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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 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 (Figure 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 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 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 4a). 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 4b). In contrast, a cross-sectional study found that mean HbA1c values were significantly lower in people prescribed antipsychotics for more than 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 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 more than 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

225 glycaemic control between groups, perhaps related to study population, design, sample size, and
226 approaches to control of confounding.
227 The association between antipsychotic prescribing and reduced mortality risk in people with
228 schizophrenia and diabetes described in a single cohort study [24] aligns with findings on
229 antipsychotic prescribing and reduced long-term mortality risk in people with schizophrenia,
230 including both people with and without diabetes [35, 36]. The findings from this cohort study [24] do
231 however contrast with previous reports of a link between antipsychotic prescribing and increased
232 cardiovascular disease risk in general populations [10, 37]. Although counter-intuitive, given their
233 adverse metabolic and cardiovascular effects [8, 38, 39], antipsychotic use alongside psychological
234 support in people with severe mental illness (SMI) may improve physical and psychosocial
235 functioning, thereby improving adherence to lifestyle modification and treatment, which in turn
236 could reduce risk of diabetes complications. The few studies on antipsychotic prescribing suggest an
237 association with poorer glycaemic control, which aligns with established adverse glycaemic effects of
238 some antipsychotics [40].
239 **4.2 Strengths and limitations**
240 To the best of our knowledge, this is the first systematic review of observational studies reporting
241 associations between antidepressant or antipsychotic drug prescribing and outcomes including
242 cardiometabolic risk factors, macrovascular and microvascular disease complications, and mortality
243 in people with diabetes. Other strengths include our use of a detailed and comprehensive search
244 strategy applied to three bibliographic databases, independent screening and data extraction by two
245 reviewers, and assessment of study quality.
246 A limitation of this review is the exclusion of outcomes related to weight changes and obesity, that
247 have previously been linked to antidepressant and antipsychotic use [38, 41], as these outcomes
248 were beyond the scope of our review. Also beyond our scope were studies which reported on
249 progression of diabetes complications or compared prescribing of different psychotropic drugs. The
250 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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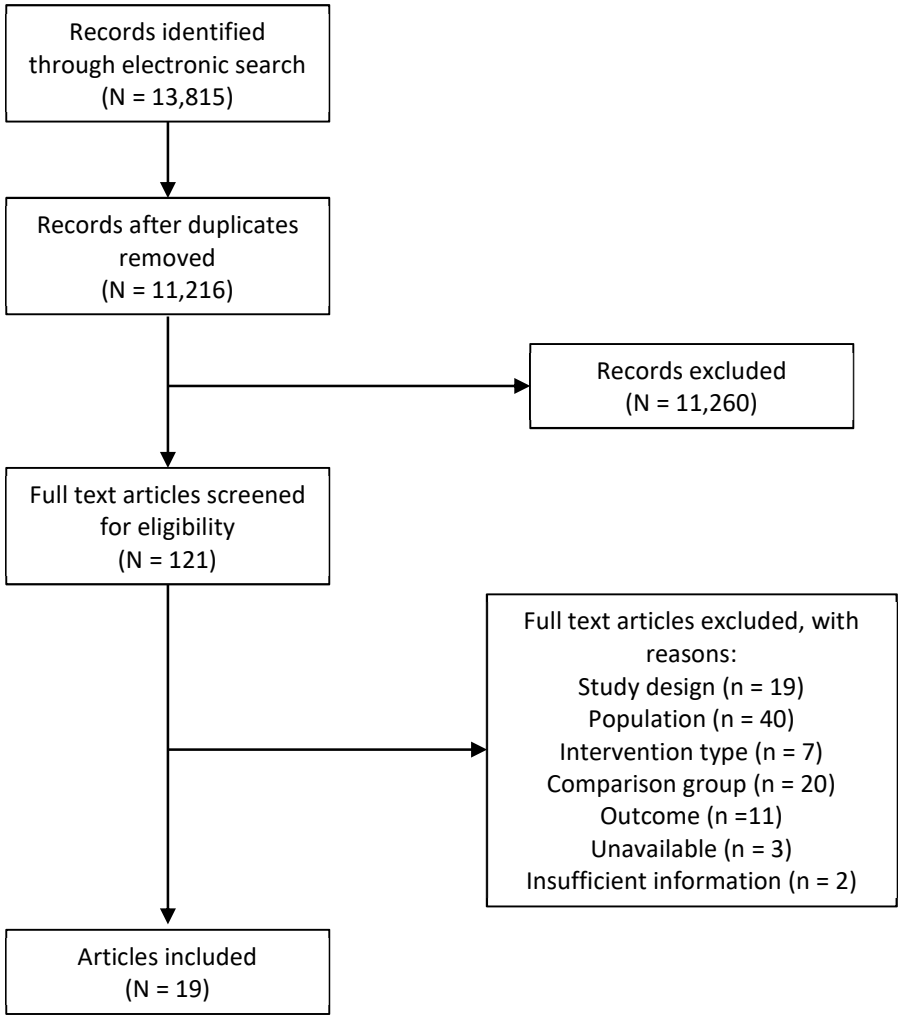
Records identified through electronic search (N = 13,815)
Records after duplicates removed (N = 11,216)
Records excluded (N = 11,260)
Full text articles screened for eligibility (N = 121)
Full text articles excluded, with reasons:
Study design (n = 19)
Population (n = 40)
Intervention type (n = 7)
Comparison group (n = 20)
Outcome (n =11)
Unavailable (n = 3)
Insufficient information (n = 2)
Articles included (N = 19)

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]
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	Routinely collected health datasets, including clinical	Comparison of outcome in the pre/post AD initiation period	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

	• No AD prescription in the 100 days prior to T2DM diagnosis & redeemed first AD prescription during follow-up	laboratory datasets	(index date being date of AD initiation)				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 and 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 and 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 and diastolic blood pressure and cholesterol

*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

AD: antidepressant; AP: antipsychotic; 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; TC: total cholesterol; TCA: tricyclic antidepressant

