Psychopharmacology for suicide prevention: a systematic review and meta-analysis

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General abstract

Background. Psychiatric disorders are associated with increased risk of suicide-related outcomes, and the impact of pharmacological treatments on these outcomes is uncertain. Although randomised controlled trials are the main approach to evaluate efficacy, they may not provide externally valid results for suicide prevention in psychiatric populations. Thus, I aimed to synthesise the evidence on the effect of psychotropic medications on suicide-related outcomes from observational studies.

Methods. In this systematic review and meta-analysis, I systematically searched Ovid (MEDLINE, Embase, APA PsychArticles, AMED, BIOSIS, Global Health, PsycINFO), and Web of Science Core Collection databases from inception to 8 December 2025 for pharmacoepidemiological and other observational studies on suicide-related outcomes in people treated with the main types of psychotropic medications: antidepressants, antipsychotics, mood stabilisers (including antiepileptics), and medications for anxiety (anxiolytics), attention deficit and hyperactivity disorder (ADHD), and substance use disorder (SUD). I included primary studies involving adults, who were prescribed medication and a comparison sample with the same diagnosis without prescribed medication (between-individual studies) or the same individuals during a non-prescription period (within-individual studies). I conducted separate analysis including only studies directly mentioning that the participants were diagnosed with common psychiatric diagnoses (schizophrenia spectrum disorders, bipolar disorder, depressive disorders, and personality disorders). Studies from selected samples and with uncommon medications were excluded. Outcomes were suicide attempts/self-harm and suicide mortality. I pooled adjusted effect sizes as odds ratios (OR), hazard ratios (HR) or risk ratios (RR) using random-effects models and assessed study quality using NOS and QUIPS tools. Study protocol was registered with PROSPERO, CRD42024515794.

Findings. Of 5653 records identified, 74 independent studies from 13 countries based on more than 6 million people (46.6% male estimated) met inclusion criteria. Across the main diagnostic categories and 70 individual medications examined, overall analysis found consistent associations with lower risks of suicide attempts for ADHD medication and second-generation antipsychotic clozapine. In specific diagnoses, associations with reducing risk of suicide mortality were found for second generation antipsychotics in schizophrenia spectrum disorders: clozapine, olanzapine; and also the first-generation antipsychotic zuclopenthixol. In bipolar disorder, lithium and valproic acid in bipolar

disorder were associated with lower suicide risks; in depression, associations with selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants were found. Benzodiazepines were associated with higher risk of suicide mortality in most diagnostic categories, except depression. The results for self-harm generally corresponded with the results for suicide mortality. There was some evidence for publication bias for lithium in bipolar disorder and clozapine in schizophrenia spectrum disorders, leading to more papers reporting lower risks of suicide-related outcomes. The risk of bias in the included studies was low to moderate, and certainty of evidence was moderate. Key gaps in research were outlined.

Interpretation. There is evidence that psychiatric diagnosis affects the observed associations between medication and suicide-related outcomes. Varying associations across different psychiatric disorders have been discovered, which implies the importance of accurate diagnosis for suicide prevention in clinical practice. The appropriate use of prescribed medications in people with high risks of suicide-related outcomes is an important part of suicide prevention strategies. Findings may be limited due to the observational nature of included studies, risk of residual confounding, high heterogeneity for some outcomes, and moderate quality of the evidence. The results are not causal. Future research should focus on examining medication in connection with diagnosis using targeted designs, such as target trial emulation and within-individual observational studies. More studies of substance use disorder and non-first choice medications are needed.

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Last, but not least, I must acknowledge my unofficial coauthor Gizmo the cat, who wrote a few important lines in various drafts of this thesis, and I specifically appreciate the depth and thoughtfulness of this one: “bnmgfm ftbitgjjnvm gtmiuh”.

This work is dedicated to everyone who has ever felt hopelessly trapped in their pain.

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List of abbreviations

ADHD – Attention deficit/hyperactivity disorder

CI – Confidence interval

DSM – Diagnostic and Statistical Manual of Mental Disorders

FDA – U.S. Food and Drug Administration

FGA – First-generation antipsychotics

GRADE – Grading of Recommendations Assessment, Development and Evaluation

HR – Hazard ratio

ICD – International Classification of Diseases

MAO – Monoamine oxidase inhibitors antidepressants

NaSSA – Noradrenergic and specific serotonergic antidepressants

NOS – Newcastle-Ottawa Scale for observational studies

OCD – Obsessive-compulsive disorder

OR – Odds ratio

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines

PTSD – Posttraumatic stress disorder

QUIPS – Quality in Prognosis Studies tool

RCT – Randomised controlled trials

RR – Risk ratio

SGA – Second-generation antipsychotics

SNRI – Serotonin-norepinephrine reuptake inhibitor antidepressants

SSRI – Selective serotonin reuptake inhibitor antidepressants

SUD – Substance use disorders

TCA – Tricyclic antidepressants

Chapter 1. Introduction

1.1 Overview

In this Chapter I present the context of this thesis. First, I provide the background by summarising previous studies and existing evidence gaps, then, I briefly overview the clinical context of psychopharmacological treatments. Finally, I frame the research questions, aims and objectives.

Chapter Two outlines methods. I briefly describe the general approach to the research questions and then provide more details into specific procedures that were carried out.

Chapter Three describes results. It consists of two parts: general results of the meta-analysis and the results of second part of the analysis, where I approached the data through the lens of diagnosis, creating a framework for data interpretation.

Chapter Four is the discussion. This thesis synthesises the data on several levels: I compare different suicide-related outcomes, diagnostic groups, medication categories, and study designs. Chapter Four is a detailed interpretation of those comparisons and findings.

Finally, I provide an overall conclusion of this study and highlight clinical and research implications.

Some of the results of this thesis were published in eClinicalMedicine, Kozhevnikova, Emilian et al. (2026).

1.2 Background

Suicide-related behaviour is a major public health concern. Although a large body of research has been published over the past decades, clinical guidelines for suicide prevention remain limited or ambiguous, particularly in terms of specific actions that healthcare providers in primary and inpatient care settings can take to reduce risk.

Prior research has consistently shown that psychiatric disorders are strongly associated with an increased risk of suicide-related outcomes. In depression, population-based studies have reported increased risks of suicide attempts during acute episodes and in partial remission (Holma, Melartin et al. 2010). In schizophrenia (Fazel, Wolf et al. 2014a) and bipolar disorder (Webb, Lichtenstein et al. 2014a), relative risks are more than 10-fold

higher for suicide attempts and suicide mortality, compared to the general population, confirmed using comparisons with non-affected siblings (Fazel, Wolf et al. 2014b, Webb, Lichtenstein et al. 2014b). Psychological autopsy investigations are consistent with these findings (Favril, Yu et al. 2022). Furthermore, several systematic reviews of longitudinal data have found associations between suicide-related outcomes and a range of other conditions, including ADHD (James, Lai et al. 2004), epilepsy (Bell, Gaitatzis et al. 2009, Wang, Zhang et al. 2023, Balazs, Kereszteny 2017), and substance use disorders (Levola, Laine et al. 2022). Consequently, suicide prevention strategies are targeted to these high-risk populations, which include pharmacological, psychological and social approaches.

Although trial evidence indicates that certain individual psychological treatments can prevent self-harm, and reducing access to means has strong and consistent observational evidence (Fazel, Runeson 2020), the evidence for the efficacy of different types of medication on suicide-related outcomes has been inconsistent. A recent synthesis of clinical trial evidence (Huang, Harris et al. 2022) found small increased risks of self-harm and suicide in general population for some selective serotonin reuptake inhibitors (SSRI) antidepressants and antipsychotics but it was moderately reduced for specific medications, such as the SSRI citalopram and antipsychotic paliperidone, and lithium reduced the risks of suicide mortality. Many other medications had uncertain findings due to low numbers of participants recruited to the trials. Moreover, due to selection criteria to participate in trials, randomised controlled trials (RCTs) do not recruit people at risk of suicidal behaviours and hence their results have limited generalisability to most clinical populations (Taipale, Schneider-Thoma et al. 2022). This may lead to the lower validity of the RCTs results in relation to suicide, as studied population and treated population can markedly differ.

Previous reviews on this topic were conducted on specific population groups, medication classes, diagnostic categories or synthesised the data from randomised controlled trials. One review with broader inclusion criteria (i.e., different populations, diagnostic categories, and study designs) (Wilkinson, Trujillo Diaz et al. 2022) limited observational studies to within-group analysis, and pooled trial and observational data together. Lithium and antipsychotic clozapine consistently showed a strong association with reduced risks of suicide-related outcomes (Hor, Taylor 2010, Wilkinson, Trujillo Diaz et al. 2022, Cipriani, Hawton et al. 2013, Nabi, Stansfeld et al. 2022, Huang, Harris et al. 2022), while findings for antidepressants and other antipsychotics varied between different population groups and diagnoses (Kishi, Matsunaga et al. 2016, Hor, Taylor 2010, Barbui, Esposito et al. 2009,

Wilkinson, Trujillo Diaz et al. 2022, Cipriani, Barbui et al. 2005, Hengartner, Amendola et al. 2021a, Huang, Harris et al. 2022, Hengartner, Amendola et al. 2021b).

To address this evidence gap, observational data are increasingly examined to assess the impact of pharmacological treatments on suicide-related outcomes. These studies apply pharmacoepidemiological methods on large populations (Porta 2014) to evaluate risk, examine medication effectiveness and adverse effects, assess patterns of medication use, and allow for comparison of findings from clinical trials with those on medication effects in clinical practice.

However, observational studies are often affected by confounding, which presents a challenge for causal interpretations. Baseline (time-invariant) factors, such as genetic predispositions or early life adversity, can differ between treatment groups. Time-varying factors, such as changes in symptom severity or life stressors, can also influence outcomes. Approaches to address this issue depend on the study design. In what are described as between-individual studies, rates of suicide-related outcomes are compared between individuals prescribed medications and those who are not. In these studies, depending on the research question, one needs to address baseline and sometimes time-varying confounding. Different methods can be used to account for measured baseline confounders, such as conditioning on them (regression adjustment) (Assimon 2021) and propensity score methods (Austin 2011). For measured time-varying confounders affected by past treatment, advanced statistical methods are required, specifically g-methods (Naimi, Cole et al. 2017). Despite accounting for measured confounders, residual confounding often cannot be definitively rule out ruled out. Using a different research design, called within-individual studies (also known as self-controlled or case-crossover studies), suicide rates in participants during the treatment period are compared to suicide rates during periods without treatment (Petersen, Douglas et al. 2016). This design inherently accounts for all time-invariant confounders (e.g., genetic risks and childhood environment). However, i) time-varying confounding is not typically addressed, ii) selection bias may occur, as included individuals in those studies need to have periods on and off medication, and iii) the findings rely on the length of the follow-up period (Lewer, Petersen et al. 2022).

Despite various sources of confounding in observational studies, they provide useful real-world evidence of medication effectiveness in clinical practice, and do not have some of the limitations inherent to trial data, such as samples that exclude some high-risk patient populations (e.g. those with a history of self-harm, expressing suicidal thoughts at the time

of trial recruitment, or who have other comorbidities) and typically small numbers of participants. Synthesising data from multiple high-quality observational studies with different methodological approaches (between- and with-individual epidemiological designs) can limit the risk of bias. This allows triangulation with other study designs to have accessible interpretation of all available evidence. There may be some RCT evidence that will form part of this triangulation.

1.3 Prescribing guidelines for psychopharmacological treatments

Below, I briefly outlined the current prescribing guidelines for psychotropic medications, as they provide a necessary context for the whole review. The mentioned diagnoses are clarified with the ICD-10 codes. As mentioned before, observational studies are conducted in the routine patients, who are usually treated according to those guidelines. It is important to take these standards into account when interpreting the synthesised data.

Antipsychotics are usually prescribed in schizophrenia and psychotic disorders (F20-29) and in bipolar disorder (F31) as mood stabilising medication. For schizophrenia, there is no established first-line medication, as they all have roughly similar effects and various adverse effects. It is stated that second generation antipsychotics have lower risks of developing problematic movement adverse effects than first generation antipsychotics (however, resulting in the metabolic consequences), and the second-generation antipsychotic clozapine is considered the most effective in relation to relapse prevention and symptom control. For bipolar disorder, there are various recommendations in different lines of treatment. To manage hypomania (F31.0), it is recommended to offer a first-generation antipsychotic haloperidol or second-generation antipsychotics olanzapine, quetiapine and risperidone. For managing depressive episodes (F31.3-4), second generation antipsychotic olanzapine in combination with SSRI fluoxetine is recommended (long-term maintenance treatment is recommended with lithium, see below). Antipsychotics are recommended to use in long-term care in bipolar disorder as a monotherapy or in combination with other medications. Prescribing two antipsychotics should be avoided except for treatment resistant schizophrenia (The American Psychiatric Association 2020, National Institute for Health and Care Excellence 2025b).

