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Review

Antidepressant and antipsychotic drug prescribing and diabetes outcomes: A systematic review of observational studies

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ABSTRACT

Aims: Psychotropic medication may be associated with adverse effects, including among people with diabetes. We conducted a systematic review of observational studies investigating the association between antidepressant or antipsychotic drug prescribing and type 2 diabetes outcomes.
Methods: We systematically searched PubMed, EMBASE, and PsycINFO to 15th August 2022 to identify eligible studies. We used the Newcastle-Ottawa scale to assess study quality and performed a narrative synthesis.
Results: We included 18 studies, 14 reporting on antidepressants and four on antipsychotics. There were 11 cohort studies, one self-controlled before and after study, two case-control studies, and four cross-sectional studies, of variable quality with highly heterogeneous study populations, exposure definitions, and outcomes analysed. Antidepressant prescribing may be associated with increased risk of macrovascular disease, whilst evidence on antidepressant and antipsychotic prescribing and glycaemic control was mixed. Few studies reported microvascular outcomes and risk factors other than glycaemic control.
Conclusions: Studies of antidepressant and antipsychotic drug prescribing in relation to diabetes outcomes are scarce, with shortcomings and mixed findings. Until further evidence is available, people with diabetes prescribed antidepressants and antipsychotics should receive monitoring and appropriate treatment of risk factors and screening for complications as recommended in general diabetes guidelines.

1. Introduction

Antidepressant and antipsychotic drugs are common psychotropic medications used in treating mental illness such as major depression, bipolar disorder, and schizophrenia [1,2], with prescribing having increased in high income countries in recent years [3,4]. This may be partly driven by longer treatment duration, but also by more frequent use, including for other indications (such as agitation and aggression in autism spectrum disorder and dementia [5], and chronic pain, migraines, and insomnia [6]). This increased use is of psychotropic drugs is of particular concern given that they appear to be associated with risk factors for cardiovascular disease and type 2 diabetes such as obesity, insulin resistance, and dyslipidaemia [7,8], as well as major cardiovascular events such as coronary heart disease and stroke [9,10].

These adverse effects must be considered in the context of their use among people with diabetes, including the bidirectional links between mental illness and diabetes [11] and the use of tricyclic antidepressants (TCA) to treat neuropathic pain occurring as a complication of diabetes [12]. Previous reviews have summarised evidence from experimental studies on the effect of antidepressants on outcomes including cardiometabolic risk factors in people with diabetes [13,14]. Although these reviews concluded that some antidepressant subtypes may be associated with improved glycaemic control, the overall evidence was inconclusive, in part due to low study quality, small sample sizes, and insufficient follow-up to adequately investigate longer-term outcomes such as vascular morbidity or mortality.

To our knowledge there is no previous systematic review of observational studies reporting the association between antidepressant or

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antipsychotic drugs and diabetes outcomes. We therefore conducted a systematic review of observational studies in people with diabetes that examined the association between antidepressant or antipsychotic drug prescribing and diabetes outcomes including cardiometabolic risk factors, macrovascular and microvascular disease complications, and mortality.

2. Materials and methods

This review is reported in accordance with the PRISMA guidelines. The review protocol was not registered.

2.1. Data sources and searches

We searched PubMed, EMBASE, and PsycINFO from point of inception to August 15th 2022 using a comprehensive electronic search strategy (Supplemental Appendix 1).

2.2. Study selection

We included cohort, case-control, self-controlled, or cross-sectional studies conducted among adults with type 2 diabetes that examined the association between prescribing of any antidepressant and/or antipsychotic drug versus no prescribing in relation to diabetes outcomes (cardiometabolic risk factors [glycaemic control; blood pressure; or lipid levels], macrovascular or microvascular disease; and all-cause or cause-specific mortality). See Supplemental Table 1 for a detailed summary of the inclusion criteria. We did not limit our search to studies published in the English language, but ultimately only included English language articles.

Two reviewers (CRLG and HWP or MFI and CAJ) independently screened titles and abstracts and the full-text of potentially eligible articles and extracted information on study and population characteristics, exposure and outcome/case definitions, statistical methods, and results from included articles. Disagreements about suitability for inclusion or data extracted were resolved through discussion with a third reviewer (CAJ or SHW).

2.3. Quality assessment

Two reviewers (CRLG and HWP or MFI and CAJ) assessed methodological study quality using the Newcastle-Ottawa scale [15]. This assesses the quality of observational studies across eight items within three domains: (i) the selection of the study groups; (ii) the comparability of the groups; (iii) the ascertainment of either the outcome or exposure of interest, where relevant.

2.4. Data synthesis and analysis

We performed a narrative synthesis since substantial clinical and methodological heterogeneity between studies precluded meta-analysis.