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) New SSRI Long-term SSRI Former SSRI	**RR 1.3 (1.1-1.5)** **RR 1.5 (1.2-1.8)** **RR 1.2 (1.1-1.4)** 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)**	↓
			No AD	Current AD	OR 0.99 (0.93-1.06)	↔

Rohde, 2021 [21]	Cox proportional hazards	Optimal glycaemic control¶		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)**	↓
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)††**	↑

*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

¶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

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

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	

*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
AP: antipsychotic; BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; CV: cardiovascular; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; HR: hazard ratio; SD: standard deviation; RR: rate ratio

Antidepressant and antipsychotic drug prescribing and complications of diabetes: a systematic review of observational studies

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Supplementary Material

Supplemental Appendix 1 Electronic search strategies

Supplemental Table 1 Study inclusion and exclusion criteria (PICO framework)

Supplemental Table 2 (a): Antidepressant drugs included in relevant studies

Supplemental Table 2 (b): Antipsychotic drugs included in relevant studies

Supplemental Table 3: Assessment of study quality: Newcastle-Ottawa Scale summary

Supplemental Table 4: Additional information on adjustment for confounding in statistical models

Supplemental Table 5 (a): Supplementary results of observational studies reporting on the association between antidepressant drug prescribing and outcomes in people with diabetes

Supplemental Table 5 (b): Supplementary results of observational studies reporting on the association between antipsychotic drug prescribing and outcomes in people with diabetes

Supplemental Appendix 1: Electronic search strategies

PubMed Search Strategy

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EMBASE Search Strategy

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or/1-2
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isocarboxazid.tw.
lofepramine.tw.
(mianserin or tolvon).tw.
(mirtazapine or remeron or zispin).tw.
(moclobemide or manerix).tw.
(nortriptyline or allegron).tw.
(paroxetine or seroxat).tw.
(phenelzine or nardil).tw.
reboxetine.tw.
(sertraline or lustral).tw.
tranylcypromine.tw.
(trazodone or molipaxin).tw.
(trimipramine or surmontil).tw.
(venlafaxine or effexor).tw.
(vortioxetine or trintellix or brintellix).tw.
antipsychotic agent/
(antipsychotic* or anti-psychotic* or anti psychotic* or neuroleptic* or major tranquilizer*).tw.
(amisulpride or solian).tw.
(aripiprazole or abilify).tw.
(asenapine or saphris or sycrest).tw.
(benperidol or anquil).tw.
(clopenthixol or clopentixol or sordinol or ciatyl).tw.

(clozapine or clozaril).tw.
(flupenthixol or flupentixol or fluanxol or depixol).tw.
(haloperidol or haldol).tw.
(lurasidone or latuda).tw.
(methotrimeprazine or levomepromazine).tw.
(olanzapine or zalasta or zyprexa).tw.
(paliperidone or trevicta).mp
(periciazine or pericyazine).tw.
perphenazine.tw.
(pimozide or orap).tw.
(prochlorperazine or buccastem or stemetil).tw.
(promazine or sparine).tw.
(quetiapine or seroquel).tw.
(risperidone or risperdal).tw.
(sulpiride or dogmatil or dolmatil or sulpor).tw.
(trifluoperazine or stelazine).tw.
(ziprasidone or geodon).tw.
(zuclopenthixol or clopixol or cisordinol or acuphase).tw.
or/4-65
outcome assessment/
health status/
mortality/
hospital admission/
haemoglobin A1c/
diabetic control/
blood pressure/
total cholesterol level/
triacylglycerol level/
ischemic heart disease/
cerebrovascular accident/
peripheral occlusive artery disease/
exp diabetic complication/
outcome*.tw.
mortality.tw.
hospital admission.tw.
(blood glucose or blood sugar).tw.
blood pressure.tw.
cholesterol.tw.
triglyceride adj2 levels.tw.
(myocardial infarction or heart attack).tw.
stroke.tw.
peripheral adj3 disease.tw.
diabetic foot.tw.
(diabet* ketoacidosis or DKA).tw.
retinopathy.tw.
neuropathy.tw.
nephropathy.tw.
or/67-94
3 and 66 and 96

PsycInfo Search Strategy

exp diabetes mellitus/
diabet*.tw.
or/1-2
exp antidepressant drugs/
(antidepress* or anti-depress* or anti depress*).tw.
(agomelatine or valdoxan).tw.
(amitriptyline or triptafen).tw.
(amoxapine or asendin).tw.
bupropion.tw.
citalopram.tw.
(clomipramine or anafranil).tw.
(desipramine or norpramin).tw.
(dothiepin or dosulepin or prothiaden).tw.
doxepin.tw.
(duloxetine hydrochloride or cymbalta).tw.
(escitalopram or cipralex).tw.
(fluoxetine or prozac).tw.
(flupenthixol or fluanxol).tw.
(fluvoxamine or faverin).tw.
imipramine.tw.
isocarboxazid.tw.
lofepramine.tw.
(mianserin or tolvon).tw.
(mirtazapine or remeron or zispin).tw.
(moclobemide or manerix).tw.
(nortriptyline or allegron).tw.
(paroxetine or seroxat).tw.
(phenelzine or nardil).tw.
reboxetine.tw.
(sertraline or lustral).tw.
tranylcypromine.tw.
(trazodone or molipaxin).tw.
(trimipramine or surmontil).tw.
(venlafaxine or effexor).tw.
(vortioxetine or trintellix or brintellix).tw.
exp antipsychotic drugs/
(antipsychotic* or anti-psychotic* or anti psychotic* or neuroleptic* or major tranquilizer*).tw.
(amisulpride or solian).tw.
(aripiprazole or abilify).tw.
(asenapine or saphris or sycrest).tw.
(benperidol or anquil).tw.
(clopenthixol or clopentixol or sordinol or ciatyl).tw.
(clozapine or clozaril).tw.