Antidepressants (National Institute of Mental Health (NIMH) 2023, National Institute for Health and Care Excellence 2025a, American Psychiatric Association 2010) are considered a first-line medication for various diagnoses, in particular, SSRIs. They are recommended for treating moderate to severe depression (F32.1-2), chronic anxiety (F40-41), panic disorder (F41.0), posttraumatic stress disorder (F43.1) and obsessive-compulsive disorder (F42). SSRI fluoxetine in combination with second generation antipsychotic olanzapine is one of the recommended schemes for initiating treatment of depressive episodes in bipolar disorder (F31.3-4). If first-line SSRIs are not effective in a patient with depression (F32-33), it is recommended to switch to serotonin-norepinephrine reuptake inhibitor (SNRI). If no first-line treatments are effective in a patient with depression, it may be recommended to switch to tricyclic antidepressant or monoamine oxidase inhibitors. These medications are

characterised by higher risk of developing adverse effects. There is evidence that MAOIs are the most effective in people with some disorders, such as atypical depression. Prescribing two antidepressants at the same time should be avoided where possible.

Antiepileptics (also referred to as antimanics and mood stabilisers) are prescribed in epilepsy (G40), chronic pain in adults, in bipolar disorder (F31) as mood stabilisers, and in anxiety disorders (F40-41) (National Institute for Health and Care Excellence 2025a). There is no first-line treatment for epilepsy (G40), as each case is different in aetiology and comorbidities. For bipolar disorder, antiepileptics lamotrigine and valproate are recommended in long-term secondary care of hypomania (F31.0) and bipolar depression (F31.3-4), if the other medications have proven ineffective. As of 2024, it is recommended against prescribing valproate, especially in female patients, except unless it has been deemed necessary by two independent doctors (National Institute for Health and Care Excellence 2025c).

Lithium is a first-line long-term treatment of bipolar disorder (F31) (American Psychiatric Association 2002). It is not recommended as a first-line treatment in short-term care in a first episode as it requires regular blood testing. If lithium monotherapy in long-term care has been proven ineffective then combination with an antipsychotic or another antiepileptic should be considered. In some cases, lithium can be considered in a unipolar depression, particularly to augment antidepressants and in more severe cases.

Benzodiazepines are the first-line treatment for acute anxiety but are recommended not be prescribed for longer than 4 weeks (National Institute for Health and Care Excellence 2025a, National Institute of Mental Health (NIMH) 2023). After 4 weeks the patient should switch to another medication, SSRIs are recommended in most cases but other medications can be considered (e.g. buspirone, beta-blockers).

1.4 Aims and objectives of the study

For this thesis, I aimed to synthesise the observational data on associations between commonly prescribed psychopharmacological treatments and suicide-related outcomes. To guide this, I developed three key research questions.

I. What are the associations between commonly prescribed psychotropic medications and suicide-related outcomes?
   I examined both suicide attempts (which includes self-harm) and suicide mortality. Since it was not possible, I did not analyse suicide attempts separately from non-suicidal self-harm. In this thesis, I use suicide attempts to refer to all non-fatal suicide-related outcomes, and suicide mortality to refer to deaths by suicide.

II. Do these associations differ across major psychiatric diagnoses?
   Many medications are prescribed across diagnostic categories, and their effects may vary depending on the underlying condition. For example, lamotrigine is used both as an antiepileptic and as a mood stabiliser in bipolar disorder. To explore this, I categorised studies by diagnosis after the initial analysis.

III. How do different observational study designs affect the findings?
   Observational studies handle confounding in different ways, either statistically (e.g. propensity scores) or through design (e.g. within-individual comparisons). I compared the results from within-individual and between-individual studies to understand how design choices may influence reported associations.

Chapter 2. Methods

2.1 Approach

Systematic reviews is one of the foundations of the evidence-based medicine (Higgins, Thomas et al. 2019, Khan, Zamora 2023). They identify studies on a certain topic, appraise their quality and summarise their results. Unlike other types of review (such as scoping literature reviews), systematic reviews allow replicability and ensure the quality and trustworthiness of obtained results. Broadly, the systematic review process has a strict methodological process that consists of the following stages: framing the research question(s), formulating inclusion and exclusion criteria, identifying relevant studies, screening studies, and synthesising the data. Here, I will briefly outline the process in general, highlighting important methodological nuances relevant to this work, and in the sections below I will describe research methods of this thesis in greater detail.

The research question in the systematic review of intervention studies usually consists of five key components: participants, interventions, comparators, outcomes, study design (PICOS). Based on the established PICOS, inclusion and exclusion criteria for the studies are specified. These components are also used to specify the search strategy to identify relevant studies. It is important to establish these parts of study methods prior to conducting the review and screening literature to prevent biases and the common practice is to prepare a study protocol. I prepared a protocol (available in Appendix A1) before carrying out the search and validated it with my supervisors.

After the literature search had been conducted, the identified studies are screened according to the inclusion/exclusion criteria. The screening is usually carried out by two or more reviewers independently. The participation of more than one reviewer is also a prevention measure for systemic biases. An agreement between reviewers is usually calculated and reported. Although it is common to have 100% of studies screened by several reviewers, this was not feasible due to the large number of pre-identified and then identified studies, and the independent double-screening was carried out on 20% of studies. However, my agreement with the second reviewer (who was Christina Emilian, a doctoral student in the psychiatry department with a background in psychiatric epidemiology – see more details below) was excellent (Cohen's Kappa 0.96), and despite this limitation, it was my view that this approach is acceptable.

After the final included studies had been identified, they undergo the quality assessment, and the data are extracted in a standardised form and then verified by another reviewer. Then all the available evidence is synthesised depending on the data and included studies' characteristics. Since the extracted estimates were comparable, it was possible to conduct meta-analysis.

Meta-analysis is a quantitative method of data synthesis, which results in a summary effect. Simply put, meta-analysis allows researchers to simulate a large study by combining the data from a number of smaller studies. Depending on the studies' characteristics and assumptions made prior to synthesis, a meta-analysis model assigns weighting coefficient to each study's estimates and then pool them to produce an average. There are two general statistical approaches to meta-analysis: fixed-effects and random-effects models. Fixed-effects model is based on assumption of existence of one "true" effect, which is being estimated in all the pooled studies. Random-effects model is based on assumption of existence of distribution of effects that combines between-study and random variability (Khan, Zamora 2023). Since this review synthesised observational data, I considered random-effects model more appropriate, assuming naturally occurring variability. To ensure comparability between pooled estimates, they should be converted into the same measure. In this study I reported the effect estimates in odds ratios (OR). I reported heterogeneity in the percentage of total variation across studies (I^2 statistic). Where possible, I also explored probable reasons for heterogeneity.

Meta-analysis allows further investigations to be carried out, such as sensitivity, subgroup, and publication bias analysis. Sensitivity analysis ensures that the pooled estimates are not affected by an exaggerated single study. Subgroup analysis provides detailed insight into how certain studies' characteristics impact the result. Ideally, a meta-regression can be carried out, where a linear regression is used to analyse subgroup differences. However, creating too small subgroups and carrying out meta-regression creates the risk of spurious results due to regression overfitting. I have decided to not conduct meta-regression as in the final analysis the groups were too small to ensure that the findings wouldn't be artificially statistically significant. Publication bias analysis identifies whether "missing" data, i.e. unpublished studies with null result, impacted the pooled estimates. Finally, meta-analysis allows the assessment of the certainty of evidence. Using forest plots and heterogeneity characteristics of the pooled results, I could draw conclusions on the consistency, precision and directness of results.

Alternative approaches (i.e., summarising effect estimates or combining P values) would provide limited information and would not account for differences in the sizes of the studies. Vote counting, where every study counts as a vote for a certain effect, was not considered, because this procedure would count underpowered studies with no statistical significance as independent votes. Meta-analysis allowed me to synthesise the data from underpowered studies and come to the most reliable results.

2.2 Search Strategy

I followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) (Page, McKenzie et al. 2021). Several databases were searched: Ovid (MEDLINE, Embase, APAPsychArticles, AMED, BIOSIS, Global Health, PsycINFO), and Web of Science Core Collection, along with the manual search on Google Scholar. No publication date or language restrictions were set. The same keywords were used for all databases for medications and study designs (see Appendix A2). I used individual names of medications from Stahl's Prescriber's guideline (Stahl 2024) and broad medication classes (i.e. antipsychotics, antidepressants, anxiolytics, antiepileptics, and ADHD medications). Including specific medications may seem excessive, but it ensured that no studies on the medications that interest us are missed due to the indexing inaccuracies.

I excluded some newer medications from the search, including ketamine or psilocybin, due to their role in treatment-resistant and specific conditions, such as cancer, which may create a selection bias and lower comparability to more conventional treatment studies. The search was updated in December 2025. The protocol was registered with Prospero (ID CRD42024515794) and amended with study changes (see Appendix A1).

2.3 Study Eligibility

I carried out both abstract and full-text screening. A second reviewer, doctoral student Christina Emilian, independently screened a random 20% of records at both stages. All disagreements between screening decisions were resolved in discussion with my supervisors. The inter-rater reliability (Cohen's Kappa) between us was very high – 0.96, which allowed us to not double-screen the whole sample of full text reports.

Outcomes included the following for suicide-related outcomes: suicide mortality, suicide attempt, and intentional self-harm, covered by ICD-10 codes X60-84 and Y10-34, and their equivalents in ICD-8/9 (World Health Organization 2022). I have excluded suicidal ideation (which is typically measured by psychometric tests such as the Columbia-Suicide Severity Rating Scale), the collection of which relies on self-reported data. The focus of this review was self-harm and suicide, which can be more reliably collected from healthcare and mortality registries and aligns with national public health and health service priorities.

I included studies with the following designs: prospective and retrospective cohort studies (including effectiveness studies), case-control, and case-crossover studies. Cross-sectional designs and case reports were excluded. My focus was to identify studies investigating the effects of medication treatment on suicide-related outcomes. The medications examined were antidepressants, anti-anxiety medications (anxiolytics), mood stabilisers (including antiepileptics), antipsychotics, and attention deficit and hyperactivity disorder (ADHD) medications.

I have excluded papers focused on suicide-related outcomes as a side effect (i.e. after hours or days), since suicide-related outcomes as adverse events are rare (Stübner, Grohmann et al. 2018), and unlikely to be reported in observational studies (which rely on healthcare registers, where symptoms are typically not routinely reported) and I wanted to investigate medium and longer term effects. Inclusion of shorter follow-up periods would lead to potential confounding, where suicidal-related outcomes would be related to the condition rather than medication. I did not exclude non-suicidal self-harm from suicide attempt category due to diagnostic challenges in separating it from suicide attempt (Hooley, Fox et al. 2020). Instead, I included all self-harm acts as an outcome of interest and categorised them based on fatality.

I included observational studies conducted in the community setting samples and excluded studies conducted exclusively in one age group (such as children), and in selected populations (e.g. people in prison, inpatient-only samples, those who are physically ill). If a study was conducted in two different populations with different diagnoses, the data from such study were separately synthesised in both relevant categories.

2.4 Data Extraction and Quality Assessment

I extracted data using a standardised form, which included study and population characteristics and the statistic used to estimate the medication effects. Second reviewer and I then independently assessed study quality using the Newcastle-Ottawa Scale (NOS) for observational studies (Deeks, Dinnes et al. 2003) and the Quality in Prognosis Studies (QUIPS) tool (Grooten, Tseli et al. 2019). The data was independently verified and assessed by the second reviewer and all disagreements were resolved in discussion with my supervisors. To assess the certainty of evidence for the findings I also applied the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (Brennan, Johnston 2023, The GRADE Working Group 2024) framework.

2.5 Data Synthesis

2.5.1 Meta-analysis of Overall Results

I conducted random-effects meta-analyses to calculate pooled effect sizes (odds ratios) for all suicide-related outcomes and for suicide mortality, for medications investigated in two or more studies. Where possible, I excluded both crude and adjusted effect sizes. If in the included studies the adjustments were similar, those were used for pooling. In the majority of studies, variables that were adjusted for were similar: age, gender, clinical history, socio-economic background, etc, which allowed for pooling confounding-controlled data. Where raw data were not available, I used Wald-type confidence intervals to convert reported estimates to a standardised effect size (Higgins, Li et al. 2024). Due to the rarity of outcomes investigated, I could assume that hazard ratios, odds ratios and risk ratios could be considered as broadly equivalent (Cummings 2009), which is statistically appropriate for the outcomes that occur in less than 10% of study population (George, Stead et al., Zhang, Yu 1998), and in this review the mean outcome rate was 8.9%.

