760410000331 12 A
Duloxetine hydrochloride	60.000mg	322674100003311 9 A
Duloxetine hydrochloride	60.000mg	322694100003311 6 A
Duloxetine hydrochloride	30.000mg	107018410000331 15 A

Duloxetine hydrochloride	30.000mg	124759410000331 19 A
Duloxetine hydrochloride	30.000mg	322664100003311 1 A
Duloxetine hydrochloride	30.000mg	322684100003311 2 A
Duloxetine hydrochloride	20.000mg	317764100003311 2 A
Duloxetine hydrochloride	20.000mg	317784100003311 3 A
Duloxetine hydrochloride	40.000mg	317794100003311 7 A
Duloxetine hydrochloride	40.000mg	317774100003311 5 A
Duloxetine hydrochloride	60mg	6895 G
Duloxetine hydrochloride	30mg	7122 G
Duloxetine hydrochloride	40mg	7147 G
Duloxetine hydrochloride	20mg	7153 G
Duloxetine hydrochloride	30mg	13151 G
Duloxetine hydrochloride	40mg	14803 G
Duloxetine hydrochloride	60mg	14849 G
Duloxetine hydrochloride	20mg	16969 G
Duloxetine hydrochloride	60mg	51383 G

Duloxetine hydrochloride	30mg	62688 G
Duloxetine hydrochloride	60mg	63216 G
Duloxetine hydrochloride	30mg	63370 G
Duloxetine hydrochloride	60mg	63763 G
Duloxetine hydrochloride	60mg	64442 G
Duloxetine hydrochloride	20mg	65165 G
Duloxetine hydrochloride	30mg	65618 G
Duloxetine hydrochloride	30mg	65809 G
Duloxetine hydrochloride	60mg	65888 G
Duloxetine hydrochloride	60mg	65892 G
Duloxetine hydrochloride	60mg	66405 G
Duloxetine hydrochloride	30mg	66412 G
Duloxetine hydrochloride	20mg	67564 G
Duloxetine hydrochloride	60mg	68096 G
Duloxetine hydrochloride	60mg	69428 G
Duloxetine hydrochloride	60mg	69752 G
Duloxetine hydrochloride	60mg	69965 G
Duloxetine hydrochloride	20mg	70063 G
Duloxetine hydrochloride	30mg	70405 G
Duloxetine hydrochloride	30mg	70728 G
Duloxetine hydrochloride	20mg	71669 G

Duloxetine hydrochloride	60mg	72211 G
Duloxetine hydrochloride	30mg	73298 G
Duloxetine hydrochloride	60mg	73540 G
Duloxetine hydrochloride	60mg	73868 G
Duloxetine hydrochloride	60mg	74190 G
Duloxetine hydrochloride	12mg/1ml	74774 G
Duloxetine hydrochloride	30mg	74907 G
Fluoxetine hydrochloride	20.000mg	111244100003311 4 A
Fluoxetine hydrochloride	20.000mg	192314100003311 8 A
Fluoxetine hydrochloride	20.000mg	260204100003311 9 A
Fluoxetine hydrochloride	20.000mg	271044100003311 9 A
Fluoxetine hydrochloride	20.000mg	577841000033114 A
Fluoxetine hydrochloride	4.000mg/1.000ml	277064100003311 4 A
Fluoxetine hydrochloride	4.000mg/1.000ml	112954100003311 0 A
Fluoxetine hydrochloride	4.000mg/1.000ml	277054100003311 3 A

Fluoxetine hydrochloride	60.000mg	111194100003311 1 A
Fluoxetine hydrochloride	60.000mg	579041000033111 A
Fluoxetine hydrochloride	10.000mg	116038410000331 19 A
Fluoxetine hydrochloride	10.000mg	649634100003311 6 A
Fluoxetine hydrochloride	40.000mg	117075410000331 18 A
Fluoxetine hydrochloride	4.000mg/1.000ml	574944100003311 5 A
Fluoxetine hydrochloride	4.000mg/1.000ml	449864100003311 5 A
Fluoxetine hydrochloride	20.000mg	912064100003311 2 A
Fluoxetine hydrochloride	20.000mg	912074100003311 5 A
Fluoxetine hydrochloride	30.000mg	117074410000331 19 A
Fluoxetine hydrochloride	20mg	22 G
Fluoxetine hydrochloride	4mg/1ml	252 G
Fluoxetine hydrochloride	20mg	418 G
Fluoxetine hydrochloride	4mg/1ml	2548 G

Fluoxetine hydrochloride	60mg	4075 G
Fluoxetine hydrochloride	60mg	4907 G
Fluoxetine hydrochloride	20mg	14740 G
Fluoxetine hydrochloride	20mg	19183 G
Fluoxetine hydrochloride	20mg	19470 G
Fluoxetine hydrochloride	20mg	29786 G
Fluoxetine hydrochloride	4mg/1ml	30258 G
Fluoxetine hydrochloride	20mg	33071 G
Fluoxetine hydrochloride	20mg	33410 G
Fluoxetine hydrochloride	4mg/1ml	33779 G
Fluoxetine hydrochloride	20mg	34202 G
Fluoxetine hydrochloride	4mg/1ml	34216 G
Fluoxetine hydrochloride	20mg	34288 G
Fluoxetine hydrochloride	20mg	34294 G
Fluoxetine hydrochloride	20mg	34456 G
Fluoxetine hydrochloride	20mg	34849 G
Fluoxetine hydrochloride	60mg	34856 G
Fluoxetine hydrochloride	4mg/1ml	36893 G
Fluoxetine hydrochloride	4mg/1ml	37256 G
Fluoxetine hydrochloride	20mg	38890 G
Fluoxetine hydrochloride	20mg	42107 G