(flupenthixol or flupentixol or fluanxol or depixol).tw.
(haloperidol or haldol).tw.
(lurasidone or latuda).tw.
(methotrimeprazine or levomepromazine).tw.
(olanzapine or zalasta or zyprexa).tw.
(paliperidone or trevicta).mp
(periciazine or pericyazine).tw.
perphenazine.tw.
(pimozide or orap).tw.
(prochlorperazine or buccastem or stemetil).tw.
(promazine or sparine).tw.
(quetiapine or seroquel).tw.
(risperidone or risperdal).tw.
(sulpiride or dogmatil or dolmatil or sulpor).tw.
(trifluoperazine or stelazine).tw.
(ziprasidone or geodon).tw.
(zuclopenthixol or clopixol or cisordinol or acuphase).tw.
or/4-60
mortality/
hospital admission/
blood sugar/
exp blood pressure/
total cholesterol level/
lipids/
cerebrovascular accidents/
exp cardiovascular disorders/
outcome*.tw.
mortality.tw.
hospital admission.tw.
(blood glucose or blood sugar).tw.
blood pressure.tw.
cholesterol.tw.
triglyceride adj2 levels.tw.
(myocardial infarction or heart attack).tw.
stroke.tw.
peripheral adj3 disease.tw.
diabetic foot.tw.
(diabet* ketoacidosis or DKA).tw.
retinopathy.tw.
neuropathy.tw.
nephropathy.tw.
or/62-84
3 and 61 and 85

Supplemental Table 1: Study inclusion and exclusion criteria (PICO framework)

	Inclusion		Exclusion
Population	Adults with pre-existing type 2 diabetes mellitus in any location or setting		Children (< 18 years); people with type 1 diabetes mellitus; studies that did not report separately on outcomes in people with diabetes; studies where the study population was selected on the presence of a specific disease of interest and where data on psychotropic medication prescribing was reported for a sub-set of the study population with diabetes but without the provision of key descriptive characteristics of the sub-set
Intervention	All type antidepressant and/or antipsychotic drug use or prescribing		Lithium use or prescribing only
Comparison	The absence of antidepressant and/or antipsychotic drug use or prescribing		A second antidepressant and/or antipsychotic drug; no comparison group
Outcome	*Clinical complications (primary)*	Cardiovascular morbidity; retinopathy; neuropathy; nephropathy; all-cause mortality; cause-specific mortality	Outcomes related to the progression of clinical complications; weight changes/obesity; outcomes related to mental wellbeing
	Cardiometabolic risk factors (secondary)	Glycaemic control (HbA1c, hyperglycaemia, insulin initiation); blood pressure (hypertension, systolic/diastolic); lipid levels (dyslipidaemia, low-density/high-density lipoprotein cholesterol, total cholesterol, triglycerides)	
Study design	Observational studies (cohort, case-control, cross-sectional); accessible in the English language		Case reports; experimental studies; secondary studies (narrative reviews, literature reviews, meta-analyses)

Supplemental Table 2 (a): Details of antidepressant drugs included in studies reporting on antidepressant prescribing in relation to diabetes outcomes

First author, publication year, study setting [study period]	Method	SSRIs (ATC N06A-)	TCAs (ATC N06A-)	Other (ATC N06A-)
Higgins, 2007 [27] USA [July 2002]	NR	NR	NR	NR
Rubin, 2010, 2013 [21] USA [June 2001 to approx. 2005]	NR	NR	NR	NR
Noordam, 2016* [31] Netherlands [1991 to 2012]	ATC	Paroxetine (B05)	Amitriptyline (A09)	NR
Rådholm, 2015 [19] Sweden [January 2008 to December 2010]	ATC	NR	NR	NR
Yekta, 2015 [30] USA [2005 to 2008]	NR	Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Fluvoxamine (B08) Escitalopram (B10)	Desipramine (A01) Imipramine (A02) Clomipramine (A04) Trimipramine (A06) Amitriptyline (A09) Nortriptyline (A10) Protriptyline (A11) Doxepin (A12) Maprotiline (A21)	Trazodone (X05) Nefazodone (X06) Mirtazapine (X11) Bupropion (X12) Venlafaxine (X16) Duloxetine (X21)
Brieler, 2016 [15] USA [July 2008 to July 2013]	NR	Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Fluvoxamine (B08) Escitalopram (B10)	Desipramine (A01) Imipramine (A02) Clomipramine (A04) Amitriptyline (A09) Nortriptyline (A10) Doxepin (A12)	Trazodone (X05) Nefazodone (X06) Mirtazapine (X11) Bupropion (X12) Venlafaxine (X16) Duloxetine (X21) Desvenlafaxine (N06 AX23)
Kammer, 2016* [28] USA [2002 to 2009]	NR	Fluoxetine (B03) Paroxetine (B05) Sertraline (B06)	NR	NR
Würtz, 2016 [25] Denmark [July 2004 to December 2012]	ATC	Zimeldine (B02) Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Alaproclate (B07) Fluvoxamine (B08) Etoperidone (B09) Escitalopram (B10)	None	None
Hazuda, 2019 [18] USA	NR	NR	NR	NR

[June 2001 to September 2012]				
Rohde, 2021 [20] Denmark [January 2000 to October 2016]	ATC	Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Fluvoxamine (B08) Escitalopram (B10)	Imipramine (A02) Clomipramine (A04) Amitriptyline (A09) Nortriptyline (A10)	Mianserin (X03) Mirtazapine (X11) Venlafaxine (X16) Reboxetine (X18) Duloxetine (X21)
Chen, 2021 [16] Taiwan [January 1997 to December 2010]	ATC	NR	NR	NR
Wu, 2021 [24] Taiwan [2001 to 2004]	ATC	Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Fluvoxamine (B08)	Imipramine (A02) Clomipramine (A04) Amitriptyline (A09) Doxepin (A12) Dothiepin (A16) Melitracen (A14) Maprotiline (A21)	Trazodone (X05) Nefazodone (X06) Mirtazapine (X11) Bupropion (X12) Venlafaxine (X16) Milnacipran (X17) Duloxetine (X21) Moclobemide (G02)
Chen, 2022 [17] Taiwan [1999 to 2013]	NR	NR	NR	NR
Rohde, 2022 [26] Denmark [January 2000 to October 2016]	ATC	Fluoxetine (B03) Citalopram (B04) Paroxetine (B05) Sertraline (B06) Fluvoxamine (B08) Escitalopram (B10)	Imipramine (A02) Clomipramine (A04) Amitriptyline (A09) Nortriptyline (A10)	Mianserin (X03) Mirtazapine (X11) Venlafaxine (X16) Reboxetine (X18) Duloxetine (X21)