3. Results

3.1. Study characteristics

Our search yielded 11,216 articles, with 19 eligible articles representing 18 studies ultimately included (Fig. 1).

Study characteristics are described in Table 1. Details of the antidepressant and antipsychotic drugs included within each study are given in Supplemental Table 2. Eleven studies were cohort [16–26], one was a self-controlled before and after study [27], two were case-control [28,29], and four were cross-sectional [30–33]. Two studies included overlapping study populations [21,27], but adopted different study designs to address a similar question and so both were included in the narrative synthesis. There was considerable heterogeneity between

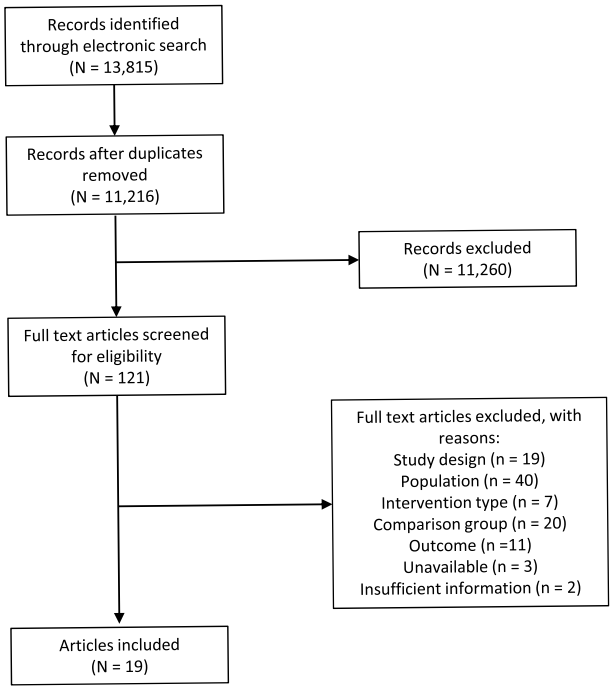

Fig. 1. Flow diagram of article selection.

studies in terms of study population, exposure definitions, and outcomes analysed. All studies were from high-income countries. Study populations were most frequently derived from people with newly diagnosed diabetes in the general population, with two studies conducted in low-income study populations [30,31]. Two studies included a study population with comorbid mental illness and diabetes (one with depression [25] and one with schizophrenia [24]).

3.2. Quality assessment

Methodological study quality ranged from three to eight out of nine stars (Supplemental Table 3). Concerns arising in some studies included: poor comparability due to insufficient adjustment for relevant confounders including confounding by indication; use of self-report for exposure and/or outcome assessment; poor representativeness of the population; low precision due to small sample sizes; and no description of the response rate and/or attrition (where applicable).

3.3. Antidepressant prescribing and diabetes outcomes

3.3.1. Glycaemic control

Of 14 studies reporting on antidepressant prescribing, six studies reported outcomes in relation to glycaemic control [16,21,22,27,29,31], with mixed findings. Of the three cohort studies, two reported no statistically significant difference in the association between antidepressant prescribing and optimal glycaemic control [21,22]. The third study reported that antidepressant prescribing was associated with reduced risk of sub-optimal glycaemic control [16]. Interestingly, a pre-post study reported lower HbA1c levels following antidepressant medication initiation [27]. One cohort study also reported that antidepressant prescribing was associated with increased odds of prescribing of glucose lowering drugs (GLDs) [21]. Similarly, a case-control study found that among people with newly diagnosed diabetes, current receipt of selective serotonin reuptake inhibitor (SSRI) antidepressant prescriptions was associated with more than two-fold increased risk of insulin prescription [29]. Similar associations were observed for other antidepressant subtypes and for other durations, with no associations observed for past prescriptions (Table 2). A cross-sectional study among people

Table 1
Characteristics of included studies.

