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Clinical factors associated with relapse in depression in a sample of UK primary care patients who have been on long-term antidepressant treatment

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Original Article

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Abstract

Background. This paper investigates whether age of onset of depression, duration of the last episode, number of episodes, and residual symptoms of depression and anxiety are associated with depression relapse in primary care patients who have been on long–term maintenance antidepressant treatment and no longer meet ICD10 criteria for depression.

Methods. An observational cohort using data from ANTLER ($N = 478$), a double-blind placebo-controlled trial. The primary outcome was time to relapse using the retrospective CIS-R. Participants were followed for 12 months.

Results. Primary outcome was available for 468 participants. Time to relapse in those with more than five previous episodes of depression was shorter, hazard ratio (HR) 1.84 (95% confidence interval [CI] 1.23–2.75) compared to people with two episodes; HR 1.57 (95% CI 1.01–2.43) after adjustment. The residual symptoms of depression at baseline were also associated with increased relapse: HR 1.05 (95% CI 1.01–1.09) and HR 1.06 (95% CI 1.01–1.12) in the adjusted model. There was evidence of reduced rate of relapse in older age of onset group: HR 0.86 (95% CI 0.78–0.95); HR attenuated after adjustment HR 0.91 (95% CI 0.81–1.02). There was no evidence of an association between duration of the current episode and residual anxiety symptoms with relapse.

Conclusions. The number of previous episodes and residual symptoms of depression were associated with increased likelihood of relapse. These factors could inform joint decision making when patients are considering tapering off maintenance antidepressant treatment or considering other treatments to prevent relapse.

Introduction

Depression is a common debilitating mental health problem affecting around 280 million people worldwide ('Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx)', n.d.). Understanding the course of depressive illness and its determinants has clinical and scientific importance. For instance, accurate differentiation of patients at high risk of relapse from patients at low risk may help to improve decisions around clinical treatment (Hardeveld, Spijker, De Graaf, Nolen, & Beekman, 2010). There are some effective treatments that can prevent future episodes, including maintenance antidepressant treatment (Lewis et al., 2021) and psychological treatments such as CBT (Teasdale et al., 2001) and mindfulness (Kuyken et al., 2015), and monitoring within primary care.

Primary care patients who feel well but still take antidepressants as maintenance treatment are commonly seen in clinical practice. There has been a rise in primary care patients staying on antidepressant medication long-term (Mars et al., 2017; Moore et al., 2009) with 10% of antidepressant users receiving a 'chronic' treatment (5 + years) (McCrea et al., 2016). However, prolonged antidepressant treatment could lead to side effects such as emotional numbness (Goodwin, Price, De Bodinat, & Laredo, 2017), weight gain, sleep disturbance, and sexual dysfunction (Fava, Gatti, Belaise, Guidi, & Offidani, 2015; Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998) (Fava et al., 2015). There is comprehensive evidence on the clinical effectiveness of antidepressants as maintenance treatment (Geddes et al., 2003; Glue, Donovan, Kolluri, & Emir, 2010; Johnson et al., 2012; Kaymaz, Van Os, Loonen, & Nolen,

2008), though to manage treatment it might also be useful to know the likelihood of a future relapse in this population. The current NICE guidelines (National Institute for Health Care and Excellence, 2022) recognize that some people are at increased risk of relapse and in those cases are recommend continued maintenance treatment for up to 2 years. For NICE, an increased risk was defined as a history of recurrent episodes, incomplete response to treatment, a history of severe depression, unhelpful coping styles amongst other factors. However, NICE acknowledged the low quality of the evidence supporting this recommendation and the lack of research in the primary care population where the vast majority of depression is treated. Our study addresses that gap by investigating factors that could be easily assessed clinically within the primary care setting to better inform treatment decisions for people who feel better and are considering stopping maintenance treatment.

Existing evidence from systematic reviews of antidepressant maintenance, albeit from regulatory trials, suggest that residual depressive symptoms and history of depression are the main factors that influence risk of relapse. However, the evidence suggest that patients with one or more previous episodes have higher risk of relapse than patients with a first episode irrespective of treatment (Geddes et al., 2003; Kaymaz et al., 2008). There is also evidence that residual symptoms are associated with relapse in depression, though the type and intensity of the symptoms are yet to be fully determined, as some studies had no minimum score set for symptoms severity (Iovieno, Van Nieuwenhuizen, Clain, Baer, & Nierenberg, 2011). The evidence for the episode length and age of onset as risk factors is sparse because the studies that investigated these factors may lack power and the studies (Fava et al., 2009; McGrath et al., 2006) have not considered that these factors are potentially confounded. It is also possible that these factors are less researched as they are considered less important than other potential risk factors.

Even without these limitations, the previous evidence comes from studies conducted in specialist mental healthcare services and is unlikely to be generalizable to UK primary care settings where most people with depression seek help (Kendrick et al., 2009). For example, patients with fewer than three previous episodes of depression were excluded in one study (Conradi et al., 2007) or studies enrolled patients who had relatively brief periods on antidepressants, 6 months or less. However, many primary care patients take antidepressants for many years, they did not start them after diagnostic criteria and other exclusions (Kendrick et al., 2009; Simon et al., 2015) were applied. Therefore, the results from the previous literature might be difficult to generalize to patients currently being treated with maintenance antidepressant treatment in UK primary care.

We are only aware of two relevant studies that examined factors associated with relapse in depression in primary care patients receiving long-term antidepressants medication (Conradi, de Jonge, & Ormel, 2008; Gopinath, Katon, Russo, & Ludman, 2007). Conradi et al. (2008) reported that number of previous episodes were associated with relapse but not duration of the longest episode, nor residual symptoms of depression and anxiety. However, this sample of 110 patients from Netherlands primary care (Conradi et al., 2008) was small and likely lacked statistical power. Gopinath et al. (2007) in a larger cohort of 386 primary care patients in US (Gopinath et al., 2007) found that residual depressive symptoms, an increasing number of prior episodes, and comorbid anxiety or panic symptoms were associated with relapse. However, the study used a sample limited to patients with either three previous depressive episodes or dysthymia.