I synthesised the data for all medications separately, due to trial data previously reporting different effects of individual medications within one medication class (Huang, Harris et al. 2022); if only medication class was mentioned in the included studies, those were included separately and I referred to them as unspecified. In some cases, a single study provided multiple comparisons (e.g., different augmentation strategies). In these cases, I used a multilevel random-effects model to account for clustering within study. Study ID was included as a grouping factor to avoid counting control groups multiple times.

I conducted all analyses in R version 4.3.1 using the “Metafor” package, and all plots were created using the “ggplot2” package. Data analysis was conducted using the ‘Metafor’ and data were visualised using the ‘ggplot2’ packages in R version 4.3.1.

SNRI antidepressants (Venlafaxine, Nefazodone), and noradrenergic and specific serotonergic antidepressants (NaSSA; mirtazapine) were analysed as one category because they were reported together in one included investigation (Sondergård, Lopez et al. 2007). The data for both outcomes is visualised together for better interpretability.

2.5.2 Meta-analysis by Diagnostic Category

To explore diagnostic-specific effects, I repeated the meta-analysis following the procedure described above using only studies that reported outcomes within defined diagnostic groups. Studies that did not specify the diagnosis were excluded from this analysis. For example, a study that analysed clozapine effects on suicide-related outcomes in bipolar disorder and schizophrenia (Lee, Lim et al. 2025) was included in both analyses with two corresponding diagnosis samples separately. If it was impossible to separate the disorder samples, the study was excluded from the analysis on this stage.

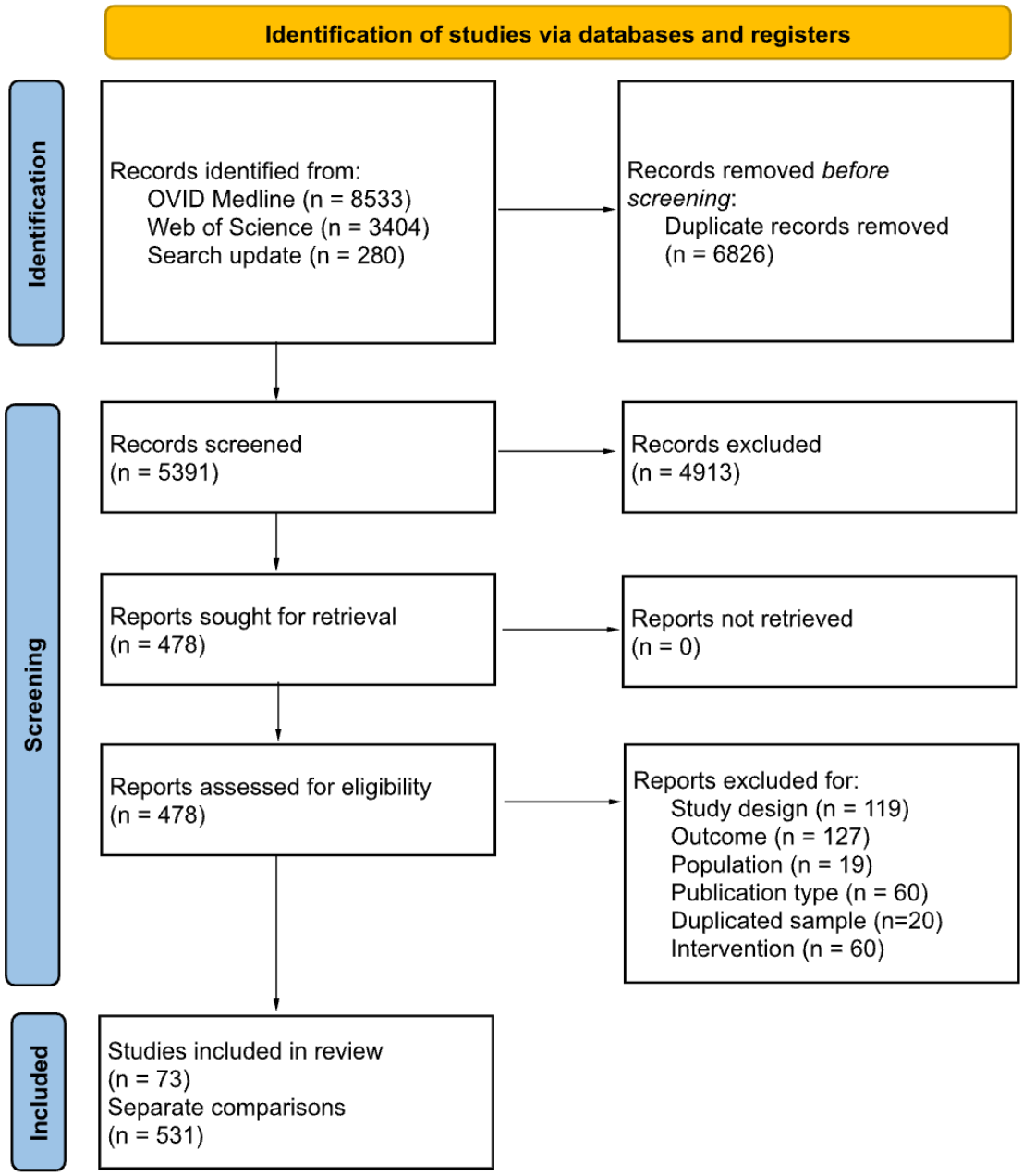
2.6 Sensitivity analysis and publication bias

I conducted a “leave-one-out” sensitivity analysis and the funnel plot publication bias analyses for the results where the number of medication studies were ≥5. Since statistical testing for publication bias is recommended to be only conducted in the analyses with ten or more included studies (Deeks, Higgins et al. 2024), I could not further investigate potential publication bias for most of the results. For the results with number of studies of 10 and more, I used the Egger’s test to explore potential small-study effect (Egger, Smith et al. 1997) and the trim-and-fill analysis (Shi, Lin 2019) to assess publication bias more thoroughly and to ensure that high heterogeneity would not affect the accuracy of Egger’s test.

Chapter 3. Results

3.1 Overall results

Figure 1. PRISMA flowchart of the review.



73 studies were included with 531 comparisons of a medication with no-use (Figure 1). The overview table of all included studies is available at the end of Results section, and all of studies excluded on the full-text screening stages are presented in the Appendix (A5).

3.1.1 Study characteristics

Table 1. Summary of characteristics of all included studies, by the medication group. * – unspecified medications from this group count as one. ** – within-individual studies participants are only counted as exposed.

Medication group	Number of studies (comparisons)	Number of participants (exposed**)	Mean male %	Mean participant age, years	Mean follow-up time, weeks (years)	Number of medications studied	Number of countries
Antidepressants	36 (125)	1,904,513 (846,915)	42.7	40.1	298.0 (5.7)	25	10
Antipsychotics	27 (193)	4,109,769 (906,820)	46.9	40.5	399.8 (7.7)	24	12
Antiepileptics (including in epilepsy)	24 (87)	1,208,519 (391,010)	47.5	41.8	375.3 (7.2)	21	12
Lithium (or unspecified mood stabiliser)	19 (34)	368,389 (216,652)	40.5	40.7	426.0 (8.2)	2*	8
Benzodiazepines (or unspecified anxiety medication)	20 (35)	3,230,539 (642,463)	52.9	44.8	209.3 (4.0)	2*	13
ADHD medication	8 (17)	4,754,592 (4,522,033)	44.9	33.9	225.3 (4.3)	6	4
SUD medication[1]	2 (6)	69,531 (50,583)	67.1	33.3	286.0 (5.5)	5	3

The summary of the characteristics of the studies included in the review is presented in Table 1. The total number of participants was 13,122,596 people (mean age 40.1 years; 47.2% of male). 90 different medications were examined in the included studies. The most evidence was found for antidepressants and antipsychotics (Table 1). ADHD and SUD medications data were insufficient to conduct meta-analysis; hence the results were synthesised narratively.

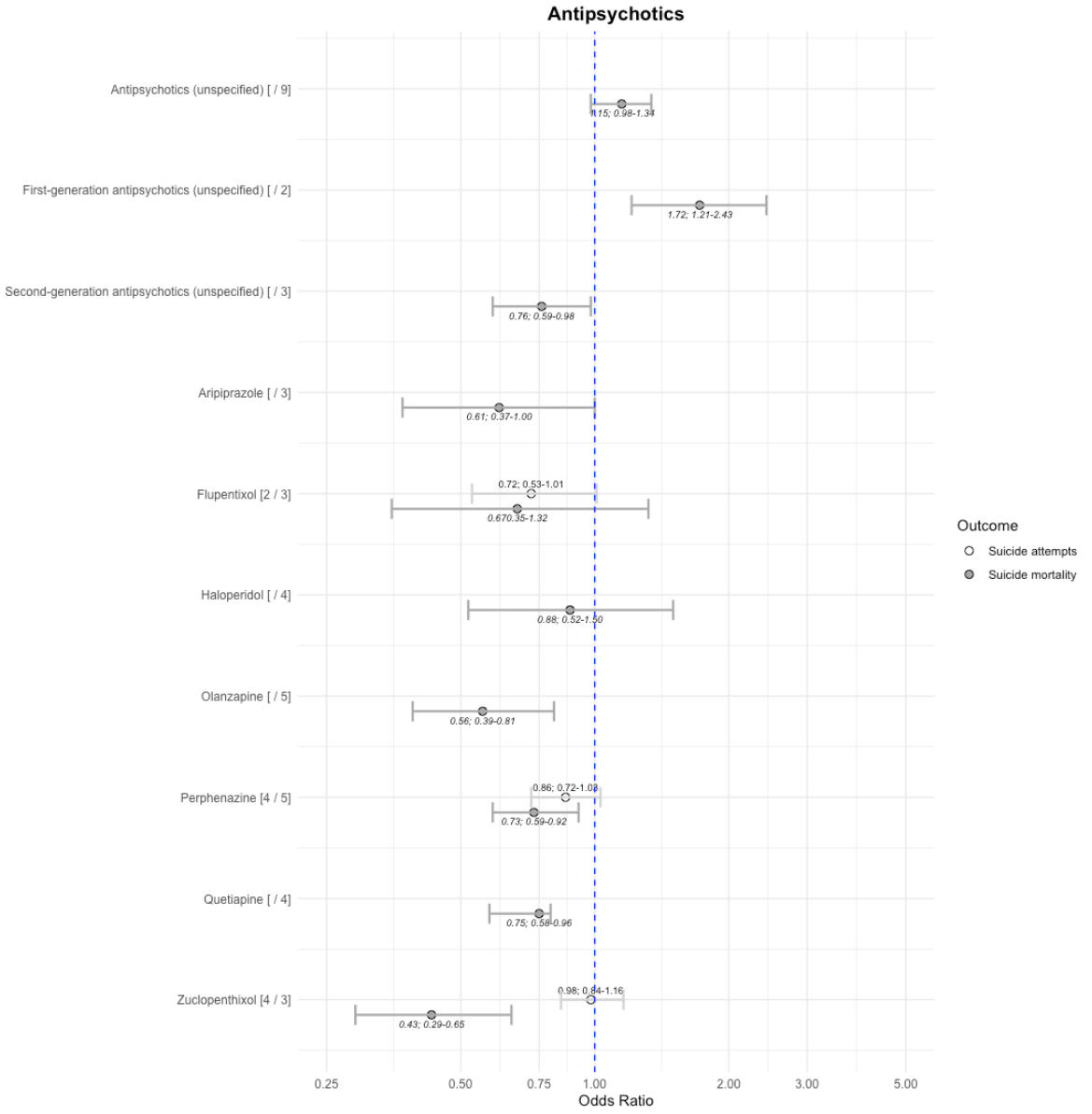
In the first part of the thesis, the results are presented based on all psychiatric populations, irrespective of diagnosis. They are reported for suicide attempts (including non-suicidal self-harm) and suicide mortality separately. First, I present the results for between-individual studies and then all the findings from within-individual studies. For the medications that did not have enough data to conduct meta-analysis, I synthesised all the

[1] Opioid agonists, including methadone; acamprosate, buprenorphine, naltrexone.

results narratively. In the second part of the thesis (3.2 onwards), I examine these findings separately by psychiatric diagnosis.