First author, year, study setting	Study population	Data source	Exposure definition	Total participants [exposed | not exposed] †	Mean age*, years (±SD)	Male (%)	Outcome/case definition [follow-up duration] ‡
COHORT STUDIES							
Spoelstra, 2004 [23] Netherlands	• Newly diagnosed T2DM (based on oral GLDs only) from 6 cities • Exclusions: prescribed insulin within 3 months of T2DM diagnosis	Outpatient pharmacy dispensing records	Any versus no AP prescription	3,001 [248 | 2,743]	63 (SE 0.24)	49	First insulin prescription [5 years]
Rubin, 2010, 2013 [22] USA	• Overweight/obese, aged 45–76 years with verified self-reported T2DM included in a weight loss trial • Exclusions: SMI; poor glucose control; hypertension; raised cholesterol; failed exercise test	Trial	Any versus no AD prescription (ascertained from prescriptions brought to assessments)	5,145 [1,389 | 3,756]	59 (6.8)	41	Glycaemic control, insulin prescription, hypertension, dyslipidaemia [4 years]
Rådholm, 2015 [20] Sweden	• Aged 45–84 years with diabetes (classified by prescription of GLDs only)	National registers	Any versus no AD prescription; national drug register	241,787 [43,412 | 198,375]	NR	NR	First fatal/non-fatal MI; national MI register [3 years]
Brieler, 2016 [16] USA	• Aged 18–90 years with T2DM, classified by depression & AD treatment status • Exclusions: prescribed ADs for reasons other than depression	Primary care data registry	Any versus no AD prescription	1,399 [treated depression: 225 | untreated depression: 40]	62 (12.8)	41	Optimal glycaemic control [3 years]
Wu, 2016 [24] Taiwan	• Schizophrenia & newly diagnosed T2DM • Exclusions: diabetes complications (pre-existing or within 6 months of diagnosis	National health insurance database	Regular and irregular AP prescription versus no AP prescription	17,629 [irregular: 5,871; regular: 8,531 | 3,227]	47 (12.3)	49	CV morbidity, microvascular morbidity, all-cause mortality [11.5 years]
Würtz, 2016 [26] Denmark	• T1DM or T2DM & first-ever hospitalisation for stroke	National registers (including pharmacy dispensing)	Current, new, long-term, or former SSRI prescription versus no SSRI prescription	12,620 [current: 1,432; former: 233 | 10,955]	<60: 14.4% 60–69: 23.1% 70–79: 31.9% ≥80: 30.6%	57	Mortality (30 days following stroke) [30 days]
Hazuda, 2019 [19] USA	• Overweight/obese, aged 45–76 years with verified self-reported T2DM included in a weight loss trial • Exclusions: SMI; poor glucose control; hypertension; raised cholesterol; failed exercise test	Trial	Any versus no AD prescription (prescriptions brought to annual assessment visits)	5,145 [848 | 4,297]	59 (6.8)	41	Composite CV outcomes [median 9.6 years]
Chen, 2021 [17] Taiwan	• Aged ≥50 years with diabetes diagnosed 1997–2010 • Exclusions: incomplete data; history of MI before diabetes diagnosis; AD use of 1–27 cDDD during follow-up • Created two cohorts: one based on total diabetes population & a matched cohort	National health insurance database	AD prescription of >180 days versus no AD prescription & AD cumulative prescription ≥28 cDDD versus no AD prescription	500,990 [162,057 | 338,933]	50–59: 43% 60–69: 37% 70–79: 17% ≥80: 3%	51	First inpatient recorded diagnosis of MI
Rohde, 2021 [21] Denmark	• Aged ≥30 years with newly diagnosed T2DM in defined geographical area	Laboratory & pharmacy dispensing datasets	Current or former AD prescription versus no AD prescription	87,650 [current: 9,963; former: 4,809 | 65,101]	Current AD: median 66 (IQR 55–77); no AD: median 65 (IQR 55–74)	Current AD: 42%; no AD: 60	Optimal glycaemic control, first GLD prescription, LDL cholesterol [1 year]
Wu, 2021 [25] Taiwan	• Aged ≥20 years with depressive disorder (but not schizophrenia or bipolar disorder), incident diabetes diagnosed 2001–2014 & no complications at 6 months post-diabetes diagnosis	National health insurance database	AD prescription defined using an adherence measure (no use, poor use, partial use, & regular use)	36,276 [NR | NR]	20–44: 27.2% 45–64: 55.6% ≥65: 17.1%	39	Macrovascular morbidity, microvascular morbidity, all-cause mortality [median 5 years]

(*continued on next page*)

Table 1 (*continued*)