We conducted secondary analyses of a randomized controlled trial of discontinuing antidepressant treatment in a primary care population on maintenance antidepressants who did not meet criteria for ICD10 depression. On the basis of previous literature, we investigated whether clinical factors of age of onset, duration of last episode number of previous episodes and residual symptoms of depression and anxiety were associated with relapse.

Methods

Study design and participants

We conducted secondary analyses of the ANTidepressants to prevent reLapse in dEpRession (ANTLER) study. ANTLER was a double blind individually randomized parallel group-controlled trial that was registered with ISRCTN (ISRCTN15969819). The full protocol and results (Duffy et al., 2019, 2021; Lewis et al., 2021) are published, in brief: participants were recruited from 150 primary care practices at four study sites: London, Bristol, Southampton and York. Patients were identified via database searches or during consultation and were eligible if they were aged 18 to 74, had experienced at least two episodes of depression; had been taking antidepressants for 9 months or more but were well enough to consider stopping medication. We excluded those who had a comorbid psychiatric disorder, current depression diagnosis according to ICD-10 at baseline, were unable to complete the questionnaires in English, or who had major alcohol or substance abuse. The trial compared maintenance with one of citalopram 20 mg, sertraline 100 mg, fluoxetine 20 mg or mirtazapine 30 mg with discontinuation of medication after a tapering period, with replacement by placebo. The randomization was minimized by the four study sites, the four medications and severity of depressive symptoms at baseline (two categories measured using the Clinical Interview Schedule, Revised (CIS-R [Lewis, Pelosi, Araya, & Dunn, 1992]) a self-administered computerized diagnostic questionnaire.

The ANTLER trial was approved by the National Research Ethics Service committee, East of England – Cambridge South (ref: 16/EE/0032). Clinical trial authorization was granted by the Medicines and Healthcare Products Regulatory Agency (MHRA). All participants provided written informed consent.

Measures

There are methodological challenges in distinguishing relapse (re-experience of a current episode) and recurrence (a new episode of depression after a period of recovery) due to a requirement for frequent and regular assessments and limitations of the scales used to measure depressive symptoms (Duffy, Marston, Lewis, & Lewis, 2023). In our study the term 'relapse' refers to any new reappearance of depressive symptoms.

Time to relapse of depression was the primary outcome, assessed by the retrospective CIS-R (rCIS-R) (Lewis et al., 2021), which asked about the previous 12 weeks, at the 12, 26, 39 and 52 week follow-ups. Five sections (depressive mood, depressive ideas, concentration, sleep, and fatigue) were used to assess symptoms, their duration, their intensity during the worst week and when the symptom/s began. In our analysis, relapse on the rCIS-R was defined according to ICD10 criteria: the participant must have two of depressed mood, loss of interest,

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reduction in energy plus at least two of the remaining seven symptoms (loss of confidence/self-esteem, recurrent thoughts of suicide or death, change in appetite and weight change, change in psychomotor activity (agitation or retardation), diminished ability to think or concentrate, sleep disturbance).

The results of test-retest reliability study of the rCIS-R and its construct validity in relation to a Global Rating Question about worsening mood, participants stopping their study medication and Patient Health Questionnaire (PHQ-9) scores are described in a separate paper. (Duffy et al., 2023). There is strong evidence that rCIS-R is a reliable and valid measure of assessing relapse in depression.

At each time point, participants also completed the Patient Health Questionnaire (PHQ-9), a nine-item self-administered questionnaire for measuring DSM-IV depressive symptoms. Each of the nine symptom items have four response options ranging from '0' (not at all) to '3' (nearly every day). Total scores range from zero to 27. We used clinical judgment to create three categories: mild (a score 3 and under), moderate (a score between 4 and 8 inclusive) and high (a score of 9 and above) to indicate the level of residual symptoms. The categories are for descriptive purposes and in the analysis we used PHQ-9 as a continuous variable. At the same time points participants also completed GAD-7, a seven-item questionnaire, that measures anxiety. Each item has four possible responses ranging from not at all (0) to nearly every day (3). The score from each item is added to give a total ranging from 0 to 21. We used clinical judgment to create three categories: mild (a score of 2 and less), moderate (scores between 3 and 6 inclusive) and high (scores between 7 and 21) to show level of residual symptoms of anxiety. The categories are for descriptive purposes and in the analysis we used GAD-7 as a continuous variable. If one or two items were missing from either questionnaire, they were replaced by the mean of the items present. If more than two items were missing, the questionnaire was considered missing for that participant.

At baseline we measured sociodemographic factors (age, gender, ethnicity, education, employment, housing and marital status), alcohol consumption, financial difficulties, undergoing psychological therapies as well as history of depression (age of onset of depression, number of episodes, duration of the current (or index) episode) considered as relevant clinical risk factors of relapse.

Statistical methods

We examined differences in baseline demographic characteristics for those who did and did not relapse using χ^2 tests.

To investigate predictors of time to relapse, we defined the whole sample as a cohort and adjusted for randomized group as a covariate. We used Cox proportional hazards modeling to investigate the degree to which each clinical factor (age of onset, number of episodes, duration of the current (or index) episode, residual symptoms of depression measured by PHQ-9 and residual symptoms of anxiety measured by GAD-7 at baseline) was associated with time to relapse, adjusting for potential confounders (baseline demographic characteristics). The outcome was time to relapse and clinical factors were classified as exposures. We included three models: the first is adjusted for group allocation, second included group allocation and mutually adjusted clinical factors and the last model was adjusted for all socio-demographic factors as well as group allocation and clinical factors. We believe such an approach provided clinically useful information as clinicians would want to know which factor/s are associated with relapse as they cannot 'adjust' for socio-economic and demographic factors. Our choice of confounders included all available variables (gender, age, ethnicity, education, marital status, employment status, tenure)

Table 1. Baseline characteristics of participants (*n*, %) in relation to relapse status