Fluoxetine hydrochloride	10mg	42499 G
Fluoxetine hydrochloride	4mg/1ml	42803 G
Fluoxetine hydrochloride	20mg	45224 G
Fluoxetine hydrochloride	20mg	45247 G
Fluoxetine hydrochloride	20mg	45316 G
Fluoxetine hydrochloride	20mg	45329 G
Fluoxetine hydrochloride	20mg	48220 G
Fluoxetine hydrochloride	20mg	57532 G
Fluoxetine hydrochloride	20mg	59358 G
Fluoxetine hydrochloride	20mg	60138 G
Fluoxetine hydrochloride	20mg	60534 G
Fluoxetine hydrochloride	4mg/1ml	60619 G
Fluoxetine hydrochloride	20mg	60962 G
Fluoxetine hydrochloride	20mg	61335 G
Fluoxetine hydrochloride	20mg	62155 G
Fluoxetine hydrochloride	20mg	62335 G
Fluoxetine hydrochloride	20mg	66744 G
Fluoxetine hydrochloride	20mg	67092 G
Fluoxetine hydrochloride	10mg	67431 G
Fluoxetine hydrochloride	30mg	67496 G
Fluoxetine hydrochloride	40mg	67562 G

Fluoxetine hydrochloride	20mg	67736 G
Fluoxetine hydrochloride	20mg	67758 G
Fluoxetine hydrochloride	20mg	67769 G
Fluoxetine hydrochloride	60mg	67888 G
Fluoxetine hydrochloride	4mg/1ml	68266 G
Fluoxetine hydrochloride	20mg	69525 G
Fluoxetine hydrochloride	20mg	69542 G
Fluoxetine hydrochloride	4mg/1ml	69685 G
Fluoxetine hydrochloride	10mg	69941 G
Fluoxetine hydrochloride	20mg	71852 G
Fluoxetine hydrochloride	4mg/1ml	73414 G
Fluoxetine hydrochloride	400microgram/1 ml	74886 G
Fluoxetine hydrochloride	40mg	75068 G
Fluoxetine hydrochloride	60mg	75247 G
Fluoxetine hydrochloride	500microgram/1 ml	75645 G
Fluoxetine hydrochloride	20mg	75688 G
Fluoxetine hydrochloride	20mg	75799 G
Fluoxetine hydrochloride	4mg/1ml	75943 G
Fluvoxamine maleate	50.000mg	563341000033115 A

Fluvoxamine maleate	50.000mg	595541000033113 A
Fluvoxamine maleate	100.000mg	592841000033116 A
Fluvoxamine maleate	100.000mg	561941000033115 A
Fluvoxamine maleate	100mg	2290 G
Fluvoxamine maleate	50mg	2880 G
Fluvoxamine maleate	50mg	2897 G
Fluvoxamine maleate	100mg	12123 G
Fluvoxamine maleate	100mg	43518 G
Fluvoxamine maleate	100mg	44861 G
Fluvoxamine maleate	100mg	48045 G
Imipramine hydrochloride	10.000mg	755541000033119 A
Imipramine hydrochloride	25.000mg	754241000033115 A
Imipramine hydrochloride	25.000mg	145084100003311 7 A
Trimipramine maleate	50.000mg	138944100003311 2 A
Trimipramine maleate	50.000mg	145474100003311 5 A

Trimipramine maleate	10.000mg	147134100003311 6 A
Trimipramine maleate	10.000mg	139674100003311 2 A
Trimipramine maleate	25.000mg	139684100003311 9 A
Trimipramine maleate	25.000mg	147144100003311 0 A
Imipramine hydrochloride	5.000mg/1.000m l	545414100003311 8 A
Imipramine hydrochloride	5.000mg/1.000m l	532874100003311 7 A
Imipramine hydrochloride	5.000mg/1.000m l	144944100003311 3 A
Imipramine hydrochloride	10mg	1310 G
Imipramine hydrochloride	25mg	1809 G
Trimipramine maleate	25mg	2039 G
Trimipramine maleate	50mg	2531 G
Trimipramine maleate	25mg	2532 G
Imipramine hydrochloride	10mg	2579 G
Trimipramine maleate	50mg	3196 G
Trimipramine maleate	10mg	4310 G
Imipramine hydrochloride	5mg/1ml	4404 G