First author, year, study setting	Study population	Data source	Exposure definition	Total participants [exposed | not exposed] †	Mean age*, years (±SD)	Male (%)	Outcome/case definition [follow-up duration] ‡
Chen, 2022 [18] Taiwan	• Aged ≥18 years with diabetes diagnosed 1999–2013 • Exclusions: record of AD prescription within the prior 2 years; prior PAD or venous thromboembolism or malignant neoplasm; follow-up of <1 year • Additional propensity score-matched cohort included	National health insurance database	SSRI prescription versus no SSRI prescription	5049 [459 | 4590]	18–44: 16% 45–64: 52% ≥65: 32%	42	PAD [14 years]
SELF-CONTROLLED STUDIES							
Rohde, 2022 [27] Denmark	• Aged ≥30 years with T2DM diagnosed 2000–2016, without a psychotic or bipolar disorder, in defined geographical area • No AD prescription in the 100 days prior to T2DM diagnosis & redeemed first AD prescription during follow-up	Routinely collected health datasets, including clinical laboratory datasets	Comparison of outcome in the pre/post AD initiation period (index date being date of AD initiation)	14,919 initiated AD medication [NA]	Median 65 (IQR 54–75)	54%	Mean HbA1c and LDL levels [32 months; 16 months pre-index date & 16 months post-index date]
CASE-CONTROL STUDIES							
Lipscombe, 2009 [28] Canada	• Aged ≥66 years with diabetes, in defined geographical area • Exclusions: receiving dialysis or palliative care	Regional routine databases	Current & recent past AP prescription versus remote AP prescription	13,817 [1,594 cases (current: 909; recent past: 251) | 14,370 controls (current: 7,455; recent past: 3,008)	Cases, insulin: 76 (6.1); oral medication: 78 (6.6); none: 78 (7.0)	Cases, insulin: 47; oral medication: 51; none: 50	Hospitalisation for hyperglycaemia [5 years]
Noordam, 2016 [29] Netherlands	• Aged ≥45 years with T2DM (classified by oral GLDs only), in defined geographical area who agreed to participate	Routinely collected pharmacy data	Current and past SSRI & TCA prescription versus no AD prescription	1,677 [304 cases (current SSRI: 9; past SSRI: 32; current TCA: 8; past TCA: 40) | controls unclear]	72 (9.7)	44	First insulin prescription [NR]
CROSS-SECTIONAL STUDIES							
Higgins, 2007 [30] USA	• Men aged ≥40 years with T2DM, attending a mostly low-income veterans treatment centre • Exclusions: prescribed ADs for neuropathy	Survey	Any versus no AD prescription (treatment centre electronic records)	8,185 [1,598 | 6,587]	Depression: >60: 43%; No depression: >60: 70%	100	CVD (through treatment centre electronic records)
Yekta, 2015 [33] USA	• Aged 40–85 years with self-reported T2DM or HbA1c values ≥6.5%/48 mmol/mol • Exclusions: prescribed insulin at diagnosis; blindness, eye infections, or eye patches; immunological disorders	Annual national survey	Any versus no AD prescription; self-report in interviews	1,144 [186 | 958]	Median 64	48	Retinopathy (retinal imaging assessed by experienced graders)
Kammer, 2016 [31] USA	• Aged 40–79 years with self-reported T1DM and T2DM, attending community health clinics in low-income areas • Exclusions: did not provide a blood sample; sickle cell anaemia	Survey	SSRI, SNRI, TCA, other AD, or multiple AD prescription versus no AD prescription; self-report in interviews	462 [92 | 370]	40–49: 40% 50–65: 48% >65: 12%	14	HbA1c (standardised measurements following interview)
Wake, 2016 [32] Scotland	• T1DM & T2DM	National diabetes register	Any versus no AP prescription	25,982¶ [2,362 | 23,620]¶	64	NR	Retinopathy, HbA1c, systolic/diastolic BP, cholesterol

AD: antidepressant; AP: antipsychotic; BP: blood pressure; cDDD: cumulative defined daily dose; CV: cardiovascular; CVD cardiovascular disease; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; IQR: interquartile range; LDL: low-density lipoprotein; MI: myocardial infarction; NR: not reported; PAD: peripheral artery disease; SD: standard deviation; SE: standard error; SMI: severe mental illness; SNRI: selective-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; T1DM/T2DM: type 1/type 2 diabetes mellitus; TCA: tricyclic antidepressant.

* Mean age and standard deviation where reported unless otherwise stated.

† Gives the number of people in the exposed (AD or AP) and unexposed (AD or AP) groups, with more detailed subgroups or cases and controls specified where applicable.

‡ Maximum follow-up time unless otherwise stated.

¶ Exposed patients matched 1:10 to unexposed controls; total number of participants and number of participants unexposed deduced from this.

Table 2
Results of observational studies reporting on the association between antidepressant drug prescribing and outcomes in people with diabetes.