Baseline characteristics	Relapse *n* = 204, (%)	Did not relapse *n* = 273, (%)	*p* value
Age at randomization			0.282
Above median (55 years old)	114 (56)	139 (51)	
Gender			0.190
Female	155 (76)	192 (70)	
Ethnicity			0.497
White	192 (94)	255 (93)	
Highest educational qualification			0.012
Degree/higher degree	91 (45)	87 (32)	
Diploma/A levels or equivalent	62 (31)	86 (32)	
GCSE or equivalent/ other/none	50 (24)	94 (34)	
Employment status			0.965
Employed	124 (61)	167 (61)	
Retired	59 (29)	79 (29)	
Other	21 (10)	26 (10)	
Tenancy			0.399
Homeowner	159 (79)	211 (77)	
Renting	31 (15)	49 (18)	
Other	12 (6)	14 (5)	
Marital status			0.393
Married	123 (61)	184 (67)	
Single	29 (14)	32 (12)	
Separated or divorced	33 (16)	38 (14)	
Widowed	19 (9)	18 (7)	
Site			0.894
London	85 (41)	113 (41)	
Bristol	42 (21)	60 (22)	
Southampton	44 (22)	52 (19)	
York	33 (16)	48 (18)	
Antidepressant			0.710
Sertraline	35 (17)	43 (16)	
Citalopram	96 (47)	126 (46)	
Fluoxetine	64 (32)	96 (35)	
Mirtazapine	9 (4)	8 (3)	
Psychological therapies			0.705
Had psychological therapy at baseline	20 (45)	24 (55)	

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Table 2. Number of episodes in relation to baseline characteristics and possible confounding factors

Characteristics	Two episodes *n* = 102 (%)	Between 3 and 5 episodes *n* = 166 (%)	More than 5 episodes *n* = 209 (%)	*p* value
Age				0.564
Below median (55 years old)	48 (47)	80 (48)	110 (53)	
Above median	54 (53)	86 (52)	99 (47)	
Gender				0.014
Male	35 (34)	32 (19)	62 (30)	
Female	67 (66)	134 (81)	147(70)	
Ethnicity				0.238
White	99 (98)	155 (93)	194 (95)	
Not white	2 (2)	11 (7)	11 (5)	
Highest educational qualification[a]				0.534
Degree/higher degree	32 (32)	69 (42)	77 (38)	
Diploma/A levels or equivalent	33 (32)	48 (29)	67 (32)	
GCSE or equivalent/other/ none	36 (35)	48 (29)	61 (30)	
Employment status				0.951
Employed	61 (59)	100 (60)	131(63)	
Retired	32 (32)	49 (30)	57 (27)	
Other	9 (9)	17 (10)	21 (10)	
Tenancy				0.278
Homeowner	84 (82)	127 (76)	159 (76)	
Renting	16 (16)	31 (19)	34 (17)	
Other	2 (2)	8 (5)	16 (8)	
Marital status				0.093
Married	67 (65)	98 (59)	142 (68)	
Single	11 (11)	31 (19)	19 (9)	
Separated or divorced	13 (12)	24 (14)	35 (17)	
Widowed	11 (12)	13 (8)	13 (6)	
Site				0.363
London	45 (44)	65 (39)	88 (42)	
Bristol	28 (27)	33 (20)	41 (20)	
Southampton	18 (18)	34 (20)	44 (21)	
York	11 (11)	34 (20)	36 (17)	
Antidepressant				0.129
Sertraline	16 (16)	24 (15)	38 (18)	
Citalopram	57 (56)	71 (43)	94 (45)	
Fluoxetine	25 (24)	62 (37)	73 (35)	
Mirtazapine	4 (4)	9 (5)	4 (2)	
Alcohol[b]				0.369
Once a month or less or never	29 (29)	56 (34)	58 (28)	
Up to 3 times per week	49 (50)	87 (53)	109 (53)	
Four or more times per week	21 (21)	21 (13)	38 (19)	
Money[b]				0.253
Living comfortably	50 (50)	69 (42)	80 (39)	

(*Continued*)

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Table 2. (*Continued.*)

Characteristics	Two episodes $n = 102$ (%)	Between 3 and 5 episodes $n = 166$ (%)	More than 5 episodes $n = 209$ (%)	p value
Doing alright	37 (38)	61 (37)	85 (41)	
Struggling	12 (12)	34 (21)	40 (20)	
Duration of the current episode				0.070
Last two years	23 (22)	57 (34)	49 (24)	
Three to five years	35 (34)	58 (35)	67 (32)	
Six to 10 years	20 (20)	29 (18)	51 (24)	
11 years or more	24 (24)	22 (13)	42 (20)	
Age of onset of depression				<0.001
Between 18 and 22	14 (14)	54 (33)	87 (42)	
Between 23 and 39	32 (31)	68 (41)	63 (30)	
Between 40 and 75	56 (55)	44 (26)	59 (28)	
Residual symptoms of depression				0.003
PHQ-9 score of 3 and under	72 (70)	93 (56)	103 (50)	
PHQ-9 score between 4 and 8	23 (23)	60 (36)	74 (35)	
PHQ-9 score of 9 and above	7 (7)	13 (8)	31 (15)	
Residual symptoms of anxiety				0.001
GAD-7 score of 2 and under	70 (69)	96 (58)	94 (45)	
GAD-7 score between 3 and 6	21 (20)	49 (29)	86 (41)	
GAD-7 score of 7 and above	11 (11)	21 (13)	28 (14)	
Psychological therapies				0.410
Had psychotherapy at baseline	7 (7)	19 (11)	18 (9)	
Did not have psychotherapy	96 (93)	147 (89)	190 (91)	

[a]$n = 468$.
[b]$n = 470$.
The number of relapses within each group is presented as percentage.

as they have been flagged as potential confounders in reviewed literature. We report output as hazard ratios (HR) and 95% confidence interval (95% CI). We plotted time to relapse in depression, using Kaplan–Meier plots.

The literature investigating factors associated with relapse has commonly employed secondary data analysis of data from randomized controlled trials (Cipriani et al., 2018; Glue et al., 2010; Kaymaz et al., 2008). In contrast to other studies, our analyses were adjusted for the randomized allocation. In effect, we have the average association between factor and relapse whether the individuals remained on their antidepressant or were discontinued. We have not investigated whether the clinical factors moderated the effect of discontinuation as this will be a low statistical power interaction test and the average association with relapse across both arms of the trial could be argued as an estimate of clinical interest.