Imipramine hydrochloride	25mg	7910 G
Imipramine hydrochloride	5mg/1ml	8055 G
Trimipramine maleate	10mg	8928 G
Imipramine hydrochloride	10mg	32863 G
Imipramine hydrochloride	10mg	33074 G
Imipramine hydrochloride	10mg	34222 G
Imipramine hydrochloride	25mg	34355 G
Imipramine hydrochloride	25mg	34813 G
Imipramine hydrochloride	25mg	34872 G
Imipramine hydrochloride	25mg	41408 G
Imipramine hydrochloride	10mg	41681 G
Trimipramine maleate	10mg	42228 G
Imipramine hydrochloride	5mg/1ml	42247 G
Trimipramine maleate	25mg	45226 G
Trimipramine maleate	10mg	53808 G
Imipramine hydrochloride	25mg	56501 G
Trimipramine maleate	25mg	57978 G
Trimipramine maleate	10mg/1ml	65213 G
Trimipramine maleate	50mg	65445 G
Trimipramine maleate	5mg/1ml	66493 G
Trimipramine maleate	50mg	66919 G

Imipramine hydrochloride	10mg	67935 G
Imipramine hydrochloride	10mg	70287 G
Imipramine hydrochloride	10mg	71253 G
Isocarboxazid	10.000mg	787141000033110 A
Isocarboxazid	10mg	12207 G
Isocarboxazid	10mg	12503 G
Isocarboxazid	10mg	41731 G
Lofepramine hydrochloride	70.000mg	626241000033115 A
Lofepramine hydrochloride	70.000mg	221554100003311 8 A
Lofepramine hydrochloride	70.000mg	850141000033116 A
Lofepramine hydrochloride	14.000mg/1.000 ml	599664100003311 1 A
Lofepramine hydrochloride	14.000mg/1.000 ml	599674100003311 9 A
Lofepramine hydrochloride	14.000mg/1.000 ml	849241000033115 A
Lofepramine hydrochloride	14.000mg/1.000 ml	207884100003311 4 A
Lofepramine hydrochloride	70mg	114 G
Lofepramine hydrochloride	70mg	2093 G

Lofepramine hydrochloride	14mg/1ml	4218 G
Lofepramine hydrochloride	14mg/1ml	25444 G
Lofepramine hydrochloride	70mg	34046 G
Lofepramine hydrochloride	70mg	34578 G
Lofepramine hydrochloride	70mg	34672 G
Lofepramine hydrochloride	70mg	34950 G
Lofepramine hydrochloride	70mg	41627 G
Lofepramine hydrochloride	14mg/1ml	43534 G
Lofepramine hydrochloride	14mg/1ml	56229 G
Lofepramine hydrochloride	70mg	56703 G
Lofepramine hydrochloride	70mg	58450 G
Lofepramine hydrochloride	70mg	60591 G
Lofepramine hydrochloride	70mg	66100 G
Lofepramine hydrochloride	70mg	67742 G
Lofepramine hydrochloride	70mg	68657 G
Lofepramine hydrochloride	70mg	71067 G
Lofepramine hydrochloride	70mg	74586 G
Maprotiline hydrochloride	10.000mg	870441000033114 A
Maprotiline hydrochloride	10.000mg	853441000033119 A

Maprotiline hydrochloride	25.000mg	853541000033118 A
Maprotiline hydrochloride	25.000mg	870741000033119 A
Maprotiline hydrochloride	50.000mg	870841000033112 A
Maprotiline hydrochloride	50.000mg	853641000033117 A
Maprotiline hydrochloride	75.000mg	853741000033114 A
Maprotiline hydrochloride	75.000mg	870941000033116 A
Maprotiline hydrochloride	25mg	8549 G
Maprotiline hydrochloride	25mg	10645 G
Maprotiline hydrochloride	50mg	12100 G
Maprotiline hydrochloride	10mg	12222 G
Maprotiline hydrochloride	75mg	13558 G
Maprotiline hydrochloride	50mg	14410 G
Maprotiline hydrochloride	10mg	16727 G
Maprotiline hydrochloride	75mg	20405 G
Mianserin hydrochloride	10.000mg	917541000033110 A
Mianserin hydrochloride	20.000mg	917641000033111 A

Mianserin hydrochloride	30.000mg	917741000033119 A
Mianserin hydrochloride	10mg	3083 G
Mianserin hydrochloride	20mg	4329 G
Mianserin hydrochloride	30mg	6255 G
Mianserin hydrochloride	10mg	7468 G
Mianserin hydrochloride	20mg	8144 G
Mianserin hydrochloride	30mg	8585 G
Mianserin hydrochloride	20mg	11956 G
Mianserin hydrochloride	30mg	12192 G
Mianserin hydrochloride	10mg	12368 G
Mianserin hydrochloride	20mg	47363 G
Mirtazapine	30.000mg	919641000033115 A
Mirtazapine	30.000mg	155804100003311 8 A
Mirtazapine	15.000mg	325674100003311 8 A
Mirtazapine	15.000mg	302964100003311 2 A
Mirtazapine	15.000mg	302984100003311 3 A

Mirtazapine	30.000mg	307854100003311 5 A
Mirtazapine	30.000mg	297484100003311 4 A
Mirtazapine	45.000mg	325684100003311 1 A
Mirtazapine	45.000mg	302974100003311 5 A
Mirtazapine	45.000mg	302994100003311 7 A
Mirtazapine	15.000mg/1.000 ml	305874100003311 3 A
Mirtazapine	30mg	742 G
Mirtazapine	30mg	4726 G
Mirtazapine	15mg	6421 G
Mirtazapine	45mg	6481 G
Mirtazapine	30mg	6488 G
Mirtazapine	15mg	6795 G
Mirtazapine	15mg	6846 G
Mirtazapine	45mg	6854 G
Mirtazapine	30mg	10083 G
Mirtazapine	45mg	15268 G
Mirtazapine	15mg/1ml	16154 G