First author, year	Statistical methods	Results				
		Outcome	Reference	Antidepressant prescription	Effect estimate (CI)*	Direction of association†
COHORT STUDIES						
Rubin, 2010, 2013‡ [22]	GEE	Sub-optimal glycaemic control¶ or insulin prescription	No AD	AD in prior year	OR 1.13 (0.96–1.32)	↔
Rådholm, 2015 [20]	Descriptive	First fatal or non-fatal MI	No AD	AD (2 year run-in)	*Men, 45–64 years:* 7.6 versus 6.0 per 1,000 years	↑§
					Women, 45–64 years: 5.4 versus 3.7 per 1,000 years	↑§
					Men, 65–84 years: 16.2 versus 12.6 per 1,000 years	↑§
					Women, 65–84 years: 13.3 versus 10.3 per 1,000 years	↑§
Brieler, 2016 [16]	GEE	Optimal glycaemic control¶	Depression with no AD	Depression with AD (4 year observation)	**OR 1.95 (1.02–3.71)**	↓(of sub-optimal glycaemic control)
Würtz, 2016 [26]	Cox proportional hazards	Mortality (30 days following stroke)	No SSRI	Current SSRI (any)	**RR 1.3 (1.1–1.5)**	↑
				New SSRI	**RR 1.5 (1.2–1.8)**	↑
				Long-term SSRI	**RR 1.2 (1.1–1.4)**	↑
				Former SSRI	RR 1.3 (1.0–1.7)	↔
Hazuda, 2019# [19]	Cox proportional hazards	CV morbidity and mortality	No AD	Baseline AD**	*Men:* HR 0.95 (0.71–1.27)	↔
					***Women:* HR 0.71 (0.53–0.95)**	↓
Chen, 2021 [17]	Cox proportional hazards (of matched cohort)	First MI	No AD	No AD	**HR 0.68 (0.66–0.71)**	↓
Rohde, 2021 [21]	Cox proportional hazards	Optimal glycaemic control¶	No AD	Current AD	OR 0.99 (0.93–1.06)	↔
				Former AD	**OR 1.07 (1.01–1.14)**	↓ (of sub-optimal glycaemic control)
		GLD prescription (including insulin)	No AD	Current AD	**OR 1.39 (1.34–1.44)**	↑
				Former AD	**OR 1.35 (1.31–1.40)**	↑
Wu, 2021 [25]	None	Macrovascular morbidity	No AD	AD	69.2 versus 65.6 per 1000 person-years	↑§
		Microvascular morbidity		AD	42.4 versus 40.9 per 1000 person-years	↑§
		All-cause mortality		AD	19.8 versus 17.3 per 1000 person-years	↑§
Chen, 2022 [18]	Cox proportional hazards	PAD	No SSRI	SSRI	HR 1.13 (0.76–1.69)	↔
SELF-CONTROLLED STUDIES						
Rhode, 2022 [27]	Mean percent change	Mean HbA1c	Pre-post AD initiation comparison		−0.16% (95% CI, −0.18% - −0.13%)	↓
					Age-sex reference population: −0.03% (95% CI, −0.04% - −0.01%)	↓
		Mean LDL	Pre-post AD initiation comparison		−0.17% (95% CI, −0.19% - −0.15%)	↓
					Age-sex reference population: −0.15% (95% CI, −0.16% - −0.13%)	↓
CASE-CONTROL STUDIES						
Noordam, 2016 [29]	Conditional logistic regression	Insulin prescription	No AD	Current SSRI (any)	HR 1.81 (0.89–3.71)	↔
				Current TCA (any)	HR 1.40 (0.67–2.96)	↔
				Current SSRI (>90 days)	**HR 2.17 (1.02–4.60)**	↑
				Current TCA (>90 days)	HR 1.90 (0.89–4.06)	↔
				Past SSRI	HR 0.99 (0.65–1.51)	↔
				Past TCA	HR 0.94 (0.65–1.38)	↔
CROSS-SECTIONAL STUDIES						
Higgins, 2007 [30]	Logistic regression	CVD (composite)	No AD	AD	**OR 1.19 (CI not available, P = 0.005)**	↑
		MI	No AD	AD	**OR 1.27 (CI not available, P = 0.011)**	↑
Yekta, 2015 [33]	Logistic regression	Retinopathy	No AD	AD	**OR 0.48 (0.24–0.95)**	↓
					Without depression: OR 0.61 (0.07–5.20)	↔
					***With depression*: OR 0.41 (0.24–0.70)**	↓

(*continued on next page*)

Table 2 (*continued*)

First author, year	Statistical methods	Results				
		Outcome	Reference	Antidepressant prescription	Effect estimate (CI)*	Direction of association†
Kammer, 2016 [31]	Linear regression	Log HbA1c	No AD	SSRI	−0.03 (SE 0.04)	↔
				SNRI	−0.05 (SE 0.11)	↔
				TCA	−0.08 (SE 0.11)	↔
				Other	0.03 (SE 0.10)	↔
				Multiple	**0.12 (SE 0.09)**††	↑

AD: antidepressant; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; GEE: generalised estimating equations; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; HR: hazard ratio; LDL: low-density lipoprotein; MI: myocardial infarction; OR: odds ratio; PAD: peripheral artery disease; RR: rate ratio; SE: standard error; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

* Results given for fully adjusted or matched models unless otherwise stated (full details of factors adjusted for given in Supplemental Table 4); estimates in bold are statistically significant at the P <0.05 level.

† ↑ = increased risk of outcome; ↓ = decreased risk of outcome; ↔ = no association (with statistical significance at the P <0.05 level, unless otherwise stated).

‡ Results given for the control arm (diabetes support and education) of the clinical trial from which the cohort is derived.

¶ Optimal glycaemic control HbA1c <7%/53 mmol/mol.