3.1.2 Antipsychotics

Figure 2. Risk of suicide-related outcomes in antipsychotics using between-individual study design[2].



Most of the second-generation antipsychotics were associated with lower risks of suicide mortality. Additionally, second-generation antipsychotics clozapine (k = 8; OR = 0.48; 0.30-

[2] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity $I^2 < 50\%$.

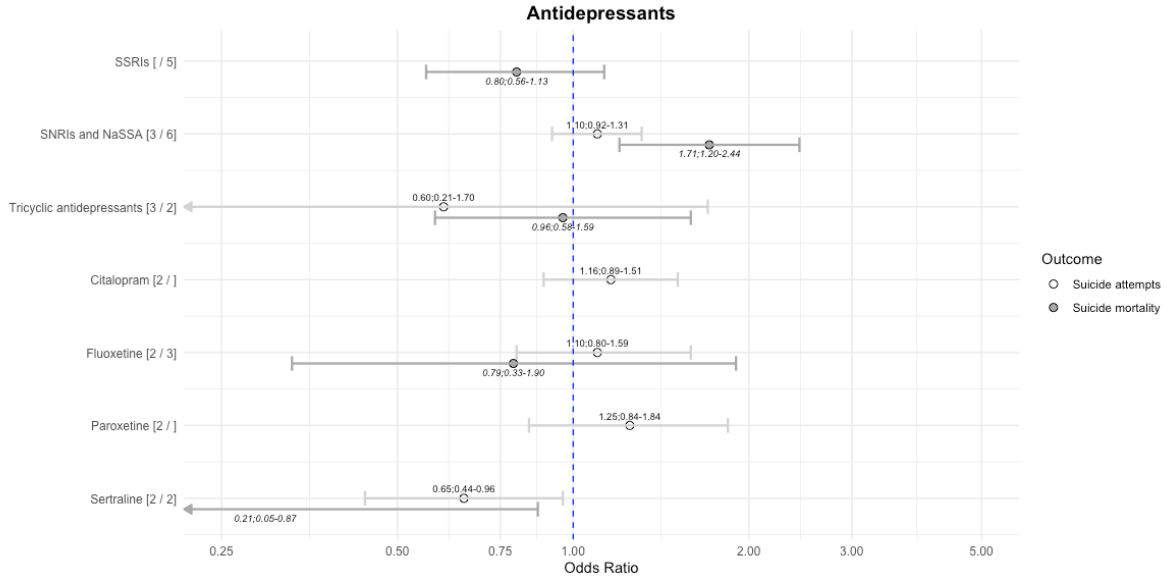
0.76; I^2 = 61%) and risperidone (k = 4; OR = 0.57; 0.37-0.87; I^2 = 66%) were associated with lower risks of suicide mortality with higher heterogeneity.

For suicide attempts investigated in between-individual studies, there were no statistically significant associations for antipsychotics in any direction that would reach heterogeneity below 50%. However, first-generation antipsychotic flupentixol and second-generation antipsychotic perphenazine showed results with 95% confidence intervals close to statistically significant associations with lower risks of suicide attempts. Second-generation antipsychotic risperidone was associated with lower risks of suicide attempts with higher heterogeneity (k = 5; OR = 0.67; 0.55-0.82; I^2 = 64%). Additionally, second-generation antipsychotic clozapine (k = 7; OR = 0.62; 0.37-1.02; I^2 = 88%) showed result close to being statistically significant with high heterogeneity.

For suicide attempts, investigated in within-individual studies, second-generation antipsychotic clozapine was associated with lower risks (k = 3; OR = 0.66; 0.53-0.82; I^2 = 0%). First-generation antipsychotic haloperidol was associated with higher risks (k = 3; OR = 1.53; 1.18-1.98; I^2 = 0%), and second-generation antipsychotics aripiprazole (k=3; OR = 1.40; 1.19-1.65; I^2 = 0%), olanzapine (k = 3; OR = 1.23; 1.08-1.40; I^2 = 0%), and first-generation antipsychotic zuclopenthixol (k = 3; OR = 1.53; 1.13-2.09; I^2 = 32%) were also associated with higher risks of suicide attempt in within-individual studies.

3.1.3 Antidepressants

Figure 3. Risk of suicide-related outcomes in antidepressants using between-individual study design[3].



SSRI sertraline was associated with lower risks of suicide mortality, while SNRI and NaSSA antidepressants were associated with higher risks of suicide mortality.

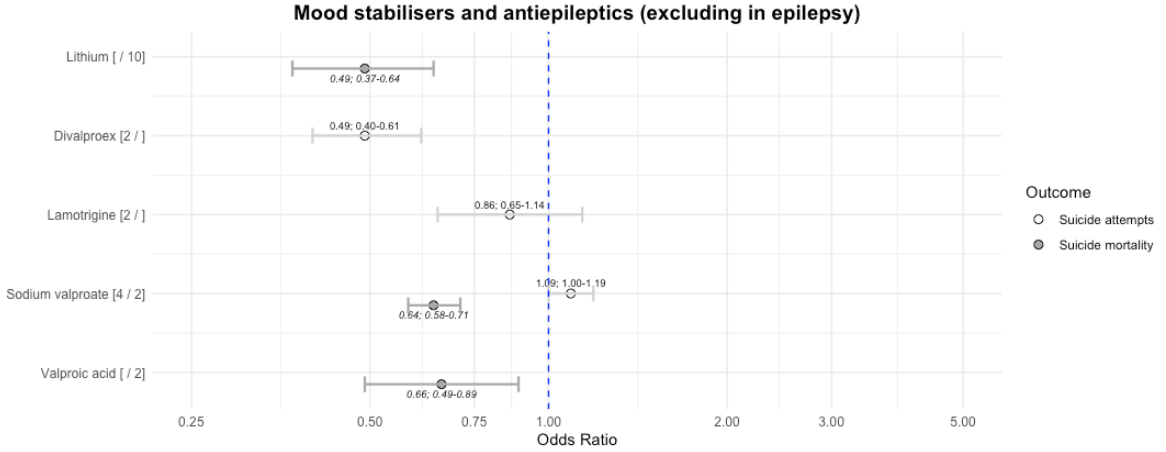
For suicide attempts investigated in between-individual studies, sertraline was also associated with lower risks.

For suicide attempts studied in within-individual studies, SNRI and NaSSA (k = 2; OR = 1.30; 1.14-1.49; I^2 = 8%) and SSRI duloxetine (k = 2; OR = 1.39; 1.17-1.63; I^2 = 88%) were associated with higher risks of suicide-related outcomes.

[3] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity I^2 < 50%. SSRIs – selective serotonin reuptake inhibitors. SNRI – Serotonin-norepinephrine reuptake inhibitor. NaSSA – noradrenergic and specific serotonergic antidepressants.

3.1.4 Mood stabilisers and antiepileptics

Figure 4. Risk of suicide-related outcomes in mood stabilisers and antiepileptics (excluding epilepsy diagnosis) using between-individual study design[4].



I have investigated antiepileptics separately in all diagnoses, excluding epilepsy (Figure 4). Epilepsy was analysed separately, and the results are presented in the Section 3.2. This decision ultimately has led to the existence of the whole section of separate analyses in different diagnostic categories, although initially I separated it because epilepsy is not a solely psychiatric diagnosis, and antiepileptics, while being anti-seizure medications, serve a very different purpose in most psychiatric diagnoses, being mood stabilisers.

For suicide mortality, lithium, sodium valproate, and valproic acid (were associated with lower risks of suicide death. When analysed together, valproates showed similar result (k = 4; OR = 0.65; 0.59-0.71; I^2 = 0%). The initial separation of valproates was made since in some countries valproates are indicated for different diagnoses (Delage, Palayer et al. 2023). Additionally, unspecified mood stabilisers were also associated with lower risks of suicide mortality (k = 4; OR = 0.75; 0.59-0.95; I^2 = 58%) with higher heterogeneity.

For suicide attempts investigated in between-individual studies, valproate derivative divalproex was associated with lower risks of suicide attempts, while sodium valproate was associated with higher risks.

For suicide attempts investigated in within-individual studies, only lithium was associated with lower risks of outcomes (k=7; OR=0.60; 0.44-0.81; I^2=82%) with higher heterogeneity.

[4] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity $I^2 < 50$.

3.1.5 ADHD, SUD, and anti-anxiety medications

ADHD medications were presented as psychostimulants (mostly methylphenidate). Psychostimulants were associated with lower risks of suicide mortality (k = 2; OR = 0.57; 0.36-0.91; I^2 = 8%) and with lower risks of suicide attempts in both between-individual studies (k = 2; OR = 0.69; 0.66-0.72; I^2 = 0%) and within-individual studies (k = 4; OR = 0.66; 0.54-0.81; I^2 = 10%).

SUD medications were investigated in two studies. In the within-individual study (Padmanathan, Forbes et al. 2022) unspecified opioid agonists therapy was associated with lower risks of suicide attempts (OR = 0.37; 0.31-0.43). Furthermore, methadone was associated with lower risks of suicide attempt (HR = 0.60; 0.40-0.88) in the within-individual analysis (Molero, Zetterqvist et al. 2018).

Anti-anxiety medications (anxiolytics) were either presented as the group of unspecified medications or as benzodiazepines. Benzodiazepines were associated with higher risks of suicide mortality (k = 9; OR=2.14; 1.49-3.06; I^2 = 42%) and, despite higher heterogeneity, with higher risks of suicide attempts in both between-individual studies (k = 5; OR = 2.94; 1.31-6.60; I^2 = 85%) and within-individual studies (k = 3; OR = 2.12; 1.51-2.97; I^2 = 98%). Unspecified anxiolytics were associated only with higher risks of suicide attempts in within-individual studies (k = 2; OR = 1.42; 1.06-1.90; I^2 = 77%) with higher heterogeneity.

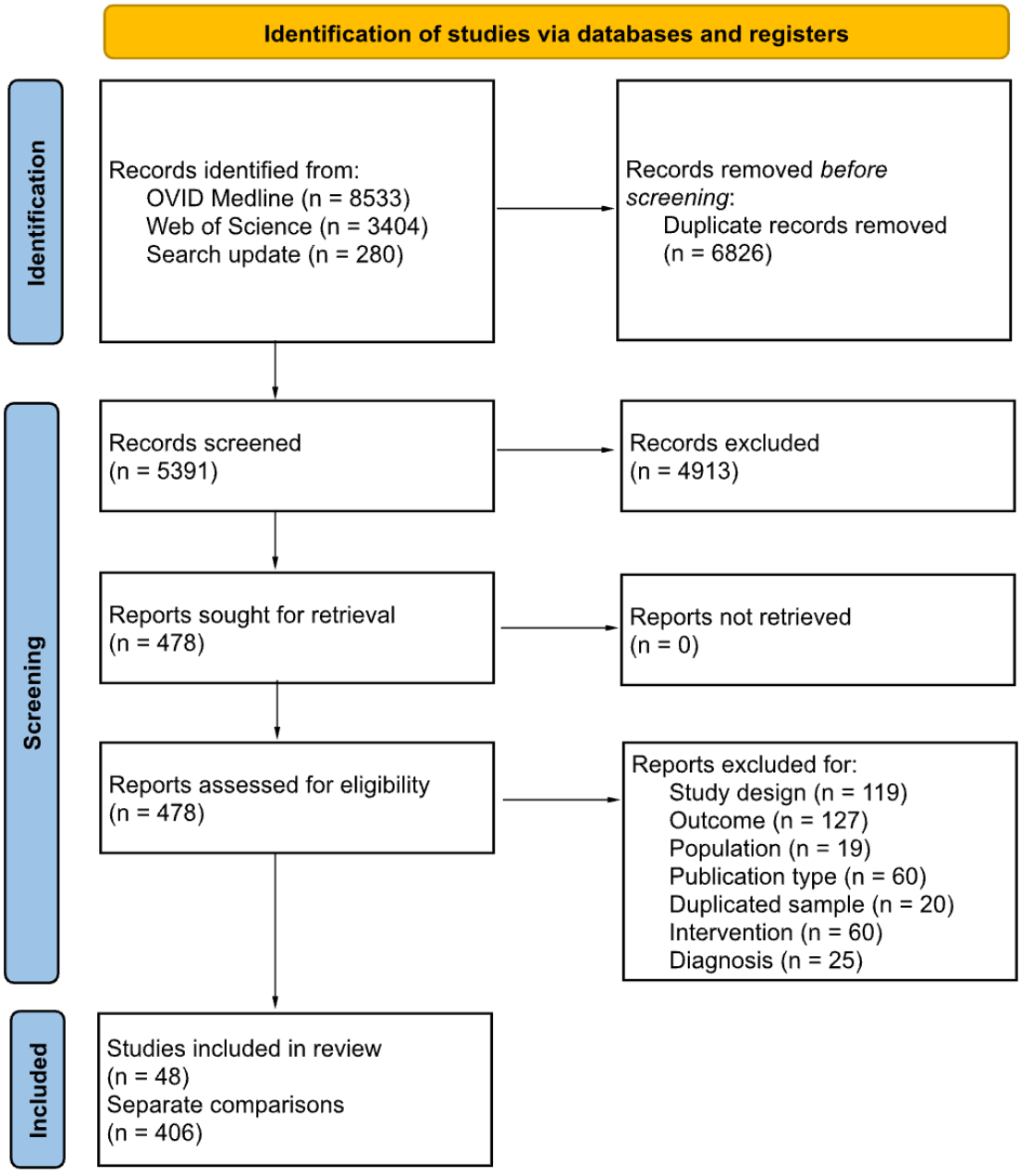
3.1.6 Summary

Overall, the results of this meta-analysis were characterised by high heterogeneity and low to moderate certainty of evidence, mostly due to imprecision, and inconsistency. Overall, only second-generation antipsychotic clozapine and psychostimulants were consistently associated with lower risks of suicide-related outcomes across all types of study designs and outcomes, and benzodiazepines were consistently associated with higher risks of suicide-related outcomes.