All analyses were conducted using the statistical software package STATA 14.

Results

Sample characteristics

We included all participants from the ANTLER trial. Out of 478 participants recruited in the trial, one participant was missing data on the main outcome as well as data on clinical factors and was excluded from the analysis. A further nine participants had missing data on the timing of relapse and were excluded from the survival analysis. As previously described (Lewis et al., 2021) the maintenance and discontinuation groups were similar in baseline characteristics. Our analysis of differences in baseline characteristics with respect to relapse is shown in Table 1. Apart from education where there were more relapses among more educated participants, there was little difference between the two groups (relapses *v.* non-relapses) in terms of the sociodemographic and clinical characteristics.

Table 2 shows those with higher number of previous episodes were more likely to be female, to have a younger age of onset of depression and higher residual symptoms of depression and anxiety at baseline than those with fewer episodes.

Participants with a higher level of residual symptoms of depression at baseline were likely to be female, experiencing financial struggles; had higher level of residual symptoms of anxiety at baseline and higher number of previous episodes of depression (Table 3). Of note, in our sample a PHQ-9 total score of 19 was the highest score.

Similar tables for other clinical factors (i.e. age of onset, duration of current episode and residual symptoms of anxiety) can be found in online Supplementary Tables S1–S3.

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Table 3. Residual symptoms of depression in relation to baseline characteristics and possible confounding factors

Characteristics	PHQ-9 score of 3 and under, $n = 268$ (%)	PHQ-9 score between 4 and 8, $n = 157$ (%)	PHQ-9 score of 9 and above, $n = 51$ (%)	p value
Age				0.101
Below median (55 years old)	131 (49)	93 (59)	29 (57)	
Above median	137 (51)	64 (41)	22 (43)	
Gender				0.010
Male	60 (22)	48 (31)	21 (41)	
Female	208 (78)	108 (69)	30 (59)	
Ethnicity				<0.001
White	252 (95)	152 (99)	42 (82)	
Not white	13 (5)	2 (1)	9 (18)	
Highest educational qualification[a]				0.497
Degree/ higher degree	102 (39)	61 (40)	14 (28)	
Diploma/ A levels or equivalent	86 (32)	43 (28)	19 (38)	
GCSE or equivalent/ other/ none	77 (29)	50 (32)	17 (34)	
Employment status				0.178
Employed	171 (64)	90 (58)	29 (57)	
Retired	72 (27)	53 (34)	13 (25)	
Other	25 (9)	13 (8)	9 (18)	
Tenancy				0.034
Homeowner	221 (82)	115 (74)	33 (65)	
Renting	37 (14)	30 (19)	13 (25)	
Other	10 (4)	11 (7)	5 (10)	
Marital status				0.329
Married	182 (68)	95 (61)	29 (57)	
Single	29 (11)	22 (14)	10 (20)	
Separated or divorced	35 (13)	26 (17)	10 (20)	
Widowed	22 (8)	13 (8)	2 (4)	
Site				0.869
London	110 (41)	66 (42)	22 (43)	
Bristol	58 (22)	36 (23)	8 (16)	
Southampton	51 (19)	31 (20)	13 (25)	
York	49 (18)	24 (15)	8 (16)	
Antidepressant				0.006
Sertraline	36 (13)	25 (16)	17 (33)	
Citalopram	134 (50)	67 (43)	20 (39)	
Fluoxetine	87 (33)	62 (39)	11 (22)	
Mirtazapine	11 (4)	3 (2)	3 (6)	
Alcohol[b]				0.232
Once a month or less or never	76 (29)	45 (29)	22 (45)	
Up to 3 times per week	143 (54)	82 (54)	19 (39)	
Four or more times per week	46 (17)	26 (17)	8 (16)	
Money[b]				0.007
Living comfortably	126 (48)	60 (39)	13 (26)	

(*Continued*)

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Table 3. (*Continued.*)

Characteristics	PHQ-9 score of 3 and under, *n* = 268 (%)	PHQ-9 score between 4 and 8, *n* = 157 (%)	PHQ-9 score of 9 and above, *n* = 51 (%)	*p* value
Doing alright	102 (38)	60 (39)	20 (41)	
Struggling	37 (14)	33 (22)	16 (33)	
Duration of the current episode				0.796
Last two years	68 (25)	49 (32)	12 (23)	
Three to five years	92 (34)	47 (30)	19 (37)	
Six to 10 years	58 (22)	33 (21)	9 (18)	
11 years or more	50 (19)	27 (17)	11 (22)	
Age of onset of depression				0.808
Between 18 and 22	85 (32)	50 (32)	19 (37)	
Between 23 and 39	92 (34)	57 (37)	14 (28)	
Between 40 and 75	91 (34)	49 (31)	18 (35)	
Number of episodes				0.003
Up to 2 episodes	72 (27)	23 (15)	7 (14)	
Between 3 and 5 episodes	93 (35)	60 (38)	13 (25)	
More than 5	103 (38)	74 (47)	31 (61)	
Residual symptoms of anxiety				<0.001
GAD-7 score of 2 and under	202 (75)	53 (34)	5 (10)	
GAD-7 score between 3 and 6	59 (22)	80 (51)	17 (33)	
GAD-7 score of 7 and above	7 (3)	24 (15)	29 (57)	
Psychological therapies				0.053
Had psychotherapy at baseline	19 (7)	15 (10)	9 (18)	
Did not have psychotherapy	249 (93)	142 (90)	42 (82)	

The number of relapses within each group is presented as percentage.
[a]*n* = 468.
[b]*n* = 470.

The Kaplan–Meier plots (online Supplementary Figs S1–S3 and Figs 1, 2) show the proportion of participants that relapsed during the 52-week trial in relation to categories within each clinical factor. We are presenting Figs 1 and 2 for number of episodes and residual depression as we had evidence for an association with relapse. Other results are in online Supplementary Figs S1–S3 in the Supplement.