Mirtazapine	45mg	33337 G
Mirtazapine	30mg	40160 G
Mirtazapine	45mg	43234 G
Mirtazapine	45mg	43235 G
Mirtazapine	45mg	43236 G
Mirtazapine	15mg	43237 G
Mirtazapine	15mg	43239 G
Mirtazapine	15mg	43241 G
Mirtazapine	15mg	43242 G
Mirtazapine	15mg	43246 G
Mirtazapine	45mg	43247 G
Mirtazapine	15mg	43248 G
Mirtazapine	30mg	43250 G
Mirtazapine	15mg	43253 G
Mirtazapine	45mg	43256 G
Mirtazapine	15mg	43257 G
Mirtazapine	15mg	46668 G
Mirtazapine	30mg	47945 G
Mirtazapine	15mg/1ml	47966 G
Mirtazapine	30mg	48185 G
Mirtazapine	15mg	48698 G

Mirtazapine	45mg	49820 G
Mirtazapine	15mg	50892 G
Mirtazapine	15mg/1ml	53321 G
Mirtazapine	30mg	53543 G
Mirtazapine	30mg	53648 G
Mirtazapine	15mg	53699 G
Mirtazapine	15mg	54012 G
Mirtazapine	15mg	54342 G
Mirtazapine	15mg	54644 G
Mirtazapine	30mg	54792 G
Mirtazapine	15mg	55482 G
Mirtazapine	30mg	56209 G
Mirtazapine	15mg	58291 G
Mirtazapine	45mg	58625 G
Mirtazapine	30mg	59694 G
Mirtazapine	15mg	59953 G
Mirtazapine	45mg	59954 G
Mirtazapine	15mg	60370 G
Mirtazapine	30mg	60538 G
Mirtazapine	15mg/1ml	61547 G
Mirtazapine	15mg	61856 G

Mirtazapine	30mg	63403 G
Mirtazapine	15mg	64101 G
Mirtazapine	45mg	64139 G
Mirtazapine	45mg	64223 G
Mirtazapine	15mg	65555 G
Mirtazapine	15mg	66183 G
Mirtazapine	15mg	66580 G
Mirtazapine	15mg	66752 G
Mirtazapine	30mg	67272 G
Mirtazapine	30mg	68052 G
Mirtazapine	2mg	68544 G
Mirtazapine	15mg	68680 G
Mirtazapine	30mg	68933 G
Mirtazapine	30mg	69005 G
Mirtazapine	30mg	69420 G
Mirtazapine	30mg	71543 G
Mirtazapine	15mg	74557 G
Moclobemide	150.000mg	937241000033118 A
Moclobemide	150.000mg	868841000033115 A

Moclobemide	300.000mg	868941000033111 A
Moclobemide	300.000mg	937841000033119 A
Moclobemide	150mg	2883 G
Moclobemide	300mg	5187 G
Moclobemide	300mg	5832 G
Moclobemide	150mg	9206 G
Moclobemide	150mg	41747 G
Moclobemide	150mg	67305 G
Nefazodone hydrochloride	100.000mg	489741000033113 A
Nefazodone hydrochloride	100.000mg	966141000033116 A
Nefazodone hydrochloride	200.000mg	966241000033111 A
Nefazodone hydrochloride	200.000mg	489841000033115 A
Nefazodone hydrochloride	100mg	3391 G
Nefazodone hydrochloride	200mg	4011 G
Nefazodone hydrochloride	200mg	4297 G
Nefazodone hydrochloride	100mg	4554 G
Nefazodone Hydrochloride		9534 G

Nefazodone hydrochloride	50mg	63827 G
Nefazodone hydrochloride	50mg	67757 G
Nortriptyline hydrochloride	50.000mg	122923410000331 16 A
Nortriptyline hydrochloride	50mg	69317 G
Oxitriptan	50.000mg	465514100003311 3 A
Oxitriptan	100mg	62427 G
Paroxetine hydrochloride	20.000mg	104214100003311 7 A
Paroxetine hydrochloride	20.000mg	127834100003311 1 A
Paroxetine hydrochloride	30.000mg	127844100003311 7 A
Paroxetine hydrochloride	30.000mg	104224100003311 2 A
Paroxetine hydrochloride	10.000mg	407904100003311 5 A
Paroxetine hydrochloride	10.000mg	407914100003311 6 A
Paroxetine hydrochloride	40.000mg	117554410000331 19 A
Paroxetine hydrochloride	2.000mg/1.000ml	166244100003311 4 A