However, during data extraction, I have noticed potential patterns: some medications, such as antipsychotics, seemed to have different effects in schizophrenia spectrum disorders and in bipolar disorder, when used as mood stabilisers. Additionally, as discussed above, I have initially excluded epilepsy as neuropsychiatric disorder. This observation led me to further explore potential differences in various diagnostic categories. The results are presented below in the Section 3.2.

3.2 Results by diagnosis

Figure 5. PRISMA flowchart for the review of studies that reported diagnosis.



3.2.1 Study characteristics

The characteristics of studies included on this stage are presented in Table 2. Overall, 48 studies were included with 406 comparisons of medication with no medication (Figure 9). The total number of participants was 6,489,573 people (estimated mean age 41.6 years;

estimated 46.6% male). The full results of all pooled results with the heterogeneity I^2 are available in Supplementary Materials.

Table 2. Characteristics of pharmacological studies examining suicide outcomes by psychiatric disorder. * – the proportion of male participants is estimated, as not all studies reported these data. ** – within-individual studies participants are only counted as exposed.

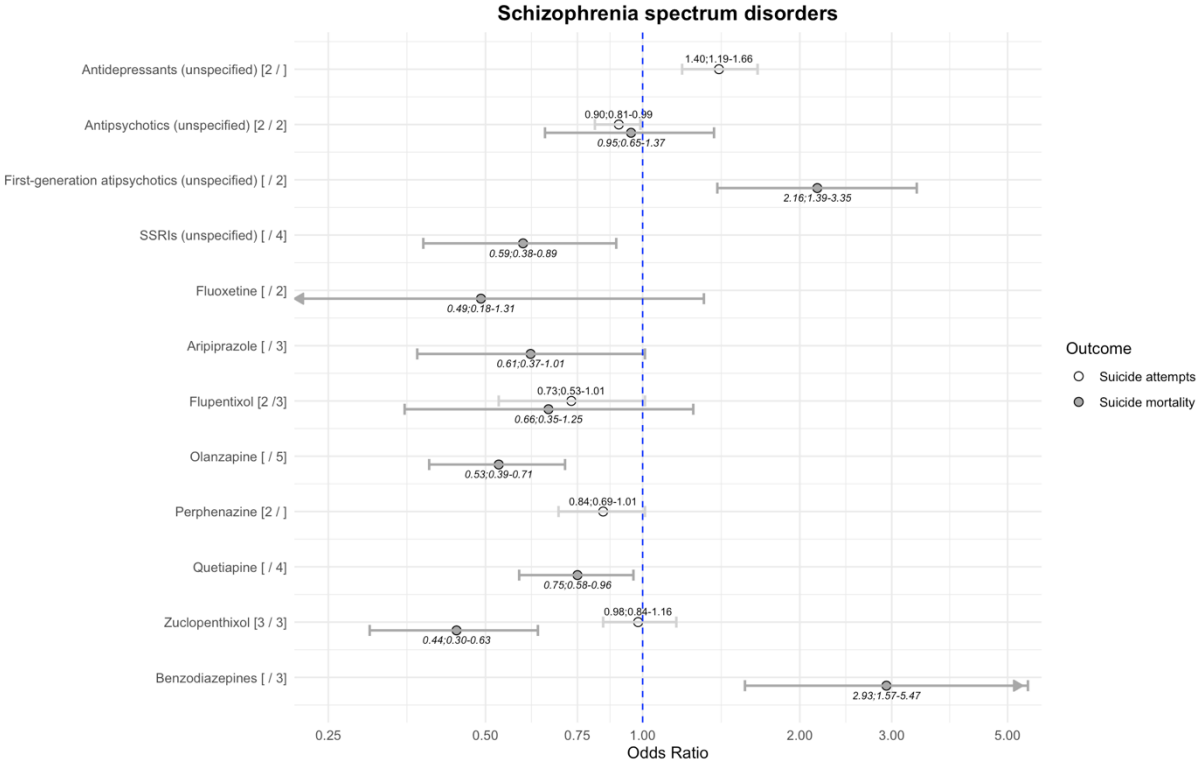
Diagnosis	Number of studies (comparisons)	Number of participants (exposed**)	Mean male %*	Mean follow-up time, weeks (years)	Mean participant age, years	Number of medications studied	Number of countries
Schizophrenia spectrum disorders	19 (195)	1,486,136 (701,287)	54.5	384.7 (7.4)	40.8	44	11
Bipolar disorder	17 (107)	768,845 (365,427)	42.5	454.9 (8.7)	41.6	32	9
Depression	14 (53)	348,992 (186,229)	41.6	140.8 (2.7)	40.0	24	6
Personality disorders	5 (51)	454,484 (307,289)	19.0	357.7 (6.9)	29.7	37	3

Seventy individual medications were examined, with the highest number in schizophrenia spectrum disorders and bipolar disorder (Table 2). In personality disorder, it was mostly focused on borderline (emotionally unstable) personality disorder, where there were a lower mean age and proportion of men compared with other diagnostic groups. There were not enough studies for ADHD and substance use disorder to include these diagnoses in this section, due to only one eligible study for each medication reported.

Results are presented for suicide attempts and suicide mortality separately. First, I present quantitative results for between-individual studies, and then present findings from within-individual studies.

3.2.2 Schizophrenia spectrum disorders

Figure 6. Risk of suicide-related outcomes in schizophrenia spectrum disorders using between-individual study designs[5].



For suicide mortality, most second-generation antipsychotics were associated with lower risks. First-generation antipsychotics as a class were associated with elevated risks (Figure 6). Unspecified antipsychotics were associated with lower risk of suicide attempts. In relation to individual medications, there was weak evidence for flupentixol and perphenazine being associated with lower risk of suicide attempts. Antidepressants were associated with higher risk of suicide attempts.

Benzodiazepines were associated with higher risks of both outcomes. Risperidone was associated with lower risks of both suicide attempts (k = 3; OR = 0.61; 0.52-0.72; I^2 = 57%) and suicide mortality (k = 4; OR = 0.55; 0.38-0.79; I^2 = 64%) with high heterogeneity. Olanzapine was associated with lower risks of suicide attempts (k = 4; OR = 0.76; 0.60-0.98; I^2 = 84%) with high heterogeneity, and clozapine was associated with lower risks of suicide mortality (k = 7; OR = 0.40; 0.26-0.60; I^2 = 60%) with high heterogeneity. Overall,

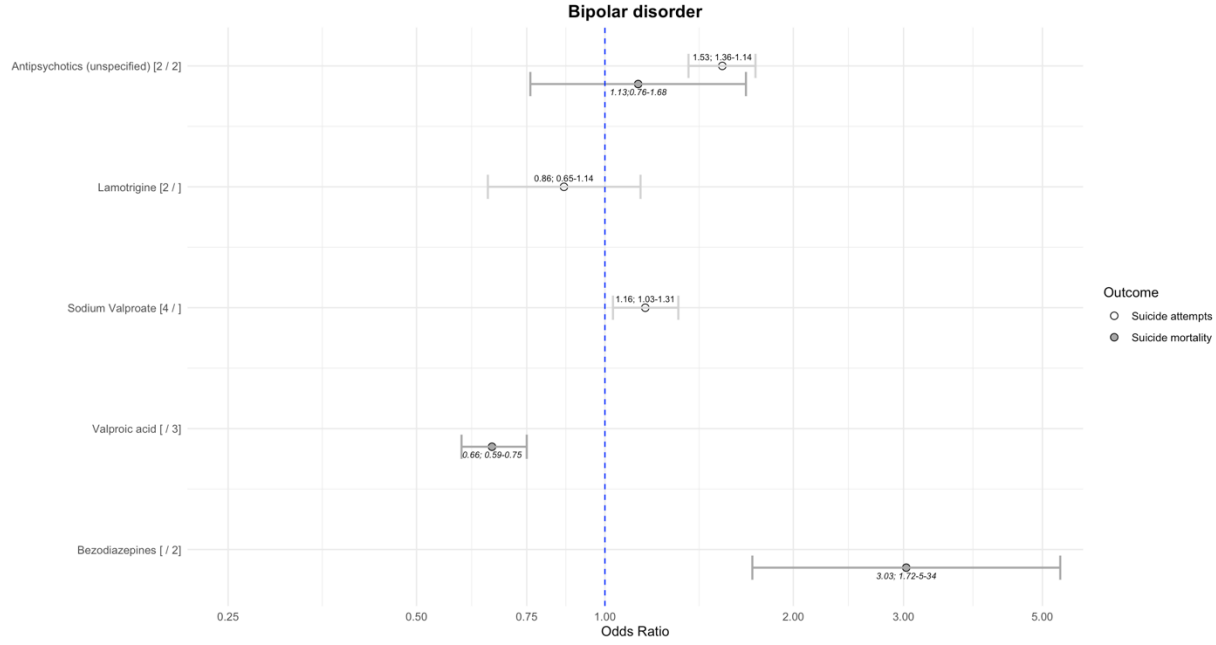
[5] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity I^2 < 50%. SSRIs – selective serotonin reuptake inhibitors.

there was consistency in the direction of effects if the outcome was suicide attempt or suicide mortality.

I identified one within-individual study (Taipale, Lähteenvuo et al. 2021) based on Nordic cohorts. Second-generation antipsychotics were mostly associated with lower risk, whereas first-generation antipsychotics showed elevated risk of suicide attempts. There was also one study each for antiepileptic/mood stabiliser gabapentin (Gibbons, Hur et al. 2010) and ADHD medication methylphenidate (Rohde, Salagre et al. 2021), which did not show associations with suicide-related outcomes in any direction ($p > 0.05$).

3.2.3 Bipolar disorder

Figure 7. Risk of suicide-related outcomes in bipolar disorder using between-individual study design[6].



Unspecified antipsychotics and sodium valproate were associated with higher risk of suicide attempts (Figure 7). Valproic acid was associated with lower risks of suicide mortality, and benzodiazepines were associated with elevated risks of suicide mortality. Unspecified mood stabilisers (k = 2; OR = 0.68; 0.56-0.83; I^2 = 61%) and lithium (k = 6; OR = 0.38; 0.28-0.50; I^2 = 67%) were associated with lower risks of suicide mortality.