Compared to those with age of onset between 40 to 75 years, early age of onset was associated with increased relapse: those with age of onset between 23- and 39-years old group HR was 1.62 (95% CI 1.13–2.33) and in the age of onset between 18 to 22 group HR 1.37 (95% CI 0.90–1.97) in the model adjusted for group allocation (Table 4). After adjusting for baseline characteristics and other clinical factors the HRs in the two younger groups became similar: age between 23- and 39-years old HR 1.33 (95% CI 0.87–2.02) and age between 18- and 22- years old HR 1.28 (95% CI 0.86–1.92), compared to the reference group. Cox regression analysis of the age of onset as a continuous variable produced strong evidence of association with hazard of relapse: HR 0.86 (95% CI 0.78–0.95) in the model adjusted for group allocation; the HR attenuated in the fully adjusted model HR 0.91 (95% CI 0.81–1.02).

There was weak evidence that longer duration of the current episode (over 10 years) compared with duration between 2 and 10 years, was a risk factor of relapse: HR 1.17 (95% CI 0.88–1.55) in the model adjusted for group allocation and HR 1.24 (95% CI 0.91–1.68) in the fully adjusted model.

The hazard of relapse was highest in participants who had more than five episodes of depression HR 1.84 (95% CI 1.23–2.75) in the model adjusted for group allocation, with 49% patients relapsing in the more than five episodes group compared with 42% in between 3 and 5 episodes group and 32% in up to two episodes group. The HR attenuated slightly after adjusting for baseline characteristics and other clinical factors HR 1.57 (95% CI 1.01–2.43) (Table 4).

There was also evidence that residual symptoms of depression at baseline were associated with increased relapse; with 51% patients relapsing in the PHQ-9 score of 9 and above group compared with 44% relapsed in the PHQ-9 score of between 4 and 8, and 41% relapsed in the score of 3 or below group. Analysis of the PHQ-9 score as a continuous variable found an increase in relapse for each one-unit change in PHQ-9 score: HR 1.05 (95% CI 1.01–1.09) in the model adjusted for group allocation and HR 1.06 (95% CI 1.01–1.12) in the model adjusted for group allocation, baseline characteristics and other clinical factors.

There was no evidence of an association between residual symptoms of anxiety at baseline and relapse.

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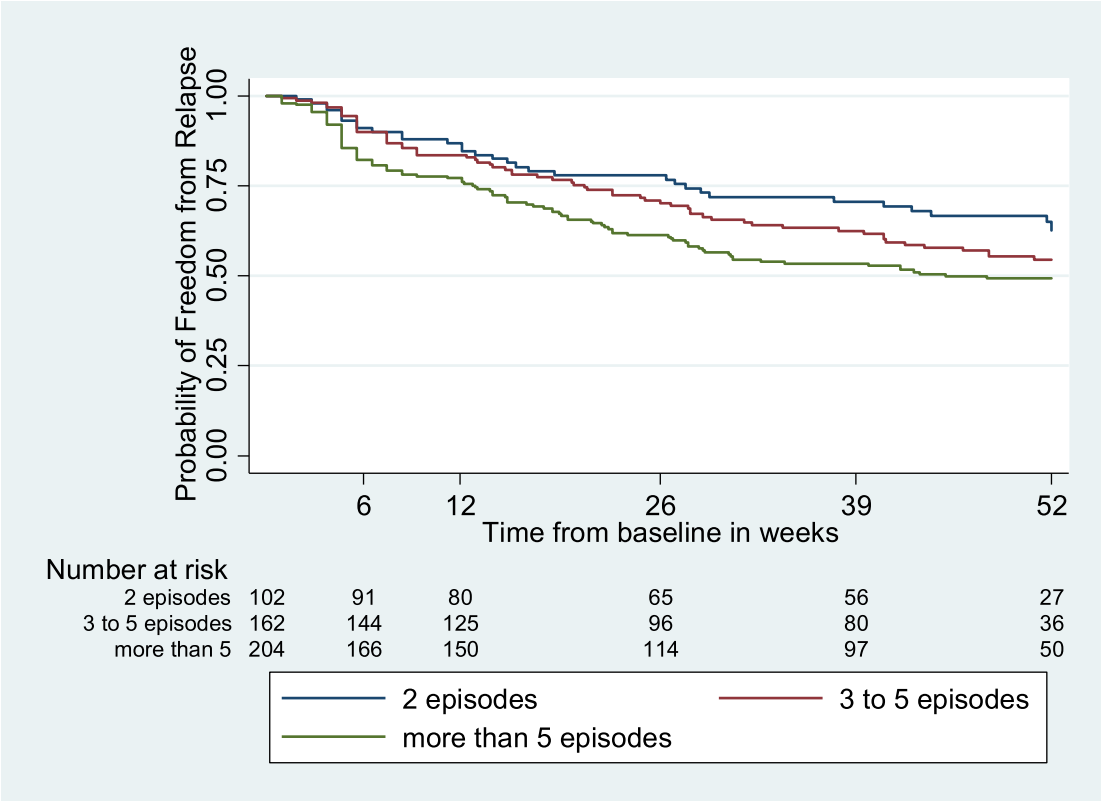

Figure 1. Kaplan–Meier analysis of the first relapse of depression by 52 weeks among three categories: those with two and less previous episodes or depression, those with between three and five episodes and those with over five episodes.