*List not comprehensive, authors specified commonly prescribed drugs only
AD: antidepressant; ATC: Anatomical Therapeutic Chemical; MAOI: monoamine oxidase inhibitor; NR: not reported; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant
NB. The ATC classification system is the gold standard for identifying drugs in international drug research. It is maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology (www.whocc.no). ADs are classified at the third level, N06A, and divided into groups at higher levels according to their therapeutic, pharmacological, and chemical properties. Relevant groups include SSRIs (N06AB-), TCAs (N06AA-), MAOIs, (N06AF/G-), and other (N06AX-). Drugs including venlafaxine (X16) and duloxetine (X21) may also be classified as SNRIs.

Supplemental Table 2 (b): Details of antipsychotic drugs included in studies reporting on antipsychotic prescribing in relation to diabetes outcomes

First author, publication year, study setting [study period]	Method of identification	FGAs (ATC N05A-)	SGAs (ATC N05A-)
Spoelstra, 2004 [22] Netherlands [January 1991 to June 1999]	ATC	NR	Clozapine (H02) Olanzapine (H03) Quetiapine (H04) Risperidone (X08)
Lipscombe, 2009* [32] Canada [April 2002 to March 2006]	NR	NR	Olanzapine (H03) Quetiapine (H04) Risperidone (X08)
Wake, 2016 [29] UK [2010]	BNF subsection 4.2.†‡	NR	NR
Wu, 2016 [23] Taiwan [2001 to 2012]	ATC	Chlorpromazine (A01) Levomepromazine (A02) Promazine (A03) Fluphenazine (B02) Perphenazine (B03) Prochlorperazine (B04) Trifluoperazine (B06) Thioridazine (C02) Pipotiazine (C04) Haloperidol (D01) Flupentixol (F01) Zuclopenthixol (F05) Pimozide (G02) Loxapine (H01)	Clozapine (H02) Olanzapine (H03) Quetiapine (H04) Sulpiride (L01) Amisulpride (L05) Risperidone (X08) Zotepine (X11)

*Included APs funded by the Ontario Drug Benefit programme during the study period
†The BNF is a reference for drug prescribing used in the UK
‡Subsection 4.2.1 refers to APs, this excludes: depot injection formulations (BNF subsection 4.2.2); prochlorperazine (B04) and droperidol (D08) (BNF section 4.6, drugs used for vertigo); and asenapine (H05) and lithium (N01) (BNF section 4.2.3, drugs used for mania and hypomania)
AP: antipsychotic; ATC: Anatomical Therapeutic Chemical; BNF: British National Formulary; FGA: first-generation antipsychotic; NR: not reported; SGA: second-generation antipsychotic
NB. The ATC classification system is the gold standard for identifying drugs in international drug research. It is maintained by the World Health Organization Collaborating Centre for Drug Statistics Methodology (www.whocc.no). APs are classified at the third level, N05A, and divided into groups at higher levels according to their therapeutic, pharmacological, and chemical properties. Relevant groups include FGAs and SGAs.

Supplemental Table 3: Assessment of study quality: Newcastle-Ottawa Scale summary

First author, year	Selection	Comparability	Outcome/Exposure	Total stars
COHORT STUDIES				
Spoelstra, 2004 [22]	****	*	***	8/9
Rubin, 2010, 2013 [21]	***	*	**	6/9
Rådholm, 2015 [19]	****		***	7/9
Brieler, 2016 [15]	****	*	***	8/9
Wu, 2016 [23]	****	*	***	8/9
Würtz, 2016 [25]	****		***	7/9
Hazuda, 2019 [18]	***	*	**	6/9
Rohde, 2021 [20]	****	*	***	8/9
Chen, 2021 [16]	****	*	***	8/9
Wu, 2021 [24]	****	*	**	7/9
Chen, 2022 [17]	****	*	***	8/9
Rohde, 2022 [26]	****	*	**	7/9
CASE-CONTROL STUDIES				
Lipscombe, 2009 [32]	****	*	***	8/9
Noordam, 2016 [31]	****	*	***	8/9
CROSS-SECTIONAL STUDIES				
Higgins, 2007 [27]	***		**	5/9
Yekta, 2015 [30]	**	*	***	6/9
Kammer, 2016 [28]		*	**	3/9
Wake, 2016 [29]	****	*	*	6/9

Studies were awarded a maximum of four stars for study selection, two stars for group comparability, and three stars for ascertainment of outcome or exposure, to a maximum total of nine. Separate versions of the scale were used for cohort, case-control, and cross-sectional studies.