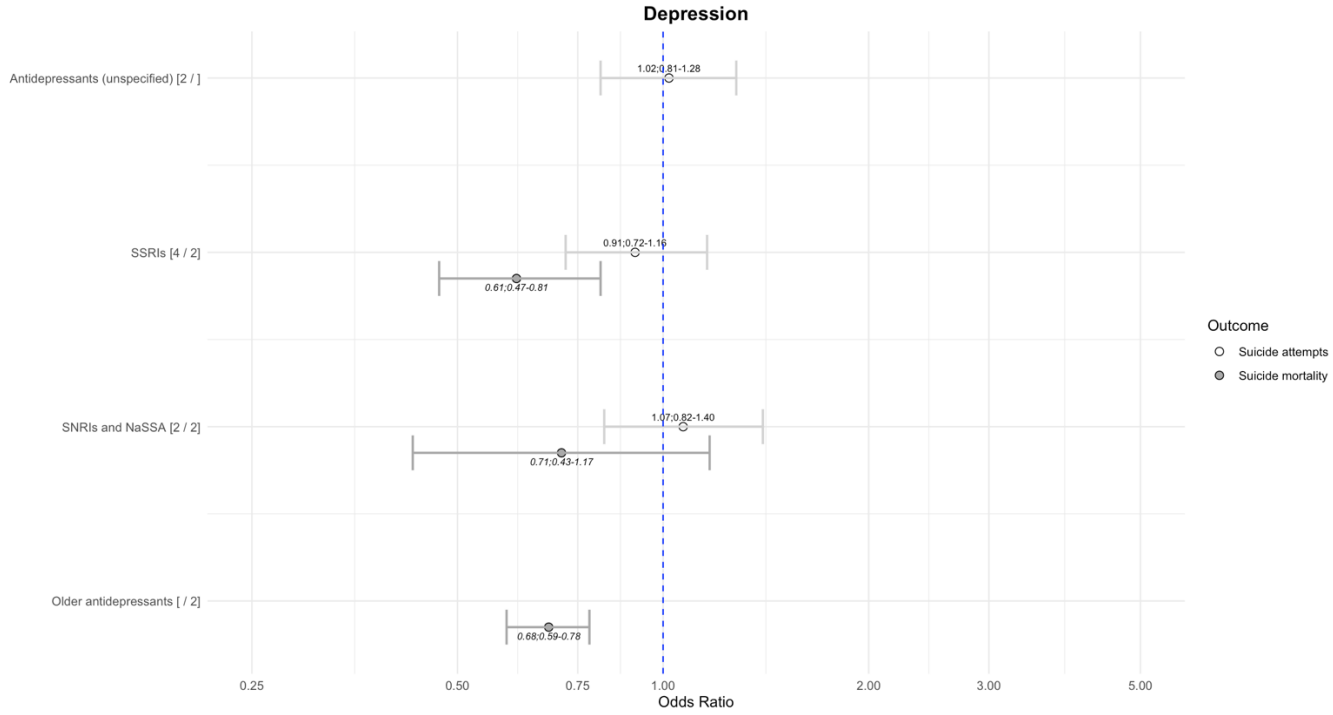
For within-individual studies, lithium was associated with lower risk of suicide attempts (k = 6; OR = 0.60; 0.44-0.82; I^2 = 92%). Results for topiramate did not reach statistical

[6] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity $I^2 < 50\%$.

significance (k = 2; OR = 0.60; 0.26-1.40; I^2 = 0%). Findings for other medications showed no strong association with suicide-related outcomes and had high heterogeneity.

3.2.4 Depression

Figure 8. Risk of suicide-related outcomes in depression using between-individual study design[7].



For suicide mortality, SSRIs and older antidepressants (i.e., tricyclic antidepressants) were associated with reduced risks of suicide (Figure 8). Findings for other medications showed no strong association with suicide-related outcomes and had high heterogeneity.

For suicide attempts, there was no strong evidence of association in any direction for antidepressants. Antipsychotics as a class were associated with higher risk of suicide attempts (k = 3; OR = 2.43; 1.37-4.33; I^2 = 72%), but with high heterogeneity.

There were three within-individual studies. One study (Rohde, Brink et al. 2020) found that methylphenidate was associated with lower risk of suicide-related outcomes in depression (OR=0.45; 95% CI=0.29-0.69). Other investigations showed lower risks of suicide for lithium (Leon, Fiedorowicz et al. 2014) and gabapentin (Gibbons, Hur et al. 2010).

[7] The numbers after the medication name reflect the number of comparisons in suicide attempts and suicide mortality. All results visualised have heterogeneity I^2 < 50%. SSRIs – selective serotonin reuptake inhibitors. SNRI – Serotonin-norepinephrine reuptake inhibitor. NaSSA – noradrenergic and specific serotonergic antidepressants.

3.2.5 Borderline and other personality disorders

In between-individual studies, benzodiazepines were associated with elevated risk of suicide-related outcomes in personality disorders (with low/moderate heterogeneity). There was a link between benzodiazepines and suicide mortality (k=2; OR=4.29; 3.28-5.60; I^2=0%).

In within-individual studies, methylphenidate (Rohde, Salagre et al. 2021) was associated with lower risk of suicide-related outcomes. Antipsychotics analysed in men and women separately (Herttua, Crawford et al. 2022) were also associated with lower risk, while in the same study they were associated with higher risk in between-individual analysis. One of the studies (Hayes, Hardoon et al. 2022) analysed suicide-related outcomes each month a year before and after quetiapine initiation. In comparison to 12 months before treatment, quetiapine was associated with higher risk of suicide-related outcomes, but there is evidence that suicide risk was growing for a year and then had a two-fold decrease in the first month after starting quetiapine. In another study (Lieslehto, Tiihonen et al. 2023), antidepressants and antipsychotics were mostly associated with elevated risk of suicide-related outcomes, except for antidepressant vortioxetine which was linked with lower risk. Methylphenidate and lisdexamfetamine were also associated with lower risk of suicide-related behaviour in that study. However, despite showing associations with lower risks of suicide attempts in two separate studies, methylphenidate showed result with high heterogeneity and no statistical significance in meta-analysis.

3.2.6 Epilepsy

One study (Park, Lee et al. 2015) investigated suicide mortality in epilepsy and found association with higher risks of suicide death for levetiracetam (OR = 4.50; 1.10-19.00).

For suicide attempts, the meta-analysis of between-individual studies did not find associations for unspecified antiepileptics in any direction (k = 3; OR = 1.02; 0.76-1.36; I^2 = 28%). The between-individual study that investigated separate antiepileptic medications (Andersohn, Schade et al. 2010) discovered potential association of conventional antiepileptics (carbamazepine, sodium valproate, phenytoin, ethosuximide, acetazolamide) with lower risks of suicide attempts, despite the result not being statistically significant (OR = 0.74; 0.53-1.03), specifically, for sodium valproate (OR = 0.68; 0.46-1.01). The same study found statistically significant association of new antiepileptics, labelled as “high-risk of depression” (levetiracetam, tiagabine, topiramate, and vigabatrin), with higher risks of

suicide attempts (OR = 3.08; 1.22-7.77), specifically, for levetiracetam (OR = 6.42; 1.24-33.36).

For suicide attempts investigated using within-individual studies, carbamazepine and oxcarbazepine were associated with lower risks of suicide attempts (k = 2; OR=0.52; 0.31-0.90; I^2 = 0%), and lamotrigine was associated with higher risks of suicide attempts (k = 2; OR=2.60; 1.24-5.43; I^2=0%).

Table 3. All included studies sorted by the first author in an alphabetical order. BI – between-individual study design, WI – within-individual study design. QUIPS – Quality in Prognosis Studies tool assessment results. NOS – Newcastle-Ottawa Scale assessment result.

Study	Country	Study design	Diagnoses	Medications included	Outcomes studied	Risk of bias
Andersohn, Schade et al. (2010)	UK	BI	Epilepsy	Antiepileptics: conventional, new, barbiturates, carbamazepine, ethosuximide, gabapentin, lamotrigine, levitiracetam, phenobarbital, phenytoin, primidon, topiramate, valproate, vigabatrin	Suicide attempt	QUIPS – low, NOS – 9
Antolín-Concha, Lähteenvuo et al. (2020)	Finland	WI	Bipolar disorder	Antidepressants: unspecified, amitriptyline, citalopram, doxepin, duloxetine, escitalopram, fluoxetine, mianserin, mirtazapine, moclobemide, paroxetine, sertraline, venlafaxine; Antipsychotics: unspecified; Antiepileptics: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, valproic acid; Anxiolytics unspecified; Mood stabilisers unspecified, lithium	Self-harm repetition	QUIPS – low, NOS – 9
Arana, Wentworth et al. (2010)	UK	BI	Bipolar disorder, depression, epilepsy	Antiepileptics (unspecified)	Suicide attempt	QUIPS – low, NOS – 9
Asp, Ambrus et al. (2021)	Sweden	BI	Depression	Antipsychotics (unspecified)	Suicide attempt	QUIPS – low, NOS – 8
Boggs, Lindrooth et al. (2020)	USA	BI	Anxiety	Benzodiazepines	Suicide death	QUIPS – low, NOS – 9
Cato, Holländare et al. (2019)	Sweden	BI	Anxiety, bipolar disorder, depression, personality disorder, schizophrenia, SUD, ADHD	Antiepileptics (unspecified), antipsychotics (unspecified), antidepressants (unspecified), benzodiazepines, lithium, psychostimulants	Suicide death	QUIPS – low, NOS – 8
Chang, Quinn et al. (2020)	USA	BI, WI	ADHD	Psychostimulants	Self-harm	QUIPS – low, NOS – 9

Chen, Tsai et al. (2023)	Taiwan	BI	Bipolar disorder	Mood stabilisers: unspecified, lithium, carbamazepine, lamotrigine, valproic acid, zotepine;	Suicide death	QUIPS – low, NOS – 9
Chen, Chen et al. (2024)	Taiwan	BI	Schizophrenia	Amisulpride, aripiprazole, chlorpromazine, clotiapine, clozapine, flupentixol, haloperidol, olanzapine, paliperidone, quetiapine, risperidone, zotepine	Suicide death	QUIPS – low, NOS – 9
Ekinci, Ekinci (2022)	Turkey	BI	Schizophrenia	Benzodiazepines	Suicide attempt	QUIPS – low, NOS – 9
Fitzgerald, Christensen et al. (2022)	Denmark	BI, WI	Bipolar disorder	Antipsychotics (unspecified), mood stabilisers (unspecified), lithium, valproate	Self-harm, suicide death	QUIPS – low, NOS – 9
Gibbons, Hur et al. (2009)	USA	BI, WI	Bipolar disorder	Antiepileptics: unspecified, carbamazepine, divalproex, gabapentin, lamotrigine, lithium, oxcarbazepine, topiramate	Suicide attempt	QUIPS – low, NOS – 9
Gibbons, Hur et al. (2010)	USA	WI	Bipolar disorder, depression, epilepsy, schizophrenia	Gabapentin	Suicide attempt repetition	QUIPS – low, NOS – 9
Gibbons, Hur et al. (2024)	USA	WI	Not specified	Alprazolam	Suicide attempt	QUIPS – low, NOS – 9
Grimaldi-Bensouda, Nordon et al. (2017)	France	BI	Epilepsy	Antiepileptics (unspecified)	Suicide attempt	QUIPS – low, NOS – 9
Haukka, Tiihonen et al. (2008)	Finland	BI	Schizophrenia	Antidepressants: unspecified, citalopram, fluoxetine, mianserin, paroxetine, sertraline; Antipsychotics: unspecified, clozapine, haloperidol, olanzapine, perphenazine, zuclopenthixol	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Hayes, Hardoon et al. (2022)	UK	WI	Personality disorders	Quetiapine	Self-injury	QUIPS – low, NOS – 9
Herttua, Crawford et al. (2022)	Denmark	Bi, WI	Personality disorders	Antipsychotics (unspecified), in men and women separately	Suicidal behaviour	QUIPS – low, NOS – 9
Irigoyen, Porras-Segovia et al. (2019)	Spain	BI	Unspecified	Antipsychotics (unspecified), anxiolytics (unspecified)	Suicide reattempt	QUIPS – risk of attrition bias, NOS – 7

Isometsä, Sund et al. (2014)	Finland	BI	Bipolar disorder	Lithium	Suicide death	QUIPS – low, NOS – 9
Jakobsen, Larsen et al. (2023)	Denmark	WI	Unspecified	SSRIs	Suicide reattempt	QUIPS – low, NOS – 9
Katz, Randall et al. (2020)	Canada	BI	Unspecified	Antidepressants (unspecified)	Suicide attempt	QUIPS – risk of confounding, NOS – 7
Kim, Yang et al. (2024)	South Korea	BI	Various, depression	Antidepressants (unspecified)	Suicide reattempt	QUIPS – risk of confounding, NOS – 7
Kiviniemi, Suvisaari et al. (2013)	Finland	BI	Schizophrenia	Antidepressants: unspecified, citalopram, fluoxetine, mirtazapine, venlafaxine; Antipsychotics: unspecified, FGA, SGA, chlorprothiexine, clozapine, levomepromazine, olanzapine, perphenazine, quetiapine, risperidone, thioridazine	Suicide death	QUIPS – low, NOS – 9
Lagerberg, Fazel et al. (2022)	Sweden	WI	Unspecified	SSRIs, citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Suicide attempt	QUIPS – low, NOS – 9
Lagerberg, Matthews et al. (2023)	Sweden	BI	Depression	SSRIs	Suicide attempt	QUIPS – low, NOS – 9
Lee, Lim et al. (2025)	South Korea	BI	Bipolar disorder, schizophrenia	Clozapine, lithium, valproate	Suicide death	QUIPS – low, NOS – 9
Leon, Solomon et al. (2011)	USA	BI	Affective disorders	Antidepressants (unspecified)	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Leon, Demirtas et al. (2012)	USA	WI	Unspecified	Antidepressants (unspecified), antiepileptics (unspecified)	Suicide attempt	QUIPS – low, NOS – 9
Leon, Fiedorowicz et al. (2014)	USA	WI	Bipolar disorder, depression	Antidepressants (unspecified), lithium, SGA	Suicide death	QUIPS – low, NOS – 9
Lieslehto, Tiihonen et al. (2023)	Sweden	BI, WI	Borderline personality disorder	ADHD medications: unspecified, atomoxetine, dexamfetamine, lisdexamphetamine, methylphenidate;	Suicide attempt	QUIPS – low, NOS – 9