Paroxetine hydrochloride	2.000mg/1.000ml	1686141000033119 A
Paroxetine hydrochloride	20mg	50 G
Paroxetine hydrochloride	2mg/1ml	527 G
Paroxetine hydrochloride	20mg	841 G
Paroxetine hydrochloride	30mg	1397 G
Paroxetine hydrochloride	30mg	1575 G
Paroxetine hydrochloride	2mg/1ml	3601 G
Paroxetine hydrochloride	20mg	32899 G
Paroxetine hydrochloride	20mg	33978 G
Paroxetine hydrochloride	20mg	34351 G
Paroxetine hydrochloride	20mg	34419 G
Paroxetine hydrochloride	30mg	34587 G
Paroxetine hydrochloride	10mg	35021 G
Paroxetine hydrochloride	10mg	35112 G
Paroxetine hydrochloride	30mg	40165 G
Paroxetine hydrochloride	20mg	40892 G
Paroxetine hydrochloride	20mg	55023 G
Paroxetine hydrochloride	30mg	55537 G
Paroxetine hydrochloride	10mg	59288 G
Paroxetine hydrochloride	30mg	64785 G

Paroxetine hydrochloride	10mg	66292 G
Paroxetine hydrochloride	2mg/1ml	67259 G
Paroxetine hydrochloride	40mg	68325 G
Paroxetine hydrochloride	20mg	73589 G
Paroxetine hydrochloride	20mg	73668 G
Paroxetine hydrochloride	20mg	74588 G
Paroxetine Hydrochloride		75054 G
Phenelzine sulfate	15.000mg	1079341000033111 A
Phenelzine sulfate	15.000mg	955241000033110 A
Phenelzine sulfate	15mg	3349 G
Phenelzine sulfate	15mg	4321 G
Reboxetine mesilate	4.000mg	496741000033118 A
Reboxetine mesilate	4.000mg	116564100003311 5 A
Reboxetine mesilate	4mg	2356 G
Reboxetine mesilate	4mg	15163 G
Sertraline hydrochloride	50.000mg	1278841000033119 A
Sertraline hydrochloride	50.000mg	854241000033118 A

Sertraline hydrochloride	100.000mg	854141000033113 A
Sertraline hydrochloride	100.000mg	127874100003311 2 A
Sertraline hydrochloride	20.000mg/1.000 ml	597534100003311 9 A
Sertraline hydrochloride	10.000mg/1.000 ml	414834100003311 6 A
Sertraline hydrochloride	50mg	488 G
Sertraline hydrochloride	100mg	727 G
Sertraline hydrochloride	50mg	1612 G
Sertraline hydrochloride	100mg	4352 G
Sertraline hydrochloride	10mg/1ml	7328 G
Sertraline hydrochloride	50mg	32401 G
Sertraline hydrochloride	50mg	42387 G
Sertraline hydrochloride	100mg	44944 G
Sertraline hydrochloride	50mg	45915 G
Sertraline hydrochloride	20mg/1ml	49519 G
Sertraline hydrochloride	5mg/1ml	54081 G
Sertraline hydrochloride	30mg/1ml	54826 G
Sertraline hydrochloride	100mg	54933 G
Sertraline hydrochloride	100mg	55146 G

Sertraline hydrochloride	50mg	55488 G
Sertraline hydrochloride	50mg	58664 G
Sertraline hydrochloride	50mg	58723 G
Sertraline hydrochloride	100mg	59600 G
Sertraline hydrochloride	100mg	61503 G
Sertraline hydrochloride	100mg	62692 G
Sertraline hydrochloride	50mg	62693 G
Sertraline hydrochloride	2.5mg/1ml	62819 G
Sertraline hydrochloride	50mg	62927 G
Sertraline hydrochloride	100mg	62950 G
Sertraline hydrochloride	50mg	63481 G
Sertraline		65771 G
Sertraline hydrochloride	100mg	66413 G
Sertraline hydrochloride	100mg	66560 G
Sertraline hydrochloride	50mg	67730 G
Sertraline hydrochloride	100mg	67928 G
Sertraline hydrochloride	100mg	68756 G
Sertraline hydrochloride	50mg	69725 G
Sertraline hydrochloride	100mg	69726 G
Sertraline hydrochloride	50mg	69898 G
Sertraline hydrochloride	4mg/1ml	73759 G

Sertraline hydrochloride	100mg	73962 G
Sertraline hydrochloride	10mg/1ml	75405 G
Sertraline hydrochloride	50mg	75952 G
Tranylcypromine sulfate	10.000mg	146944100003311 6 A
Trifluoperazine Hydrochloride/Tranylcypromine Sulphate		3356 G
Tranylcypromine sulfate	10mg	3783 G
Trifluoperazine Hydrochloride/Tranylcypromine Sulphate		3955 G
Tranylcypromine sulfate	10mg	10787 G
Trifluoperazine Hydrochloride/Tranylcypromine Sulphate	1mg + 10mg	24890 G
Tranylcypromine sulfate	10mg	41654 G
Trazodone hydrochloride	150.000mg	147364100003311 3 A
Trazodone hydrochloride	150.000mg	938741000033111 A
Trazodone hydrochloride	100.000mg	923241000033113 A
Trazodone hydrochloride	100.000mg	145524100003311 3 A
Trazodone hydrochloride	50.000mg	145464100003311 2 A
Trazodone hydrochloride	50.000mg	923041000033117 A