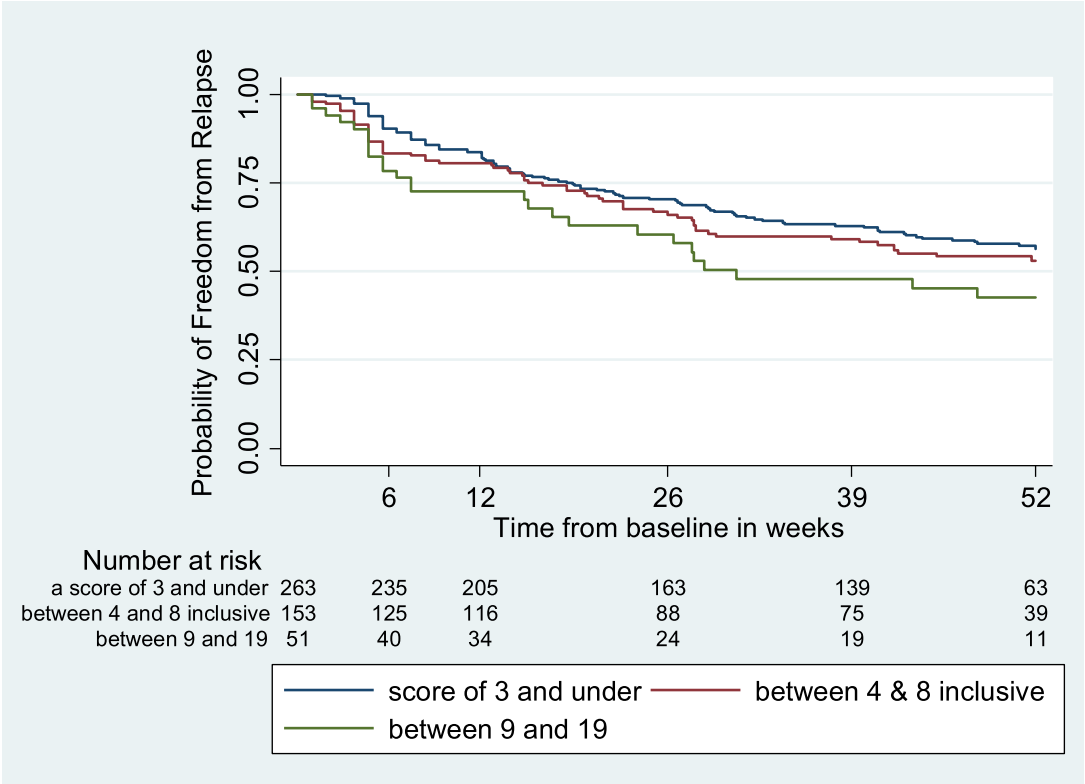

Figure 2. Kaplan–Meier analysis of the first relapse of depression by 52 weeks among three categories of the residual symptoms of depression measured by PHQ-9 at baseline: those with a PHQ-9 score of 3 and under, those with a score of between 4 and 8 and those with a score of 9 and above.

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Table 4. Hazard ratios (95% CI) for relapse according to the age of onset, duration of current episode, number of episodes, residual symptoms of depression and residual symptoms of anxiety before and after adjustment

	Number, *n*	Relapse, %	HR adjusted[a] (95% CI)	*p* value	HR adjusted[b] (95% CI)	*p* value	HR adjusted[c] (95% CI)	*p* value
Age of onset (years)	476			0.024		0.020		0.216
Between 40 and 75	158	34	1.00		1.00		1.00	
Between 23 and 39	163	47	1.62 (1.13–2.33)		1.55 (1.07–2.26)		1.33 (0.87–2.02)	
Between 18 and 22	155	48	1.37 (0.90–1.97)		1.51 (1.05–2.19)		1.28 (0.86–1.92)	
Age of onset (continuous)	476	43	0.86 (0.78–0.95)	0.003	0.88 (0.79–0.98)	0.020	0.91 (0.81–1.02)	0.106
Duration of current episode	476			0.292		0.108		0.172
Between 2 and 10	288	40	1.00		1.00		1.00	
Over 10 years	188	47	1.17 (0.88–1.55)		1.26 (0.95–1.68)		1.24 (0.91–1.68)	
Number of episodes	477			0.002		0.074		0.025
Up to 2	103	32	1.00		1.00		1.00	
Between 3 and 5	166	42	1.46 (0.96–2.24)		1.16 (0.75–1.80)		1.17 (0.74–1.85)	
More than 5	208	49	1.84 (1.23–2.75)		1.42 (0.93–2.18)		1.57 (1.01–2.43)	
Residual symptoms of depression (PHQ-9 scores)	476			0.050		0.070		0.185
Score of 3 or below	268	41	1.00		1.00		1.00	
Score between 4 & 8	157	44	1.16 (0.85–1.59)		1.16 (0.83–1.65)		1.15 (0.80–1.64)	
Score of 9 & above	51	51	1.55 (1.01–2.40)		1.52 (0.89–2.57)		1.47 (0.84–2.59)	
PHQ-9 scores (continuous)	476	43	1.05 (1.01–1.09)	0.010	1.07 (1.02–1.12)	0.007	1.06 (1.01–1.12)	0.023
Residual symptoms of anxiety (GAD-7 scores)	476			0.360		0.349		0.547
Score of 2 or below	260	43	1.00		1.00		1.00	
Score between 3 and 6	156	42	1.07 (0.78–1.47)		0.86 (0.61–1.22)		0.89 (0.62–1.28)	
Score of 7 and above	60	47	1.22 (0.80–1.86)		0.82 (0.49–1.36)		0.88 (0.52–1.49)	
GAD-7 scores (continuous)	476	43	1.04 (1.00–1.09)	0.043	1.01 (0.95–1.06)	0.835	1.02 (0.96–1.08)	0.554

[a]Adjusted for treatment group allocation.
[b]Mutuality adjusted clinical factors.
[c]Adjusted for gender, age, ethnicity, education, marital status, employment status, tenure, group allocation, psychological therapy and mutuality adjusted clinical factor.

Discussion

The results of our secondary analysis of the ANTLER trial provide strong evidence that number of previous episodes and residual symptoms of depression at baseline increased the risk of relapse in a sample of primary care patients, after adjustment for baseline characteristics and other clinical factors. There was some evidence of the age of onset being associated with relapse, though we did not find evidence that duration of last episode and residual symptoms of anxiety were associated with relapse after adjustment for baseline characteristics and other clinical factors.

An important consideration is whether our results are clinically important. One way of judging this is by comparing the 49% relapse in those with five or more episodes with 32% relapse in those with two or fewer episodes. The difference between 5 or more episodes *v.* 2 or fewer is relatively large and of the same magnitude as the size of difference, that we reported in earlier paper, between maintenance and discontinuation in the ANTLER trial. Such substantial difference within 12 months would be clinically important information to consider when managing a patient with depression. Likewise, for those scoring 9 or more on the PHQ-9, the proportion relapsing was 51% compared to 41% for those scoring 3 or less. We think these unadjusted findings are the most relevant to guide clinical practice as statistical adjustment of findings is not possible in the clinic and furthermore in our analysis adjustments only slightly attenuated the results.