				Antidepressants: unspecified, agomelatine, amitriptyline, bupropion, citalopram, clomipramine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, moclobemide, paroxetine, sertraline, venlafaxine, vortioxetine; Antipsychotics: unspecified, long-acting injectables, aripiprazole, clozapine, flupentixol, haloperidol, levomepromazine, olanzapine, quetiapine, risperidone, zuclopenthixol; Antiepileptics: carbamazepine, lamotrigine, topiramate, valproic acid; Mood stabilisers: unspecified, lithium		
Lin, Yeh et al. (2023)	Taiwan	BI	Bipolar disorder	Mood stabilisers (unspecified)	Suicide death	QUIPS – low, NOS – 9
Ma, Chang et al. (2018)	Taiwan	Bi	Schizophrenia	Amisulpride, Chlorpromazine, Clothiapine, Clozapine, Flupentixol, Haloperidol, Olanzapine, Quetiapine, Risperidone, Sulpiride, Zotepine	Self-harm	QUIPS – low, NOS – 9
Marangell, Dennehy et al. (2008)	Multiple	BI	Bipolar disorder	SSRIs, carbamazepine, oxcarbazepine, lamotrigine, lithium, valproate	Suicide attempt	QUIPS – risk of confounding, NOS – 8
Molero, Zetterqvist et al. (2018)	Sweden	WI	SUD	Acamprosate, buprenorphine, methadone, naltrexone	Suicide attempt	QUIPS – low, NOS – 9
Molero, Larsson et al. (2019)	Sweden	WI	Epilepsy	Gabapentinoids (unspecified), gabapentine, pregabalin	Suicidal behaviour	QUIPS – low, NOS – 9
Montout, Casadebaig et al. (2002)	France	BI	Schizophrenia	Benzamides, butyrophenoned, phenothiazines, thioxanthenes	Suicide death	QUIPS – low, NOS – 8
Neuner, Hübner-Liebermann et al. (2011)	Germany	BI	Schizophrenia, affective disorders	Antiepileptics (unspecified), lithium; Antipsychotics: FGA, SGA; Antidepressants: SSRIs, MAOs, NaSSAs, SNRIs, TCAs; benzodiazepines	Suicide death	QUIPS – low, NOS – 8

Neutel, Patten (1997)	Canada	BI	Unspecified	Antidepressants (unspecified), benzodiazepines	Suicide attempt	QUIPS – risk of confounding, NOS – 8
Ng, Leung et al. (2023)	Hong Kong	WI	Bipolar disorder	Antiepileptics (unspecified), antipsychotics (unspecified), lithium	Suicide attempt	QUIPS – low, NOS – 9
Öhlund, Ott et al. (2020)	Sweden	WI	Bipolar disorder, ADHD	ADHD medications (unspecified)	Suicide attempt	QUIPS – low, NOS – 9
Olesen, Hansen et al. (2010)	Denmark	WI	Epilepsy	Carbamazepine, clobazam, clonazepam, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate	Suicide attempt repetition with death as an outcome	QUIPS – low, NOS – 9
Olfson, Marcus et al. (2006)	USA	BI	Depression	Antidepressants: unspecified, SSRIs, TCAs, bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, venlafaxine	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Olfson, Marcus (2008)	USA	BI	Depression	Antidepressants: unspecified, SSRIs	Suicide attempt	QUIPS – low, NOS – 9
Padmanathan, Forbes et al. (2022)	UK	WI	SUD	Opioid agonists (unspecified)	Suicide attempt repetition, fatal repetition	QUIPS – low, NOS – 9
Park, Lee et al. (2015)	South Korea	BI	Epilepsy	Carbamazepine, lamotrigine, levitiracetam, oxcarbazepine, phenobarbital, phenytoin, tiagabine, topiramate, valproate, vigabatrin	Suicide death	QUIPS – low, NOS – 9
Pfeiffer, Kim et al. (2013)	USA	BI	Depression	Benzodiazepines	Suicide death	QUIPS – low, NOS – 8
Rahman, Alexanderson et al. (2014)	Sweden	BI	Unspecified	Antidepressants (unspecified), anxiolytics (unspecified)	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Reutfors, Bahmanyar et al. (2013)	Sweden	BI	Schizophrenia	SSRIs, clozapine, risperidone, olanzapine, ziprasidone, lithium	Suicide death	QUIPS – low, NOS – 8

Ringbäck Weitoft, Berglund et al. (2014)	Sweden	BI	Schizophrenia	Aripirazole, clozapine, flupenthixol, haloperidol, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, zuchlopenthixol	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Rohde, Brink et al. (2020)	Denmark	WI	Depression	Methylphenidate, modafinil	Suicide attempt	QUIPS – low, NOS – 9
Rohde, Salagre et al. (2021)	Denmark	WI	ADHD, personality disorders, schizophrenia	Methylphenidate	Suicide attempt	QUIPS – risk of attrition, NOS – 7
Ruengorn, Sanichwankul et al. (2012)	Thailand	BI	Depression	Antipsychotics (unspecified), benzodiazepines, SSRIs, TCAs	Suicide attempt	QUIPS – low, NOS – 8
Schuerch, Gasse et al. (2016)	UK, Denmark	WI	Epilepsy	Carbamazepine, lamotrigine, calproate	Suicide attempt	QUIPS – low, NOS – 9
Siffel, DerSarkissian et al. (2020)	USA	BI	ADHD	CNS stimulants	Suicide attempt	QUIPS – low, NOS – 9
Sondergård, Lopez et al. (2007)	Denmark	BI	Depression	Antidepressants: unspecified, older antidepressants, SSRIs, new non-SSRIs (NaSSAs and SNRI)	Suicide death	QUIPS – low, NOS – 9
Søndergård, Lopez et al. (2008)	Denmark	BI	Bipolar disorder	Antiepileptics (unspecified), lithium	Suicide death	QUIPS – low, NOS – 9
Song, Sjölander et al. (2017)	Sweden	BI, WI	Bipolar disorder	Lithium, valproate	Suicide attempt, repetition	QUIPS – low, NOS – 9
Stricker, Cheung et al. (2022)	Netherlands	BI	ADHD	Methylphenidate	Suicide death	QUIPS – low, NOS – 9
Strømme, Thue Augustsson et al. (2024)	Norway	BI	Schizophrenia	Antidepressants (unspecified), antipsychotics (unspecified), benzodiazepines	Suicide attempt	QUIPS – low, NOS – 9
Suominen, Haukka et al. (2009)	Finland	BI	Depression	Antidepressants (unspecified), antipsychotics (unspecified)	Suicide death	QUIPS – low, NOS – 9
Taipale, Tanskanen et al. (2020)	Finland	BI	Schizophrenia	Aripiprazole (oral), chlorprothiexine (oral), flupentixol (LAI & oral), fluphenazine (LAI), haloperidol (LAI & oral),	Suicide death	QUIPS – low, NOS – 9

				levomepromazine (oral), olanzapine (LAI & oral), perphenazine (LAI & oral), quetiapine (oral), risperidone (LAI & oral), zuclopenthixol (LAI & oral)		
Taipale, Lähteenvuo et al. (2021)	Finland, Sweden	BI, WI	Schizophrenia	Aripiprazole, clozapine, haloperidol, levomepromazine, olanzapine, perphenazine, quetiapine, risperidone (LAI & oral), zuclopenthixol (LAI)	Suicide attempt	QUIPS – low, NOS – 9
Takeuchi, Takenoshita et al. (2017)	Japan	BI	Unspecified	Benzodiazepines, SSRIs, NaSSAs	Suicide death	QUIPS – low, NOS – 9
Tiihonen, Suokas et al. (2012)	Finland	BI	Schizophrenia	Antidepressants (unspecified), benzodiazepines	Suicide death	QUIPS – low, NOS – 9
Toffol, Hätönen et al. (2015)	Finland	BI	Bipolar disorder	Antidepressants (unspecified), antipsychotics (unspecified), benzodiazepines, lithium, valproic acid	Suicide death	QUIPS – low, NOS – 8
Tondo, Baldessarini et al. (2020)	Multiple	BI	Bipolar disorder	Antidepressants (unspecified), antipsychotics (unspecified), lithium	Suicide attempt	QUIPS – low, NOS – 8
Tournier, Bénard-Laribière et al. (2023)	France	WI	Unspecified	Benzodiazepines	Suicide attempt repetition, repetition with death	QUIPS – low, NOS – 9
Tsai, Cheng et al. (2016)	Taiwan	BI	Bipolar disorder	Carbamazepine, divalproex, lithium	Suicide attempt, suicide death	QUIPS – low, NOS – 9
Uwai, Nabekura (2022)	Japan	BI	Bipolar disorder	Aripiprazole, carbamazepine, lithium, olanzapine, quetiapine, risperidone, valproate	Suicide attempt	QUIPS – low, NOS – 8
Valuck, Libby et al. (2016)	USA	BI	Depression	SNRIs, SSRIs, TCAs	Suicide attempt	QUIPS – low, NOS – 9
Wimberley, MacCabe et al. (2017)	Denmark	BI	Schizophrenia (treatment-resistant)	Clozapine	Self-harm, suicide death	QUIPS – low, NOS – 8
Xi, Banerjee et al. (2023)	USA	WI	Unspecified	Antidepressants (unspecified), benzodiazepines	Suicide attempt	QUIPS – low, NOS – 9

Xiang, Weng et al. (2008)	Hong Kong	BI	Schizophrenia	Benzodiazepines, clozapine	Suicide attempt	QUIPS – low, NOS – 8

3.4 Heterogeneity and sensitivity analysis

High between-study heterogeneity was observed for all suicide-related outcomes. One reason for the high heterogeneity was outcome measurement. Suicidal behaviour included many outcomes that differed by intention and severity, including mortality and non-suicidal self-injury. Heterogeneity in the studies could be also explained by clinical factors: different medications with different effects in one class, the difference in effect between diagnoses and the severity of the condition. For example, excluding a study that explored the effects of clozapine on suicide mortality in treatment-resistant schizophrenia, lowered heterogeneity to less than 50% and resulted in statistically significant finding.

I conducted a "leave-one-out" sensitivity analysis for the results with k studies ≥ 5. Overall, the results were similar, but heterogeneity was lower, which means that in some instances a single study was responsible for high heterogeneity measures. In overall results (without separation by diagnostic categories) there were more possibilities to analyse heterogeneity due to the higher number of included studies. Excluding one study (Sondergård, Lopez et al. 2007) would result in $I^2 = 0\%$ for suicide mortality in unspecified antidepressants but would not significantly change the result. For suicide mortality in unspecified antipsychotics, excluding either of two studies (Kiviniemi, Suvisaari et al. 2013, Toffol, Hätönen et al. 2015) would make the result statistically significant and result in mild association with higher risks of suicide death. For suicide mortality in SSRIs, there were two studies (Sondergård, Lopez et al. 2007, Takeuchi, Takenoshita et al. 2017) that created substantial heterogeneity but excluding them either resulted in null association or in statistically significant association with lower risk of suicide death. For suicide attempt in clozapine, excluding either of two studies (Wimberley, MacCabe et al. 2017, Xiang, Weng et al. 2008) would result in statistically significant association with lower risks. For suicide attempts in haloperidol and quetiapine with unspecified diagnosis, and for suicide death in olanzapine in people with schizophrenia, one study (Ringbäck Weitoft, Berglund et al. 2014) appeared to be the main outlier for heterogeneity results but excluding that study would not impact the pooled effect. Similarly, both for olanzapine overall and in people with schizophrenia one study (Kiviniemi, Suvisaari et al. 2013) influences heterogeneity the most. For suicide mortality in perphenazine, one subgroup of oral deposition (Taipale, Tanskanen et al. 2020) was the heterogeneity outlier. For suicide attempts for lithium in people with bipolar disorder excluding one study (Gibbons, Hur et al. 2024) would result in statistically significant association with lower risks. Overall, in most of the cases one study was the main reason for high heterogeneity in the results but did not impact the pooled effects.