Supplemental Table 4 (a): Additional information on adjustment for confounding in statistical models for the association between antidepressant prescribing and outcomes

First author, year	Statistical methods	Confounders adjusted for in analyses	Details of composite outcomes (where relevant)
COHORT STUDIES			
Rubin, 2010, 2013 [22]	GEE	Age; sex; ethnicity; education; HbA1c (prior year); history of CVD; duration of diabetes; AD prescription (prior year); year of follow-up	NA
Rådholm, 2015 [20]	Descriptive	Stratified by age and sex	NA
Brieler, 2016 [16]	GEE	Age; sex; ethnicity; anxiety disorder; obesity; hyperlipidaemia; hypertension; vascular disease; referral to dietary education; smoking; insulin prescription; other GLD prescription; primary care clinic utilisation	NA
Wu, 2016 [24]			CV morbidity (hospitalisation for CHD and stroke; PVD with stent insertion; vascular shunt or bypass; vessel repair procedure), microvascular morbidity (retinopathy; blindness; end-stage renal disease with dialysis; vessel operations for haemodialysis; kidney transplantation; hospitalisation for diabetic foot infection; lower extremity amputations), all-cause mortality
Würtz, 2016 [26]	Cox proportional hazards	Previous MI, atrial fibrillation or flutter; intermittent arterial claudication; dementia; CCI (excluding MI, PVD, and dementia); other drug prescriptions	NA
Hazuda, 2019 [19]	Cox proportional hazards	Age; ethnicity; history of CVD; HbA1c; BMI; waist circumference; insulin prescription; hypercholesterolaemia; hypertension; smoking; estimated exercise stress level; HRT prescription (women only); clinic attended; assigned clinical trial intervention	Non-fatal MI; stroke; angina; CHF; PVD; CABG; carotid endarterectomy; CV and all-cause mortality
Chen, 2021 [17]	Cox proportional hazards	Age; sex; income; urbanisation; hypertension; hypercholesterolaemia; CAD; CKD; heart failure; peptic ulcer; aspirin; clopidogrel (Plavix) prescription	NA
Rohde, 2021 [21]	Cox proportional hazards	Age; sex; marital status; HbA1c (baseline); LDL levels (baseline); obesity; kidney functioning; CCI (excluding diabetes); diabetes complications; alcohol-related disorders; smoking-associated disorders; other drug prescriptions	NA
Wu, 2021 [25]	None	Crude incidence in comparison groups	Macrovascular morbidity (IHD; stroke; PVD; vascular shunts or

			bypasses; vessel repair procedures), microvascular morbidity (retinopathy; end-stage renal disease; diabetic foot infections), all-cause mortality
Chen 2022 [18]	Cox proportional hazards	Age; sex; economic level; urbanisation; CCI score; hypertension; acute MI; hyperlipidaemia; atrial fibrillation; COPD; depression; bipolar disorder; schizophrenia; alcoholism; antithrombotic medication prescriptions*; TCA prescriptions; other AD prescriptions	NA
SELF-CONTROLLED STUDIES			
Rhode, 2022 [27]	Mean percent change	Individuals serve as their own controls, allowing adjustment for all time-stable confounders; findings externally compared to those from an age-sex matched reference population	NA
CASE-CONTROL STUDIES			
Noordam, 2016 [29]	Conditional logistic regression	Age; sex; BMI; number of prescribed oral GLDs	NA
CROSS-SECTIONAL STUDIES			
Higgins, 2007 [30]	Logistic regression	None for relevant analyses	CAD; MI; angioplasty; CABG
Yekta, 2015 [33]	Logistic regression	Age; sex; ethnicity; income; diabetes duration; HbA1c; SBP; TG levels; BMI; smoking	NA
Kammer, 2016 [31]	Linear regression	Age; sex; ethnicity; education; depression severity; BMI; smoking	NA

*Including: warfarin; acetylsalicylic acid; cilostazol; clopidogrel; prasugrel; ticagrelor; ticlopidine; dabigatran etexilate; apixaban; edoxaban; rivaroxaban
AD: antidepressant; BMI: body mass index; CABG: coronary artery bypass graft; CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; CHD: coronary heart disease; CHF: congestive heart failure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; IHD: ischaemic heart disease; MI: myocardial infarction; PAD: peripheral artery disease; PVD: peripheral vascular disease; SBP: systolic blood pressure; TCA: tricyclic antidepressant; TG: triglyceride

Supplemental Table 4 (b): Additional information on adjustment for confounding in statistical models for the association between antipsychotic prescribing and outcomes

First author, year	Statistical methods	Confounders adjusted for in analyses	Details of composite outcomes (where relevant)
COHORT STUDIES			
Spoelstra, 2004 [23]	Cox proportional hazards	Age at diabetes onset (first prescription of oral GLD); other drug prescriptions in previous 180 days*; calendar year	NA
Wu, 2016 [24]	Cox proportional hazards	Age at diabetes diagnosis; sex; calendar year of diabetes diagnosis; comorbid diagnoses[†]; other drug prescriptions[#]; number of/adherence to prescribed oral GLDs; insulin prescription; examination for HbA1c/lipids; number of outpatient visits/hospitalisations	CV morbidity (hospitalisation for CHD and stroke; PVD with stent insertion; vascular shunt or bypass; vessel repair procedure), microvascular morbidity (retinopathy; blindness; end-stage renal disease with dialysis; vessel operations for haemodialysis; kidney transplantation; hospitalisation for diabetic foot infection; lower extremity amputations); all-cause mortality
CASE-CONTROL STUDIES			
Lipscombe, 2009 [28]	Conditional logistic regression	Age; sex; neighbourhood income quintile; diabetes duration; CCI; comorbid dementia, schizophrenia, or other major psychoses; other drug prescriptions in previous 180 days[††]; health service use history	NA
CROSS-SECTIONAL STUDIES			
Wake, 2016 [32]	Student's t-test/chi-squared test	Exposed and non-exposed people, matched for: birth year; sex; diabetes type; diagnosis date; BMI; smoking	NA

*Including: beta blockers; diuretics; antiparkinsonian drugs; corticosteroids for systemic use; ADs
[†]Including: hypertension; dyslipidaemia; chronic pulmonary disease; chronic liver disease; malignancy; depression; dementia; anxiety disorders; alcohol-related disorders; substance use disorders
[#]Including: angiotensin system acting agents; beta blockers; calcium channel blockers; diuretics; lipid-lowering agents; antithrombotic agents; non-steroidal anti-inflammatory drugs; anticonvulsants; lithium; ADs; benzodiazepines
[††]Including: cytochrome P-450 2C9 inducers; cytochrome P-450 2C9 inhibitors; thiazide diuretics; corticosteroids for systemic use
BMI: body mass index; CCI: Charlson Comorbidity Index; CHD: coronary heart disease; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; PVD: peripheral vascular disease