Trazodone hydrochloride	10.000mg/1.000 ml	929541000033113 A
Trazodone hydrochloride	10.000mg/1.000 ml	146194100003311 3 A
Trazodone hydrochloride	150.000mg	146224100003311 0 A
Trazodone hydrochloride	150.000mg	929841000033110 A
Trazodone hydrochloride	20.000mg/1.000 ml	124765410000331 19 A
Trazodone hydrochloride	100mg	1730 G
Trazodone hydrochloride	50mg	3355 G
Trazodone hydrochloride	150mg	4003 G
Trazodone hydrochloride	150mg	4020 G
Trazodone hydrochloride	100mg	4194 G
Trazodone hydrochloride	50mg	4874 G
Trazodone hydrochloride	10mg/1ml	6442 G
Trazodone hydrochloride	10mg/1ml	8174 G
Trazodone hydrochloride	150mg	12710 G
Trazodone hydrochloride	150mg	13621 G
Trazodone hydrochloride	100mg	19181 G
Trazodone hydrochloride	50mg	29339 G

Trazodone hydrochloride	150mg	29857 G
Trazodone hydrochloride	150mg	30983 G
Trazodone hydrochloride	50mg	34003 G
Trazodone hydrochloride	50mg	34421 G
Trazodone hydrochloride	150mg	34470 G
Trazodone hydrochloride	100mg	34580 G
Trazodone hydrochloride	50mg	41609 G
Trazodone hydrochloride	100mg	41709 G
Trazodone hydrochloride	100mg	41710 G
Trazodone hydrochloride	30mg/1ml	55137 G
Trazodone hydrochloride	50mg/1ml	55138 G
Trazodone hydrochloride	5mg/1ml	57226 G
Trazodone hydrochloride	10mg/1ml	59931 G
Trazodone hydrochloride	15mg/1ml	61657 G
Trazodone hydrochloride	10mg/1ml	61842 G
Trazodone hydrochloride	20mg/1ml	65152 G
Trazodone hydrochloride	2mg/1ml	66749 G
Trazodone Hydrochloride		69355 G
Trazodone hydrochloride	10mg/1ml	70521 G
Trazodone hydrochloride	50mg	71031 G
Trazodone hydrochloride	20mg/1ml	72291 G

Trazodone hydrochloride	150mg	73419 G
Trazodone hydrochloride	150mg	73636 G
Trazodone hydrochloride	100mg	73639 G
Tryptophan	500.000mg	147414100003311 7 A
Tryptophan	500.000mg	100894100003311 4 A
Tryptophan	500.000mg	824794100003311 5 A
Tryptophan	500.000mg	824804100003311 7 A
Tryptophan	500mg	4422 G
Tryptophan	500mg	5611 G
Tryptophan	500mg	12221 G
Tryptophan	500mg	20504 G
Tryptophan	500mg	54686 G
Tryptophan	500mg	54747 G
Venlafaxine hydrochloride	37.500mg	151224100003311 9 A
Venlafaxine hydrochloride	37.500mg	499041000033111 A
Venlafaxine hydrochloride	37.500mg	489704100003311 6 A

Venlafaxine hydrochloride	75.000mg	489694100003311 7 A
Venlafaxine hydrochloride	75.000mg	499141000033110 A
Venlafaxine hydrochloride	75.000mg	151234100003311 2 A
Venlafaxine hydrochloride	50.000mg	151244100003311 8 A
Venlafaxine hydrochloride	50.000mg	499241000033115 A
Venlafaxine hydrochloride	75.000mg	826554100003311 2 A
Venlafaxine hydrochloride	75.000mg	930074100003311 6 A
Venlafaxine hydrochloride	75.000mg	121948410000331 16 A
Venlafaxine hydrochloride	75.000mg	123899410000331 19 A
Venlafaxine hydrochloride	75.000mg	126416410000331 14 A
Venlafaxine hydrochloride	75.000mg	498441000033112 A
Venlafaxine hydrochloride	75.000mg	150934100003311 7 A

Venlafaxine hydrochloride	75.000mg	489684100003311 3 A
Venlafaxine hydrochloride	75.000mg	489954100003311 5 A
Venlafaxine hydrochloride	75.000mg	481774100003311 9 A
Venlafaxine hydrochloride	75.000mg	482464100003311 3 A
Venlafaxine hydrochloride	75.000mg	481864100003311 2 A
Venlafaxine hydrochloride	75.000mg	489714100003311 7 A
Venlafaxine hydrochloride	75.000mg	493704100003311 5 A
Venlafaxine hydrochloride	75.000mg	493664100003311 1 A
Venlafaxine hydrochloride	75.000mg	495784100003311 1 A
Venlafaxine hydrochloride	75.000mg	481744100003311 4 A
Venlafaxine hydrochloride	75.000mg	523404100003311 9 A
Venlafaxine hydrochloride	75.000mg	602974100003311 3 A

Venlafaxine hydrochloride	75.000mg	532894100003311 9 A
Venlafaxine hydrochloride	75.000mg	581334100003311 9 A
Venlafaxine hydrochloride	75.000mg	581254100003311 5 A
Venlafaxine hydrochloride	75.000mg	557464100003311 7 A
Venlafaxine hydrochloride	75.000mg	589634100003311 2 A
Venlafaxine hydrochloride	75.000mg	588954100003311 4 A
Venlafaxine hydrochloride	150.000mg	930084100003311 4 A
Venlafaxine hydrochloride	150.000mg	826564100003311 3 A
Venlafaxine hydrochloride	150.000mg	126415410000331 13 A
Venlafaxine hydrochloride	150.000mg	123903410000331 14 A
Venlafaxine hydrochloride	150.000mg	121945410000331 18 A
Venlafaxine hydrochloride	150.000mg	588964100003311 0 A