§ Statistical comparisons not presented; significance not given.

Results given for the primary outcome.

** Authors state that similar results were obtained where analysing AD prescribing as a time-varying covariate (not reported).

†† Standardised effect estimate 0.12 reported to translate into a HbA1c effect of 1.26%/13.8 mmol/mol.

from low-income areas found that antidepressant prescribing from multiple subtypes was associated with higher values of HbA1c, after adjustment for depression severity [31], whereas there was no association between individual antidepressant subtype prescribing and HbA1c levels.

3.3.2. Other cardiometabolic risk factors

One cohort study found that antidepressant prescribing was associated with abnormal lipid profiles or receipt of lipid-lowering medication [22], whereas a second reported that antidepressant prescribing may have a small protective effect on cholesterol levels [21]. Findings were broadly consistent by prescription timing and across antidepressant subtypes (Supplemental Table 5a).

3.3.3. Macrovascular and microvascular disease complications and mortality

Eight studies reported associations with macrovascular and microvascular disease complications of diabetes, comprising six cohort [17–20,25,26] and two cross-sectional studies [30,33] (Table 2 and Supplementary Table 5a). Outcomes were heterogeneous and findings were mixed.

Receipt of antidepressant prescriptions, in comparison to no record of antidepressant prescribing, was associated with higher crude incidence of myocardial infarction (MI) [20] and of a composite macrovascular outcome [25]. However, lack of adjustment for age, sex and other factors that may differ between groups limits conclusions from these studies. A third cohort study found that SSRI antidepressant prescribing was associated with increased risk of 30-day post-stroke mortality [26], with the excess risk greatest for people whose SSRI prescription was initiated shortly before stroke. A cross-sectional study of older men of low-income from one treatment centre reported greater odds of a composite cardiovascular morbidity outcome and of MI specifically in crude analyses without control of confounding factors [30]. In contrast, a cohort study with a median of 9.6 years follow-up derived from post-hoc analyses of a clinical trial for a weight loss intervention [19] reported that antidepressant prescribing was associated with reduced cardiovascular morbidity or mortality in women, but not men. Risk of peripheral artery disease was reported to be similar in those with diabetes prescribed versus not prescribed antidepressants [18]. Finally, the only cohort study to describe microvascular complications reported higher crude incidence of a composite microvascular outcome in people prescribed antidepressants among a Taiwanese cohort of people newly treated for diabetes [25], whilst a small cross-sectional study of people with a diagnosis of diabetes or with HbA1c 6.5% who took part in the National Health and Nutrition Examination Survey in the US found that self-reported antidepressant use was associated with lower odds of retinopathy compared to people not reporting antidepressant use, after adjusting for sociodemographic and clinical characteristics [33] (Table 2). Supplemental Table 5a includes details of additional results reported in some studies, including investigations of variations of composite outcomes, interactions, and associations by antidepressant subtypes, with findings generally consistent with primary results.

3.4. Antipsychotic prescribing and diabetes outcomes

3.4.1. Glycaemic control

Just four studies reported on antipsychotic prescribing in relation to diabetes outcomes. Two studies reported a link between that antipsychotic prescribing and poorer glycaemic control [23,28], and one reported the opposite [32]. The only cohort study [23] found that receipt of an antipsychotic prescription within the first two years of diabetes diagnosis was associated with a two-fold increased risk of first insulin prescription, which attenuated to a 30% increased risk after adjustment for other drug prescriptions (Table 3). In a case-control study of older adults, receipt of an antipsychotic prescription in the previous 180 days was associated with an increased risk of hospitalisation for hyperglycaemia, regardless of diabetes medication type [28]. This effect was strongest among those receiving a first prescription of antipsychotics (Table 3) and consistent across antipsychotic subtypes (Supplemental Table 5b). In contrast, a cross-sectional study found that mean HbA1c values were significantly lower in people prescribed antipsychotics for >12 months in total compared with those who never received antipsychotics [32].

3.4.2. Other cardiometabolic risk factors

Antipsychotic prescribing was also associated with significantly lower systolic and diastolic blood pressure and total cholesterol in one study, though absolute differences were small (Supplemental Table 5b) [32].

3.4.3. Macrovascular or microvascular disease complications and mortality

Two studies reporting on the association between antipsychotic prescribing and macrovascular or microvascular disease complications of diabetes used population-based national registers [24,32]. A cohort study of people with schizophrenia found that, compared to no antipsychotic prescribing, regular antipsychotic prescribing was associated with a 20% and 27% reduced risk of cardiovascular morbidity, and all-cause mortality, respectively [24] (Table 3). There was no clear

Table 3
Results of observational studies reporting on the association between antipsychotic drug prescribing and outcomes in people with diabetes.