Supplemental Table 5 (a): Supplementary results of observational studies reporting on the association between antidepressant drug prescribing and outcomes in people with diabetes

First author, year	Statistical methods	Potential confounding factors adjusted for	Results				
			Outcome	Reference	Antidepressant prescription	Effect estimate (CI)[†]	Direction of association[‡]
Rubin, 2010, 2013 [22]	Generalised estimating equations	Age; sex; ethnicity; education; outcome of interest (prior year); history of CVD; duration of diabetes; AD prescription (prior year); year of follow-up	Sub-optimal glycaemic control (HbA1c > 7%/53 mmol/mol) or insulin prescription	No AD	AD in prior year	*Active arm:* OR 1.25 (1.08-1.46)*	↑
			SBP ≥ 130 mmHg or anti-hypertensive prescription	No AD	AD in prior year	*Control arm:* OR 1.09 (0.87-1.36)	↔
						Active arm: OR 1.18 (0.94-1.48)	↔
			DBP ≥ 80 mmHg or anti-hypertensive prescription	No AD	AD in prior year	*Control arm:* OR 1.06 (0.85-1.33)	↔
						Active arm: OR 1.39 (1.11-1.74)*	↑
			LDL ≥ 2.6 mmol/l or lipid-lowering prescription	No AD	AD in prior year	*Control arm:* OR 1.24 (0.96-1.60)	↔
						Active arm: OR 1.15 (0.90-1.46)	↔
			HDL ≤ 1.0 mmol/l or lipid-lowering prescription	No AD	AD in prior year	*Control arm:* OR 1.24 (1.03-1.50)*	↑
						Active arm: OR 1.33 (1.11-1.58)*	↑
			TC ≥ 5.2 mmol/l or lipid-lowering prescription	No AD	AD in prior year	*Control arm:* OR 1.29 (1.05-1.57)*	↑
						Active arm: OR 1.21 (1.00-1.48)	↔
			TG ≥ 1.7 mmol/l or lipid-lowering prescription	No AD	AD in prior year	*Control arm:* OR 1.23 (0.99-1.52)	↔
						Active arm: OR 1.75 (1.43-2.14)*	↑
Würtz, 2016 [26]	Cox proportional hazards	Multivariable adjusted/propensity score matched: previous MI, atrial fibrillation or flutter; intermittent arterial claudication; dementia; CCI (excluding MI, PVD, and dementia); other drug prescriptions[§]	Mortality (30 days following <u>any stroke</u>)[‖]	No SSRI	Current SSRI (any)	*Propensity score matched: RR* 1.2 (1.0-1.4)	↔
					New SSRI	*Propensity score matched: RR* 1.4 (1.0-1.9)	↔
					Long-term SSRI	*Propensity score matched: RR* 1.3 (1.1-1.6)*	↑
					Former SSRI	*Propensity score matched: RR* 1.2 (0.8-1.7)	↔
			Mortality (30 days following <u>ischaemic</u> stroke)	No SSRI	Current SSRI	Rate ratio 1.3 (1.1-1.7)*	↑
						Propensity score matched: RR 1.4 (1.0-1.8)	↔
						Men: RR 1.6 (1.2-2.2)*	↑
						Women: RR 1.2 (0.9-1.6)	↔
						Age < 60: RR 1.8 (0.7-4.5)	↔
						Age 60 to 69: RR 1.5 (0.9-2.8)	↔

						Age 70 to 79: RR 1.6 (1.1-2.4)*	↑
						Age ≥ 80: RR 1.2 (0.9-1.6)	↔
			Mortality (30 days following intracerebral haemorrhage)	No SSRI	Current SSRI	RR 1.2 (0.9-1.5)	↔
						Propensity score matched: RR 1.0 (0.7-1.3)	↔
						Men: RR 1.1 (0.7 to 1.5)	↔
						Women: RR 1.3 (0.9-1.9)	↔
						Age < 60: RR 0.7 (0.2-2.3)	↔
						Age 60 to 69: RR 1.3 (0.7-2.5)	↔
						Age 70 to 79: RR 1.3 (0.8-2.2)	↔
						Age ≥ 80: RR 1.4 (0.9- 2.0)	↔
			Mortality (30 days following subarachnoid haemorrhage)‖	No SSRI	Current SSRI	RR 0.8 (0.4-1.7)	↔
						Propensity score matched: RR 0.9 (0.4-2.0)	↔
			Mortality (30 days following unspecified stroke)‖	No SSRI	Current SSRI	RR 1.2 (1.0-1.4)	↔
						Propensity score matched: RR 1.2 (1.0-1.6)	↔
Hazuda, 2019# [19]	Cox proportional hazards	Age; ethnicity; history of CVD; HbA1c; BMI; waist circumference; insulin prescription; hypercholesterolaemia; hypertension; smoking; estimated exercise stress level; HRT prescription (women only); clinic attended; assigned clinical trial intervention	CV mortality, non-fatal MI, non-fatal stroke	No AD	Baseline AD	*Men:* HR 0.72 (0.50-1.05)	↔
						Women: HR 0.86 (0.61-1.21)	↔
			All-cause mortality, non-fatal MI, non-fatal stroke, angina	No AD	Baseline AD	*Men:* HR 1.03 (0.80-1.34)	↔
						Women: HR 0.72 (0.56-0.94)*	↓
			CV mortality, non-fatal MI, non-fatal stroke, angina, CHF, PVD, CABG, carotid endarterectomy	No AD	Baseline AD	*Men:* HR 1.07 (0.85-1.36)	↔
						Women: HR 0.76 (0.59-0.96)*	↓
Rohde, 2021 [21]	Cox proportional hazards	Age; sex; marital status; HbA1c (baseline); LDL levels (baseline); obesity; kidney functioning; CCI (excluding diabetes); diabetes complications; alcohol-related disorders; smoking-associated disorders; other drug prescriptions¶	Optimal glycaemic control (HbA1c < 7%/53 mmol/mol)	No AD	Current SSRI	OR 0.94 (0.87-1.02)	↔
					Current SNRI	OR 1.30 (1.10-1.52)*	↓ (of sub-optimal glycaemic control)
					Current TCA	OR 0.99 (0.85-1.15)	↔
					Current other AD	OR 0.98 (0.86-1.12)	↔
					Recent AD#	OR 1.02 (0.96-1.08)	↔
					Persistent AD#	OR 1.00 (0.95-1.06)	↔
			LDL < 2.6 mmol/l	No AD	Current AD	OR 1.08 (1.03-1.14)*	↓ (of sub-optimal LDL)
					Current SSRI	OR 1.04 (0.98-1.12)	↔