Strengths and limitations

We examined clinical factors that can be easily assessed and monitored in primary care. The strengths of our study are the sample size, the sample recruited from a primary care setting, the excellent follow up rate and the use of reliable outcome measure (Duffy et al., 2023).

Our sample represents only a small proportion (6%) of patients approached (23 553) either by an invitation letter or at consultation, who agreed to take part and proceeded to screening and eligibility checks (Duffy et al., 2021; Lewis et al., 2021). Therefore, representativeness of our sample might be limited because the population recruited into RCT might differ in some ways from the population that would be potentially eligible. However, in general it is thought that the inclusion criteria and

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any selection bias into a cohort study are less likely to limit the validity of comparisons within a cohort.

Our study was one of few to examine clinical factors of relapse in the primary care population. Although the sample size was substantial, our analyses were limited by relatively small numbers in some sub-groups and therefore had a limited power to detect small differences. As a result, we decided not to examine interactions though some are reported in our main trial paper (Lewis et al., 2021).

Another possible limitation was recall bias. At baseline, we asked people who have been taking antidepressants for years to recall both the history and treatment of their depressive illness. It is possible that some information was inaccurate and reduced the precision of our results, though it is unlikely to have biased the results as these data were collected before the outcome occurred. This method of asking about previous history is similar to that used in clinical practice.

The trial had a relatively short tapering period of two months, and some relapses could have been affected by withdrawal symptoms. To avoid this possibility, we used ICD10 criteria to assess relapse in depression, so it is unlikely withdrawal symptoms were mistaken for relapse.

Implications for practice

The results of our study suggest that the number of previous episodes and presence of residual symptoms are two clinical factors that are associated with relapse and can be used as prognostic factors. Asking about previous episodes and assessing residual symptoms can become a routine part of the consultation where stopping treatment is being discussed. For example, if the benefits of antidepressant maintenance followed a relative risk pattern, one would expect a greater absolute risk reduction for individuals who have a higher risk of relapse. Certainly, knowing someone already has a poor prognosis would likely affect the decision to stop or continue with any treatment.

Implications for further research

Large observational studies are needed in primary care settings investigating a range of factors that might be associated with future relapse. There is potential for identifying other clinical and psychological feature such as history of severe depression and coping styles. Considering the clinical importance and frequency of depression knowing the likely outcomes in primary care would be important information in guiding treatment decisions. Descriptive information on likely outcomes would be useful information for both patients and doctors and would influence management of the illness.

We focused on identifying the clinical factors that are important for outcome irrespective of treatment. Further research is needed to examine a range of possible factors that might affect the response to treatment.

What is already known on this topic

- Antidepressants are effective at preventing relapse of depression
- Residual depressive symptoms and history of depression are the main factors that influence risk of relapse
- Existing evidence predominately comes from studies set in specialist mental healthcare services and is unlikely to be generalizable to UK primary care settings where most people with depression seek help

What study adds

- In primary care settings the number of previous episodes is one of most relevant clinical factors affecting relapse in depression
- In primary care presence of residual symptoms is one of most relevant clinical factors affecting relapse in depression
- Making assessment of the two clinical factors routine practice may help to inform joint decision making when patients when considering future treatment.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291723002659

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Competing interest. None.

References

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., … Geddes, J. R. (2018). 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*, *391*(10128), 1357–1366.

Conradi, H. J., de Jonge, P., Kluiter, H., Smit, A., van der Meer, K., Jennifer, J. A., … Ormel, J. (2007). Enhanced treatment for depression in primary care: Long-term outcomes of a psycho-educational prevention program alone and enriched with psychiatric consultation or cognitive behavioral therapy. *Psychological Medicine*, *37*(6), 849–862. https://doi.org/10.1017/S0033291706009809

Conradi, H. J., de Jonge, P., & Ormel, J. (2008). Prediction of the three-year course of recurrent depression in primary care patients: Different risk factors for different outcomes. *Journal of Affective Disorders*, *105*(1–3), 267–271.

Duffy, L., Bacon, F., Clarke, C. S., Donkor, Y., Freemantle, N., Gilbody, S., … Lewis, G. (2019). A randomised controlled trial assessing the use of citalopram, sertraline, fluoxetine and mirtazapine in preventing relapse in primary care patients who are taking long-term maintenance antidepressants (ANTLER: ANTidepressants to prevent reLapse in dEpRes. *Trials*, *20*(1), 319. https://doi.org/10.1186/s13063-019-3390-8

Duffy, L., Clarke, C. S., Lewis, G., Marston, L., Freemantle, N., Gilbody, S., … Lewis, G. (2021). Antidepressant medication to prevent depression relapse in primary care: The ANTLER RCT. *Health Technology Assessment*, *25* (69), i–62. https://doi.org/10.3310/hta25690

Duffy, L., Marston, L., Lewis, G., & Lewis, G. (2023). Reliability of the retrospective Clinical Interview Schedule Revised (rCIS-R) to assess relapse in depression in primary care patients. *PLOS ONE 2023*;:1–12. https://doi.org/10.1371/journal.pone.0280997

Fava, G. A., Gatti, A., Belaise, C., Guidi, J., & Offidani, E. (2015). Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: A

systematic review. *Psychotherapy and Psychosomatics*, *84*(2), 72–81. https://doi.org/10.1159/000370338

Fava, M., Wiltse, C., Walker, D., Brecht, S., Chen, A., & Perahia, D. (2009). Predictors of relapse in a study of duloxetine treatment in patients with major depressive disorder. *Journal of Affective Disorders*, *113*(3), 263–271. https://doi.org/10.1016/j.jad.2008.05.023