First author, year	Statistical methods	Results					
		Outcome	Reference	Antipsychotic prescription	Effect estimate (CI)*		Direction of association†
COHORT STUDIES							
Spoelstra, 2004 [23]	Cox proportional hazards	Insulin prescription	No AP	AP within 2 years of diabetes diagnosis	2 years post diagnosis	***Adjusted for age and year:*** **HR 2.0 (1.2-3.3)**	↑
						Adjusted for medication: HR 1.7 (1.0-3.0)	↔
Wu, 2016 [24]	Cox proportional hazards‡	CV morbidity	No AP	Irregular AP	**HR 0.83 (0.70-0.98)**		↓
				Regular AP	**HR 0.80 (0.66-0.97)**		↓
		Microvascular morbidity	No AP	Irregular AP	HR 0.99 (0.81-1.22)		↔
				Regular AP	HR 0.83 (0.62-1.11)		↔
		All-cause mortality	No AP	Irregular AP	**HR 0.79 (0.69-0.90)**		↓
				Regular AP	**HR 0.73 (0.62-0.85)**		↓
CASE-CONTROL STUDIES							
Lipscombe, 2009 [28]	Conditional logistic regression	Hospitalisation for hyperglycaemia	Remote AP	Current AP (any)	RR 1.50 (1.29-1.74)		↑
					Insulin: **RR 1.40 (1.06-1.84)**		↑
					Oral GLD: **RR 1.36 (1.12-1.66)**		↑
					None: **RR 2.43 (1.61-3.66)**		↑
				Current AP (first time)	***Insulin:*** **RR 15.4 (8.12-29.2)**		↑
					Oral GLD: **RR 14.4 (8.71-23.8)**		↑
					None: **RR 8.98 (2.56-31.5)**		↑
				Current AP (prevalent)	***Insulin:*** **RR 1.36 (1.03-1.79)**		↑
					Oral GLD: **RR 1.31 (1.08-1.60)**		↑
					None: **RR 2.23 (1.48-3.37)**		↑
				Recent past AP	*Insulin:* RR 0.89 (0.63-1.27)		↔
					Oral GLD: RR 1.04 (0.80-1.34)		↔
					None: RR 1.31 (0.76-2.27)		↔
CROSS-SECTIONAL STUDIES							
Wake, 2016 [32]	Student's t-test/chi-squared test	Mean HbA1c (mmol/mol) ± SD	AP (≥12 months in total)		**55.1 ± 2.3**		↓
			No AP		58.2 ± 1.3		
		Retinopathy (prevalence, %)	AP (≥12 months in total)		**28**		↓
			No AP		32		

AP: antipsychotic; CI: confidence interval; CV: cardiovascular; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; HR: hazard ratio; SD: standard deviation; RR: rate ratio.

* Results given for fully adjusted or matched models unless otherwise stated (full details of factors adjusted for given in Supplemental Table 4); estimates in bold are statistically significant at the P <0.05 level.

† ↑ = increased risk of outcome; ↓ = decreased risk of outcome; ↔ = no association (with statistical significance at the P <0.05 level, unless otherwise stated).

‡ Time-dependent with AP prescribing measured in 6 month intervals.

evidence of an association between antipsychotics and microvascular complications. When stratifying by metabolic risk of antipsychotics, the authors found that drugs considered to have an intermediate or high metabolic risk were associated with a significantly reduced risk of all complications including cardiovascular and microvascular morbidity (Supplemental Table 5b).

A second, cross-sectional, study found that the prevalence of retinopathy was lower in people who had been prescribed antipsychotics for a total of >12 months than in a comparison group matched for age, sex, diabetes type and duration, body mass index, and smoking status that had not been prescribed antipsychotics (Table 3) [32].

4. Discussion

Our review revealed that few observational studies have investigated the association between antidepressant and antipsychotic drug prescribing and diabetes outcomes. Studies describing associations with cardiometabolic risk factors other than glycaemic control and microvascular disease or the association between antipsychotic prescribing and any diabetes outcomes were particularly limited. The published studies are highly heterogeneous, in terms of the study population, exposure definitions, and outcomes. Lack of comparability and study shortcomings highlight key gaps and limit conclusions. Tentative conclusions are that, among people with diabetes, antidepressant prescribing may be associated with an increased risk of cardiovascular morbidity or mortality, and both antidepressant and antipsychotic prescribing may be linked to poorer glycaemic control. However, evidence is mixed.

4.1. Interpretation of findings in relation to other studies

Our findings on antidepressant prescribing and reduced risk of cardiovascular morbidity or mortality in people with diabetes contrast with previous reviews which report the opposite in general populations (those that include both people with and without diabetes) [9,34]. These contrasting findings may reflect key differences in associations for different population sub-groups. Indeed, pooled results of only studies including people with, or at high risk of, cardiovascular disease similarly found that antidepressant use or prescribing was associated with a statistically non-significant reduced risk of cardiovascular morbidity [34]. Systematic reviews of trials suggest that SSRI use can improve short-term glycaemic control in people with diabetes [13,14]. Some of the observational studies we identified found similar results, but others found no differences in glycaemic control between groups, perhaps related to study population, design, sample size, and approaches to control of confounding.