					Current SNRI	OR 1.26 (1.12-1.42)*	↓ (of sub-optimal LDL)
					Current TCA	OR 1.22 (1.08-1.38)*	↓ (of sub-optimal LDL)
					Other AD	OR 0.99 (0.89-1.11)	↔
					Former AD	OR 1.06 (1.01-1.11)*	↓ (of sub-optimal LDL)
					Recent AD#	OR 1.05 (1.00-1.10)	↔
					Persistent AD#	OR 1.06 (1.01-1.11)*	↓ (of sub-optimal LDL)
			GLD prescription (including insulin)	No AD	Current AD (sub-cohort)**	OR 1.34 (1.29-1.39)*	↑
					Current SSRI	OR 1.28 (1.22-1.34)*	↑
					Current SNRI	OR 1.76 (1.63-1.89)*	↑
					Current TCA	OR 1.34 (1.23-1.46)*	↑
					Current other AD	OR 1.45 (1.35-1.56)*	↑
					Recent AD#	OR 1.37 (1.32-1.41)*	↑
					Persistent AD#	OR 1.38 (1.33-1.42)*	↑
Chen, 2021 [17]	Cox proportional hazards	Age; sex; income; urbanisation; hypertension; hypercholesterolaemia; CAD; CKD; heart failure; peptic ulcer; aspirin; clopidogrel (Plavix) prescription	First MI	No AD	TCA (>180 days)	HR 0.74 (0.69-0.79)*	↓
					SSRI (>180 days)	HR 0.66 (0.60- 0.74)*	↓
					SNRI (>180 days)	HR 0.67 (0.51- 0.88)*	↓
					AD cDDD:		
					28-180	HR 0.77 (0.73-0.81)	↓
					>180	HR 0.56 (0.52-0.60)	↓
Wu, 2021 [25]	Cox proportional hazards	Only crude incidence rates reported (adjusted models only reported for categories of use versus "poor use")	Macrovascular complications	No AD	SSRIs	69.5 versus 65.6 per 1000 person-years	↑††
					SNRIs	75.4 versus 65.6 per 1000 person-years	↑††
					TCAs	98.8 versus 65.6 per 1000 person-years	↑††
			Microvascular complications	No AD	SSRIs	41.7 versus 40.9 per 1000 person-years	↑††
					SNRIs	51.8 versus 40.9 per 1000 person-years	↑††
					TCAs	48.4 versus 40.9 per 1000 person-years	↑††
			All-cause mortality	No AD	SSRIs	18.3 versus 17.3 per 1000 person-years	↑††
					SNRIs	19.5 versus 17.3 per 1000 person-years	↑††
					TCAs	26.9 versus 17.3 per 1000 person-years	↑††

Chen, 2022 [18]	Cox proportional hazards	Age; sex; economic level; urbanisation; CCI score; hypertension; acute MI; hyperlipidaemia; atrial fibrillation; COPD; depression; bipolar disorder; schizophrenia; alcoholism; antithrombotic medication prescriptions‡‡; TCA prescriptions; other AD prescriptions	PAD	No SSRI	SSRI average dose effects:		
					cDDD: 1-83	HR 1.17 (0.74-1.83)	↔
					cDDD: ≥84	HR 1.04 (0.50-2.15)	↔

*Denotes significant $P < 0.05$

†Results given for fully multivariable adjusted or matched models unless otherwise stated

‡No association refers to no statistically significant association at $P < 0.05$

§Including: angiotensin system acting agents; beta blockers, calcium channel blockers; statins; aspirin; non-aspirin non-steroidal anti-inflammatory drugs; non-aspirin platelet inhibitors; vitamin K antagonists; corticosteroids for systemic use; APs

‖Results not given for age or sex stratified analyses

¶Including: angiotensin system acting agents; beta blockers; calcium channel blockers; diuretics; corticosteroids for systemic use; antithrombotic agents; analgesics; inhalants

#Recent AD prescription defined as prescription 101 to 365 days prior to the diagnosis of T2DM, persistent AD prescription defined as ≥ 2 prescriptions in the 2 years prior to the diagnosis of T2DM including a prescription in the year prior to the diagnosis of T2DM

**Restricted to people diagnosed with T2DM after 2007 to account for differences in treatment guidelines

††Crude incidence rates reported – unadjusted for age and sex

‡‡Including: warfarin; acetylsalicylic acid; cilostazol; clopidogrel; prasugrel; ticagrelor; ticlopidine; dabigatran etexilate; apixaban; edoxaban; rivaroxaban

AD: antidepressant; AP: antipsychotic; BMI: body mass index; CABG: coronary artery bypass graft; CCI: Charlson Comorbidity Index; cDDD: cumulative defined daily dose; CHF; congestive heart failure; CI: confidence interval; COPD: chronic obstructive pulmonary disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; HDL: high-density lipoprotein; HR: hazard ratio; HRT: hormone replacement therapy; LDL: low-density lipoprotein; MI: myocardial infarction; OR: odds ratio; PAD: peripheral artery disease; RR: rate ratio; SBP: systolic blood pressure; SNRI: serotonin–norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; T2DM: type 2 diabetes mellitus; TC: total cholesterol; TCA: tricyclic antidepressant; TG: triglyceride