Geddes, J. R., Carney, S. M., Davies, C., Furukawa, T. A., Kupfer, D. J., Frank, E., & Goodwin, G. M. (2003). Relapse prevention with antidepressant drug treatment in depressive disorders: A systematic review. *The Lancet*, *361* (9358), 653–661. https://doi.org/10.1016/S0140-6736(03)12599-8

Glue, P., Donovan, M. R., Kolluri, S., & Emir, B. (2010). Meta-analysis of relapse prevention antidepressant trials in depressive disorders. *Australian and New Zealand Journal of Psychiatry*, *44*(8), 697–705. https://doi.org/10.3109/00048671003705441

Goodwin, G. M., Price, J., De Bodinat, C., & Laredo, J. (2017). Emotional blunting with antidepressant treatments: A survey among depressed patients. *Journal of Affective Disorders*, *221*, 31–35. https://doi.org/10.1016/j.jad.2017.05.048

Gopinath, S., Katon, W. J., Russo, J. E., & Ludman, E. J. (2007). Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. *Journal of Affective Disorders*, *101*(1–3), 57–63. https://doi.org/10.1016/j.jad.2006.10.023

Hardeveld, F., Spijker, J., De Graaf, R., Nolen, W. A., & Beekman, A. T. F. (2010). Prevalence and predictors of recurrence of major depressive disorder in the adult population. *Acta Psychiatrica Scandinavica*, *122*(3), 184–191. https://doi.org/10.1111/j.1600-0447.2009.01519.x

Institute of Health Metrics and Evaluation. Global Health Data Exchange (GHDx). (n.d.). Retrieved 24 September 2021, from http://ghdx.healthdata.org/gbd-results-tool?params website: https://vizhub.healthdata.org/gbd-results/?params

Iovieno, N., Van Nieuwenhuizen, A., Clain, A., Baer, L., & Nierenberg, A. A. (2011). Residual symptoms after remission of major depressive disorder with fluoxetine and risk of relapse. *Depression and Anxiety*, *28*(2), 137–144. https://doi.org/10.1002/da.20768

Johnson, C. F., Macdonald, H. J., Atkinson, P., Buchanan, A. I., Downes, N., & Dougall, N. (2012). Reviewing long-term antidepressants can reduce drug burden: A prospective observational cohort study. *British Journal of General Practice*, *62*(604), e773–e779. https://doi.org/10.3399/bjgp12X658304

Kaymaz, N., Van Os, J., Loonen, A. J. M., & Nolen, W. A. (2008). Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: A meta-analysis of placebo-controlled randomized trials. *Journal of Clinical Psychiatry*, *69*(9), 1423–1436. https://doi.org/10.4088/JCP.v69n0910

Kendrick, T., Dowrick, C., McBride, A., Howe, A., Clarke, P., Maisey, S., … Smith, P. W. (2009). Management of depression in UK general practice in relation to scores on depression severity questionnaires: Analysis of medical record data. *BMJ* (*Online*), *338*, b750. https://doi.org/10.1136/bmj.b750

Kuyken, W., Hayes, R., Barrett, B., Byng, R., Dalgleish, T., Kessler, D., … Byford, S. (2015). Effectiveness and cost-effectiveness of mindfulness-based cognitive therapy compared with maintenance antidepressant treatment in the prevention of depressive relapse or recurrence (PREVENT): A randomised controlled trial. *The Lancet*, *386*(9988), 63–73. https://doi.org/10.1016/S0140-6736(14)62222-4

Lewis, G., Marston, L., Duffy, L., Freemantle, N., Gilbody, S., Hunter, R., … Lewis, G. (2021). Maintenance or discontinuation of antidepressants in primary care. *New England Journal of Medicine*, *385*(14), 1257–1267. https://doi.org/10.1056/nejmoa2106356

Lewis, G., Pelosi, A. J., Araya, R., & Dunn, G. (1992). Measuring psychiatric disorder in the community: A standardized assessment for use by lay interviewers. *Psychological Medicine*, *22*(2), 465–486. https://doi.org/10.1017/S0033291700030415

Mars, B., Heron, J., Kessler, D., Davies, N. M., Martin, R. M., Thomas, K. H., & Gunnell, D. (2017). Influences on antidepressant prescribing trends in the UK: 1995–2011. *Social Psychiatry and Psychiatric Epidemiology*, *52*(2), 193–200. https://doi.org/10.1007/s00127-016-1306-4

McGrath, P. J., Stewart, J. W., Quitkin, F. M., Chen, Y., Alpert, J. E., Nierenberg, A. A., … Petkova, E. (2006). Predictors of relapse in a prospective study of fluoxetine treatment of major depression. *The American Journal of Psychiatry*, *163*(9), 1542–1548. https://doi.org/10.1176/appi.ajp.163.9.1542

Moore, M., Yuen, H. M., Dunn, N., Mullee, M. A, Maskell, J., & Kendrick, T. (2009). Explaining the rise in antidepressant prescribing: A descriptive study using the general practice research database. *BMJ*, *339*, b3999. https://doi.org/10.1136/bmj.b3999

National Institute for Health Care and Excellence. (2022). *Depression in adults: Treatment and management full guideline*. London: NICE. www.nice.org.uk/guidance/ng222 (April).

Rosenbaum, J. F., Fava, M., Hoog, S. L., Ascroft, R. C., & Krebs, W. B. (1998). Selective serotonin reuptake inhibitor discontinuation syndrome: A randomized clinical trial. *Biological Psychiatry*, *44*(2), 77–87. https://doi.org/10.1016/S0006-3223(98)00126-7

Simon, G. E., Rossom, R. C., Beck, A., Waitzfelder, B. E., Coleman, K. J., Stewart, C., … Shortreed, S. M. (2015). Antidepressants are not overprescribed for mild depression. *Journal of Clinical Psychiatry*, *76*(12), E1627–E1632. https://doi.org/10.4088/JCP.14m09162

Teasdale, J., Scott, J., Moore, R., Hayhurst, H., Pope, M., & Paykel, E. (2001). How does cognitive therapy prevent relapse in residual depression? Evidence from a controlled trial [Article]. *Journal of Consulting and Clinical Psychology*, *69*(3), 347–357. https://doi.org/10.1037//0022-006X.69.3.347

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