Venlafaxine hydrochloride	150.000mg	557474100003311 4 A
Venlafaxine hydrochloride	150.000mg	581264100003311 9 A
Venlafaxine hydrochloride	150.000mg	581314100003311 7 A
Venlafaxine hydrochloride	150.000mg	532904100003311 1 A
Venlafaxine hydrochloride	150.000mg	602964100003311 6 A
Venlafaxine hydrochloride	150.000mg	589644100003311 8 A
Venlafaxine hydrochloride	150.000mg	523414100003311 5 A
Venlafaxine hydrochloride	150.000mg	481734100003311 5 A
Venlafaxine hydrochloride	150.000mg	493674100003311 9 A
Venlafaxine hydrochloride	150.000mg	495794100003311 5 A
Venlafaxine hydrochloride	150.000mg	493714100003311 6 A
Venlafaxine hydrochloride	150.000mg	489724100003311 2 A

Venlafaxine hydrochloride	150.000mg	481854100003311 1 A
Venlafaxine hydrochloride	150.000mg	482454100003311 2 A
Venlafaxine hydrochloride	150.000mg	481764100003311 1 A
Venlafaxine hydrochloride	150.000mg	489964100003311 9 A
Venlafaxine hydrochloride	150.000mg	489674100003311 5 A
Venlafaxine hydrochloride	150.000mg	150924100003311 0 A
Venlafaxine hydrochloride	150.000mg	498541000033113 A
Venlafaxine hydrochloride	7.500mg/1.000ml	449854100003311 6 A
Venlafaxine hydrochloride	7.500mg/1.000ml	600044100003311 5 A
Venlafaxine hydrochloride	15.000mg/1.000 ml	500804100003311 2 A
Venlafaxine hydrochloride	15.000mg/1.000 ml	886794100003311 8 A
Venlafaxine hydrochloride	150.000mg	829864100003311 5 A

Venlafaxine hydrochloride	150.000mg	126054410000331 17 A
Venlafaxine hydrochloride	150.000mg	482364100003311 1 A
Venlafaxine hydrochloride	150.000mg	482384100003311 2 A
Venlafaxine hydrochloride	150.000mg	505294100003311 6 A
Venlafaxine hydrochloride	75.000mg	126053410000331 11 A
Venlafaxine hydrochloride	75.000mg	829874100003311 2 A
Venlafaxine hydrochloride	75.000mg	505304100003311 4 A
Venlafaxine hydrochloride	75.000mg	482354100003311 0 A
Venlafaxine hydrochloride	75.000mg	482374100003311 9 A
Venlafaxine hydrochloride	225.000mg	126055410000331 16 A
Venlafaxine hydrochloride	225.000mg	505284100003311 2 A
Venlafaxine hydrochloride	225.000mg	505274100003311 9 A

Venlafaxine hydrochloride	37.500mg	616184100003311 8 A
Venlafaxine hydrochloride	37.500mg	616174100003311 1 A
Venlafaxine hydrochloride	37.500mg	888544100003311 8 A
Venlafaxine hydrochloride	37.500mg	888554100003311 7 A
Venlafaxine hydrochloride	37.500mg	121947410000331 14 A
Venlafaxine hydrochloride	225.000mg	107300410000331 10 A
Venlafaxine hydrochloride	225.000mg	107301410000331 14 A
Venlafaxine hydrochloride	225.000mg	116936410000331 17 A
Venlafaxine hydrochloride	225.000mg	121946410000331 17 A
Venlafaxine hydrochloride	37.5mg	301 G
Venlafaxine hydrochloride	75mg	470 G
Venlafaxine hydrochloride	37.5mg	623 G
Venlafaxine hydrochloride	75mg	1222 G
Venlafaxine hydrochloride	75mg	1474 G
Venlafaxine hydrochloride	50mg	2617 G

Venlafaxine hydrochloride	150mg	2654 G
Venlafaxine hydrochloride	150mg	5710 G
Venlafaxine hydrochloride	50mg	6274 G
Venlafaxine hydrochloride	75mg	9182 G
Venlafaxine hydrochloride	7.5mg/1ml	13237 G
Venlafaxine hydrochloride	75mg	39359 G
Venlafaxine hydrochloride	150mg	39360 G
Venlafaxine hydrochloride	75mg	39770 G
Venlafaxine hydrochloride	150mg	39809 G
Venlafaxine hydrochloride	75mg	40048 G
Venlafaxine hydrochloride	150mg	40049 G
Venlafaxine hydrochloride	225mg	40054 G
Venlafaxine hydrochloride	75mg	40059 G
Venlafaxine hydrochloride	150mg	40062 G
Venlafaxine hydrochloride	150mg	40092 G
Venlafaxine hydrochloride	75mg	40277 G
Venlafaxine hydrochloride	225mg	40407 G
Venlafaxine hydrochloride	150mg	40514 G
Venlafaxine hydrochloride	75mg	40515 G
Venlafaxine hydrochloride	150mg	40517 G
Venlafaxine hydrochloride	37.5mg	40764 G