Supplemental Table 5 (b): Supplementary results of observational studies reporting on the association between antipsychotic drug prescribing and outcomes in people with diabetes

First author, year	Statistical methods	Potential confounding factors adjusted for	Results				
			Outcome	Reference	Antipsychotic prescription	Effect estimate (CI)[†]	Direction of association[‡]
Wu, 2016 [24]	Cox proportional hazards[§]	Multivariable adjusted/propensity score matched: age at diabetes diagnosis; sex; calendar year of diabetes diagnosis; comorbid diagnoses[‖]; other drug prescriptions[¶]; number of/adherence to prescribed GLDs; insulin prescription; examination for HbA1c/lipids; number of outpatient visits/hospitalisations	All complications	No AP	Irregular AP	HR 0.90 (0.78 to 1.03)	↔
					Regular AP (stratified by metabolic risk)[#]	*Overall:* HR 0.81 (0.69 to 0.95)*	↓
						Overall, propensity score matched: HR 0.75 (0.67 to 0.84)*	↓
						Low: HR 0.85 (0.70 to 1.02)	↔
						Intermediate: HR 0.82 (0.68 to 0.99)*	↓
						High: HR 0.69 (0.53 to 0.91)*	↓
						Combination: HR 0.84 (0.66 to 1.08)	↔
			CV morbidity	No AP	Regular AP (stratified by metabolic risk)[#]	*Overall, propensity score matched:* HR 0.71 (0.62 to 0.80)*	↓
						Low: HR 0.84 (0.67 to 1.06)	↔
						Intermediate: HR 0.81 (0.64 to 1.02)	↔
						High: 0.74 (0.53 to 1.02)	↔
						Combination: HR 0.75 (0.55 to 1.04)	↔
			Microvascular morbidity	No AP	Regular AP (stratified by metabolic risk)[#]	*Overall, propensity score matched:* HR 0.87 (0.73 to 1.03)	↔
						Low: HR 0.83 (0.62 to 1.11)	↔
						Intermediate: HR 0.83 (0.62 to 1.10)	↔
						High: HR 0.61 (0.40 to 0.93)*	↓
						Combination: HR 1.03 (0.72 to 1.46)	↔
			All-cause mortality	No AP	Regular AP (stratified by metabolic risk)[#]	*Overall, propensity score matched*: HR 0.79 (0.71 to 0.89)*	↓
						Low: HR 0.66 (0.54 to 0.81)*	↓
						Intermediate: HR 0.78 (0.65 to 0.94)*	↓
						High: HR 0.62 (0.47 to 0.82)*	↓
						Combination: HR 0.82 (0.65 to 1.05)	↔
Lipscombe 2009 [28]	Conditional logistic regression	Age; sex; neighbourhood income quintile; diabetes duration; CCI; comorbid dementia, schizophrenia, or other major psychoses; other drug prescriptions in previous 180 days**; health service use history	Hospitalisation for hyperglycaemia	Remote AP	Current FGA (any)	*Insulin:* rate ratio 1.27 (0.75 to 2.12)	↔
						Oral GLD: rate ratio 1.31 (0.90 to 1.90)	↔
						None: rate ratio 3.43 (1.59 to 7.38)*	↑
					Current SGA (any)	*Insulin:* rate ratio 1.40 (1.06 to 1.85)*	↑
						Oral GLD: rate ratio 1.37 (1.12 to 1.67)*	↑
						None: rate ratio 2.37 (1.57 to 3.58)*	↑

Wake, 2016 [32]	Student's t-test/chi-squared test	Exposed and non-exposed people, matched for: birth year; sex; diabetes type; diagnosis date; BMI; smoking	Mean SBP (mmHg) ± SD	AP (≥ 12 months in total) No AP	130.7 ± 2.0* 134.5 ± 1.1	↓
			Mean DBP (mmHg) ± SD	AP (≥ 12 months in total) No AP	74.3 ± 1.2* 75.1 ± 0.7	↓
			Mean TC (mmol/l) ± SD	AP (≥ 12 months in total) No AP	4.2 ± 0.2* 4.3 ± 0.1	↓

*Denotes significant $P < 0.05$

†Results given for fully multivariable adjusted or matched models unless otherwise stated

‡No association refers to no statistically significant association at $P < 0.05$

§Time-dependent with AP prescribing measured in six month intervals

||Including: hypertension; dyslipidaemia; chronic pulmonary disease; chronic liver disease; malignancy; depression; dementia; anxiety disorders; alcohol-related disorders; substance use disorders

¶Including: angiotensin system acting agents; beta blockers; calcium channel blockers; diuretics; lipid-lowering agents; antithrombotic agents; non-steroidal anti-inflammatory drugs; anticonvulsants; lithium; ADs; benzodiazepines

#Drugs considered to have high metabolic risk included: clozapine; olanzapine, drugs considered to have intermediate metabolic risk included: paliperidone; quetiapine; risperidone; zotepine; chlorpromazine; chlorprothixene; clopentixol; clothiapine; loxapine; methotrimeprazine; perphenazine; pipotiazine; prochlorperazine; thioridazine; zuclopentixol, drugs considered to have low metabolic risk included: amisulpride; aripiprazole; sulpiride; ziprasidone; flupentixol; fluphenazine; haloperidol; pimozide; thiothixene; trifluoperazine

**Including: cytochrome P-450 2C9 inducers; cytochrome P-450 2C9 inhibitors; thiazide diuretics; corticosteroids for systemic use

AD: antidepressant; AP: antipsychotic; BMI: body mass index; CCI: Charlson Comorbidity Index; CI: confidence interval; CV: cardiovascular; DBP: diastolic blood pressure; FGA: first-generation antipsychotic; GLD: glucose lowering drug; HbA1c: glycated haemoglobin; HR: hazard ratio; SBP: systolic blood pressure; SGA: second-generation antipsychotic; TC: total cholesterol