The association between antipsychotic prescribing and reduced mortality risk in people with schizophrenia and diabetes described in a single cohort study [24] aligns with findings on antipsychotic prescribing and reduced long-term mortality risk in people with schizophrenia, including both people with and without diabetes [35,36]. The findings from this cohort study [24] do however contrast with previous reports of a link between antipsychotic prescribing and increased cardiovascular disease risk in general populations [10,37]. Although counter-intuitive, given their adverse metabolic and cardiovascular effects [8,38,39], antipsychotic use alongside psychological support in people with severe mental illness (SMI) may improve physical and

psychosocial functioning, thereby improving adherence to lifestyle modification and treatment, which in turn could reduce risk of diabetes complications. The few studies on antipsychotic prescribing suggest an association with poorer glycaemic control, which aligns with established adverse glycaemic effects of some antipsychotics [40].

4.2. Strengths and limitations

To the best of our knowledge, this is the first systematic review of observational studies reporting associations between antidepressant or antipsychotic drug prescribing and outcomes including cardiometabolic risk factors, macrovascular and microvascular disease complications, and mortality in people with diabetes. Other strengths include our use of a detailed and comprehensive search strategy applied to three bibliographic databases, independent screening and data extraction by two reviewers, and assessment of study quality.

A limitation of this review is the exclusion of outcomes related to weight changes and obesity, that have previously been linked to antidepressant and antipsychotic use [38,41], as these outcomes were beyond the scope of our review. Also beyond our scope were studies which reported on progression of diabetes complications or compared prescribing of different psychotropic drugs. The latter point is particularly important when investigating adverse effects of antidepressant and antipsychotic prescribing in people with SMI, where given the clinical need to prescribe, consideration of the risk and benefits of individual drugs is crucial. Finally, cross-sectional studies were included in our review because of the limited work in this area. However, as diabetes complications may lead to psychotropic medication prescribing further prospective studies are required.

Further limitations reflect the limitations of existing studies. Some studies were small, with low precision of effect estimates. Many had insufficient control of confounding factors, including lifestyle behaviours, socioeconomic status, and critically, are prone to confounding by indication, particularly for mental illness. Mental illness is associated with higher risk of poor diabetes outcomes [42–44], partly through higher prevalence of unhealthy lifestyle factors, including overweight/obesity, lower socioeconomic status [45], poorer treatment adherence, and in some settings, receipt of sub-optimal care [45]. Conversely, in other settings, people with diabetes comorbid with mental illness may be more likely than people with diabetes without mental illness to receive optimal routine monitoring of certain care indicators [46], perhaps due to more frequent visits to their primary care practitioner [47]. Social desirability and recall bias may have affected studies where exposure status was identified using interviews or assessment visits, leading to dilution of effect estimates. Whilst information bias and loss to follow-up will have been minimised in studies based on electronic health records, prescribing records may not necessarily reflect actual drug use. Moreover, some studies based on routine data may not have had information on outcomes where patients were not admitted to hospital.

4.3. Implications

Implications for practice are limited by the sparse existing literature in this area, with further research needed to inform clinical practice. The increased use of antidepressant and antipsychotic medications in the general population is concerning given the evident lack of understanding of potential for adverse effects and the increasing prevalence of diabetes. The striking gap in the evidence on antipsychotic drug prescribing in relation to diabetes outcomes in particular should be urgently addressed. Antidepressant and antipsychotic drugs are an essential component of the treatment of mental health conditions, and timely treatment in people with diabetes is crucial, given the poor diabetes outcomes for people with both diabetes and mental illness [48]. It is therefore important to establish treatment-associated risks of diabetes outcomes within population sub-groups to inform and enhance drug prescribing and monitoring practices for diabetes and its complications. To improve upon existing studies and advance our understanding, future studies should: be well-powered (particularly to investigate differences); include information on mental illness, lifestyle, and other confounding factors; distinguish between drug subtypes; assess whether and how risk changes over time; and consider the potential effects of cumulative exposures.

4.4. Conclusions

Few studies have described the association between antidepressant and antipsychotic prescribing and diabetes outcomes, with shortcomings and mixed findings limiting the ability to draw conclusions. While future research addresses this evidence gap, at present monitoring cardiometabolic risk factors and screening for complications in people with diabetes who are being treated with antidepressant or antipsychotic medication (irrespective of indication) should be performed at least as frequently as recommended in current guidelines for people with diabetes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110649.

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