Venlafaxine hydrochloride	75mg	40815 G
Venlafaxine hydrochloride	150mg	40817 G
Venlafaxine hydrochloride	75mg	40917 G
Venlafaxine hydrochloride	75mg	41033 G
Venlafaxine hydrochloride	75mg	41299 G
Venlafaxine hydrochloride	150mg	41314 G
Venlafaxine hydrochloride	75mg	42600 G
Venlafaxine hydrochloride	75mg	43203 G
Venlafaxine hydrochloride	150mg	43334 G
Venlafaxine hydrochloride	150mg	43673 G
Venlafaxine hydrochloride	75mg	43968 G
Venlafaxine hydrochloride	150mg	44936 G
Venlafaxine hydrochloride	75mg	44937 G
Venlafaxine hydrochloride	150mg	45664 G
Venlafaxine hydrochloride	37.5mg	45806 G
Venlafaxine hydrochloride	37.5mg	45818 G
Venlafaxine hydrochloride	75mg	45959 G
Venlafaxine hydrochloride	75mg	48199 G
Venlafaxine hydrochloride	75mg	49511 G
Venlafaxine hydrochloride	150mg	50081 G
Venlafaxine hydrochloride	30mg/1ml	50934 G

Venlafaxine hydrochloride	150mg	51280 G
Venlafaxine hydrochloride	37.5mg	51361 G
Venlafaxine hydrochloride	7.5mg/1ml	51699 G
Venlafaxine hydrochloride	75mg	52074 G
Venlafaxine hydrochloride	150mg	52516 G
Venlafaxine hydrochloride	75mg	52716 G
Venlafaxine hydrochloride	15mg/1ml	53326 G
Venlafaxine Hydrochloride		55424 G
Venlafaxine hydrochloride	150mg	55501 G
Venlafaxine hydrochloride	75mg	56457 G
Venlafaxine hydrochloride	37.5mg	56662 G
Venlafaxine hydrochloride	150mg	57751 G
Venlafaxine hydrochloride	75mg	58681 G
Venlafaxine hydrochloride	150mg	58726 G
Venlafaxine hydrochloride	37.5mg	58837 G
Venlafaxine hydrochloride	37.5mg	59035 G
Venlafaxine hydrochloride	75mg	59563 G
Venlafaxine hydrochloride	150mg	59753 G
Venlafaxine hydrochloride	37.5mg	59923 G
Venlafaxine hydrochloride	75mg	60449 G
Venlafaxine hydrochloride	150mg	60549 G

Venlafaxine hydrochloride	75mg	60843 G
Venlafaxine hydrochloride	37.5mg	60895 G
Venlafaxine hydrochloride	150mg	61236 G
Venlafaxine hydrochloride	30mg/1ml	62734 G
Venlafaxine hydrochloride	15mg/1ml	63268 G
Venlafaxine hydrochloride	75mg	63859 G
Venlafaxine hydrochloride	225mg	65666 G
Venlafaxine hydrochloride	37.5mg	65738 G
Venlafaxine hydrochloride	225mg	65899 G
Venlafaxine hydrochloride	75mg	66437 G
Venlafaxine hydrochloride	37.5mg	67271 G
Venlafaxine hydrochloride	75mg	67288 G
Venlafaxine hydrochloride	225mg	67563 G
Venlafaxine hydrochloride	37.5mg	68050 G
Venlafaxine hydrochloride	75mg	68876 G
Venlafaxine hydrochloride	37.5mg	69819 G
Venlafaxine hydrochloride	75mg	70315 G
Venlafaxine hydrochloride	37.5mg	70353 G
Venlafaxine hydrochloride	150mg	70420 G
Venlafaxine hydrochloride	225mg	70495 G
Venlafaxine hydrochloride	150mg	70806 G

Venlafaxine hydrochloride	75mg	70931 G
Venlafaxine hydrochloride	75mg	71257 G
Venlafaxine hydrochloride	150mg	71782 G
Venlafaxine hydrochloride	75mg	71806 G
Venlafaxine hydrochloride	150mg	71932 G
Venlafaxine hydrochloride	75mg	73658 G
Venlafaxine hydrochloride	37.5mg	73667 G
Venlafaxine hydrochloride	150mg	74010 G
Venlafaxine hydrochloride	75mg	74011 G
Venlafaxine hydrochloride	225mg	74516 G
Venlafaxine hydrochloride	75mg	75263 G
Venlafaxine hydrochloride	37.5mg	75525 G
Venlafaxine hydrochloride	150mg	75848 G
Venlafaxine hydrochloride	75mg	75894 G
Vortioxetine hydrobromide	10.000mg	10617041000033113 A
Vortioxetine hydrobromide	10.000mg	10617341000033110 A
Vortioxetine hydrobromide	20.000mg	10617441000033116 A
Vortioxetine hydrobromide	20.000mg	10617141000033112 A

Vortioxetine hydrobromide	5.000mg	106169410000331 12 A
Vortioxetine hydrobromide	5.000mg	106172410000331 17 A
Vortioxetine hydrobromide	5mg	65482 G
Vortioxetine hydrobromide	10mg	65483 G
Vortioxetine hydrobromide	20mg	66890 G
Vortioxetine hydrobromide	10mg	67874 G
Vortioxetine hydrobromide	20mg	69991 G
Vortioxetine hydrobromide	5mg	69992 G