3.5 Publication bias and evidence certainty

To assess the possible publication bias, funnel plots were built for results with five or more studies, and both Egger's test and trim-and-fill analysis were performed for the results with k studies 10 and more. I have performed the trim-and-fill analysis for all the results, however, for the results with lower number of included studies, it should be interpreted with caution. There was evidence of some publication bias, leading to higher reporting of studies associated with the lower risks of suicide attempts for SSRIs. There was evidence of more reporting of studies associated with lower risks of suicide mortality for unspecified antipsychotics, lithium (both overall and in people with bipolar disorder), and olanzapine (both overall and in people with schizophrenia). For publication bias favouring the reporting of the results associated with higher risks of suicide attempts, there was evidence for unspecified antipsychotics. There was evidence of publication bias favouring the reports of higher association for suicide mortality for clozapine. However, for none of these investigations the trim-and-fill analysis impacted any of the pooled effects, and Egger's test was statistically significant only for publication bias of higher reporting of lithium associated with lower risks of suicide mortality.

To assess the certainty of evidence I used the GRADE framework. I have assessed the main findings of this review in terms of potential inconsistency, indirectness, and imprecision of evidence. For most medications, there was substantial heterogeneity, which indicates inconsistency. However, for the medications with lower heterogeneity ($I^2 < 50\%$) there was little concern for inconsistency. Due to the nature of observational studies, there was a small indirectness of interventions, since the main method for categorising a person as being under treatment was prescription data. The main concern in the certainty of the main findings was imprecision: there were many small studies with wide confidence intervals. Overall, quality of evidence in this review is moderate.

Chapter 4. Discussion

4.1 Overview

This meta-analysis summarises data from over 45 years of observations in more than 13 million people from 17 countries. I included 74 studies of 534 comparisons of use and no-use of 90 different psychotropic medications. 48 studies with 406 comparisons had psychiatric diagnoses mentioned, and 7 studies with 46 comparisons were conducted on patients with epilepsy. Psychiatric diagnoses included schizophrenia spectrum disorders, bipolar disorder, depression, personality disorders, ADHD, and substance use disorders (SUD). The largest number of studies were in schizophrenia spectrum disorders (192 comparisons) and bipolar disorder (104 comparisons), and the most evidence identified was on antipsychotics (193 comparisons) and antidepressants (125 comparisons). There were too little data on ADHD and SUD and the specific medications used to treat them to pool the results quantitatively.

4.2 Principal findings

In overall synthesis, the strongest association with lower suicide risks, especially with suicide mortality, was found in second generation antipsychotics in between-individual studies. SSRI sertraline was also associated with lower risks of suicide mortality in between-individual studies, but in general the OR ranges for antidepressants were too wide to reach statistical significance. Across all study designs, only the ADHD medications and second-generation antipsychotic clozapine were consistently associated with lower risks of suicide-related outcomes, and most of the medications were not associated with higher risks, which will be discussed in detail below.

In relation to diagnosis-specific results, I have reported that second generation antipsychotics were linked to lower suicide risk in schizophrenia, while lithium and divalproex/valproic acid were associated with reduced risk in bipolar disorder. In depression, SSRIs and older generation antidepressants appeared to have protective associations in depression. Benzodiazepines, on the other hand, were linked to increased suicide risk across all diagnostic groups, except depression, where the finding was not statistically significant. For epilepsy, carbamazepine and oxcarbazepine were associated

with lower risks of suicide attempts, and lamotrigine was associated with higher risks of suicide attempts.

4.3 Insights from the results

4.3.1 Findings of this review v. previous research

Some of these findings triangulate with trial data. Lithium has been associated with lower risk of suicide (Huang, Harris et al. 2022, Cipriani, Hawton et al. 2013), and benzodiazepines linked to higher risk in randomised controlled trials (Tyler J. Dodds 2017). The evidence on SSRIs has been inconsistent: while a recent meta-analysis of RCTs suggests reduced suicidal behaviour (Li, Chen et al. 2024), the older trial data provide evidence of either elevated risk of suicide attempts (Fergusson, Doucette et al. 2005) or no effect on any suicide-related outcomes (Gunnell, Saperia et al. 2005), and our review supports the former. The study with the subgroup meta-analysis suggests that different SSRIs have different effects on suicide ideation (Huang, Harris et al. 2022), but not suicide attempts or mortality: citalopram provides evidence of lower risk, and paroxetine possibly higher. For antipsychotics, clozapine has previously shown consistent protective effects against suicide attempts: according to a systematic review of 51 studies, including 9 clinical trials (Masdrakis, Baldwin 2023), clozapine showed an 86% reduction of suicide attempts in comparison to placebo, and compared with olanzapine (HR = 0.76; 95% CI = 0.58-0.97). Our results suggest that other second-generation antipsychotics are associated with reduced risk, particularly for suicide deaths in schizophrenia. In the current review, for bipolar disorder, apart from lithium, consistent evidence of reduced suicide risk was found for valproic acid, but current guidelines advise against its use due to concerns about long-term adverse effects (National Institute for Health and Care Excellence 2025c).

The differences between this study and previous reviews may be explained by methodological differences. As stated above, trial data can have limited external validity when it comes to the suicide-related outcomes due to the ineligibility of high-risk subjects to participate (Taipale, Schneider-Thoma et al. 2022). In addition, most of the RCTs have an approach to the suicide-related outcomes as an adverse effect of a medication (Miller, McCall 2022), and it is common to measure suicide-related outcomes via self-report methods, such as psychometric tests (Yao, McCall 2023, Haddock, Davies et al. 2016). I have deliberately excluded this approach from this review, as my focus was on suicide

prevention and there is no sound evidence of any mechanism that would cause suicidal behaviour in patients (Kasper, Schindler et al. 1996, Möller 2006, Cipriani, Barbui et al. 2005). Instead, I focused on clinically documented data on events that would have been observed over the course of (non-)treatment. This approach lowers the risks of bias that may appear from self-reported data, including placebo and nocebo effects, and the indication bias that may come from comparing samples with different clinical characteristics (Cipriani, Barbui et al. 2005).

This review adds data on medication effects in suicidal behaviour. I found observational evidence of other second-generation antipsychotics protective associations on suicide, especially in relation to suicide mortality in schizophrenia spectrum disorders, determined evidence of protective associations of valproates in bipolar disorder, and in SSRIs and older antidepressants in depression. The results of this study extend what we know findings from randomised controlled trials on suicide mortality, while they are generally consistent with associations on all suicide-related outcomes (which are mostly self-harm episodes).

4.3.2 Overall findings v. findings by diagnosis

Overall findings in this review showed a high heterogeneity and many inconclusive and non-statistically significant results. As mentioned in the introduction, different medications can be prescribed in different diagnoses. In the introduction, I presented a brief overview of current standards for prescribing psychotropic medications. Antidepressants can be prescribed in different mood disorders and in other diagnoses, and some second-generation antipsychotics and antiepileptics can function as mood stabilisers apart from their respective primary mechanisms. In addition, there is always a possibility of off-label use and misdiagnosis, where the patient would be exposed to the medications that are not commonly recommended for their condition. Because of that I conducted a separate data synthesis of effects of the medications in different diagnostic categories to explore whether different diagnoses would impact reported effects and heterogeneity of the included studies. 26 studies did not specify psychiatric diagnosis, and 7 of them were conducted in epilepsy that is discussed separately in comparison of antiepileptics in other diagnoses.

For antidepressants, SSRI sertraline was associated with lower risks and NaSSAs and SNRIs was associated with the higher risk of suicide-related outcomes. Antidepressants are commonly prescribed in depression, and the result for this diagnostic category provides more insight on their effect. All SSRIs were associated with lower risks of suicide mortality

in depression (OR range 0.47-0.81). Older antidepressants, which include tricyclic antidepressants and monoamine oxidase inhibitors (MAO) were also associated with lower risks of suicide mortality (OR range 0.59-0.78). SNRIs and NaSSA did not reach statistical significance in their results and findings were characterised with uncertainty, which may be explained by them being too wide a group of medications to be analysed as one category, despite frequently being analysed that way. SSRIs were also associated with lower risks of suicide mortality in schizophrenia spectrum disorders (OR range 0.38-0.89). Unspecified antidepressants showed association with higher risks of suicide attempts in schizophrenia (OR range 1.19-1.66). Therefore, despite inconclusive results in overall data synthesis, there is strong evidence of TCAs, MAOIs and SSRIs being associated with lower risks of suicide-related outcomes in depression when synthesised separately.

For antipsychotics, there was strong evidence from overall results pooled from between-individual studies that second generation antipsychotics are generally associated with lower risks of suicide-related outcomes. However, the results of within-individual studies showed the tendency of both first- and second-generation antipsychotics being associated with higher risks of suicide attempts, with clozapine being the only exception (OR range 0.53-0.82). Most commonly, antipsychotics are prescribed in schizophrenia spectrum disorders and second-generation antipsychotics also frequently function as mood stabilisers in bipolar disorder, so closer inspection of these diagnostic categories could broaden the conclusions of the study. The results for schizophrenia spectrum disorder generally corresponded with the results of the overall synthesis. First generation antipsychotics were associated with higher risk of suicide mortality (OR range 1.36-4.31), except zuclopenthixol, and most of the second-generation antipsychotics were associated with lower risks of suicide-related outcomes. The heterogeneity was low enough to pool results on more separate medications, which added substantial evidence that aripiprazole, clozapine, olanzapine, quetiapine, risperidone and zuclopenthixol show tendency to associate with lower risks of suicidal behaviour (OR range 0.30-1.01). In bipolar disorder unspecified antipsychotics were associated with higher risks of suicide mortality, and with higher risks of suicide attempts in depression. There was some evidence that antipsychotics are associated with lower risks of suicide-related outcomes in borderline personality disorder.

For antiepileptics, the overall results were pooled for any diagnosis (including unspecified), excluding where epilepsy was specifically stated. In general, only sodium valproate was associated with higher risks of suicide attempts, but with mild effect size (OR range 1.00-

1.19). However, divalproex was associated with two-fold decrease of suicide attempts (OR range 0.40-0.61), despite being a similar medication. As antiepileptics are also commonly prescribed as mood stabilisers in bipolar disorder, the synthesis of the data on this diagnostic category provided more evidence of antiepileptic effects on suicide-related outcomes. In addition, there have been data that resulted in FDA issuing an alert on antiepileptics about them potentially inducing suicidal behaviour (Hesdorffer, Kanner 2009). Therefore, I have synthesised data on epilepsy separately to compare with the overall and bipolar disorder results. In bipolar disorder, valproic acid was associated with lower risks of self-harm (OR range 0.59-0.75). For epilepsy, lamotrigine was associated with high risks of suicide attempts (OR range 1.24-5.43), and carbamazepine/oxcarbazepine was associated with that two-fold decrease of suicide attempts risk (OR range 0.31-0.90). Given that the overall pooled results included the data from studies conducted in patients with depression and schizophrenia, which is against current prescribing standards, and it is possible that papers without specified diagnosis included patients with epilepsy and off-label exposure, the results on antiepileptics remain mostly inconclusive, and there is a need of more observational studies conducted in people with bipolar disorder and epilepsy separately. The only strong evidence of lower suicide risks in bipolar disorder was in valproic acid, but the UK prescribing guidelines now recommend prescribing valproate-containing medications only after two independent specialists had agreed that other treatments are unsuitable (National Institute for Health and Care Excellence 2025c).

Lithium is usually prescribed in bipolar disorder as a long-term intervention. In overall results, lithium was associated with the lower risks of suicide-related outcomes, but the heterogeneity of the pooled results was too high, except for suicide mortality, and this result should be interpreted with caution. However, the overall results included studies conducted on patients with depression and schizophrenia, which is not a common practice. The results from bipolar disorder results were more conclusive and lithium had a strong association with lower risks of suicide death. The results for suicide attempts were less conclusive.

Benzodiazepines are usually prescribed as a short-term intervention for anxiety disorders. The overall results for benzodiazepines were characterised by high heterogeneity, but if the results were pooled, there would be a strong association with higher risks of suicidal behaviour and suicide mortality. In the synthesis by diagnosis, heterogeneity of the benzodiazepines results was below 50%, and there was a strong association with suicidal behaviour and suicide mortality in all diagnostic categories, except depression. However,

the follow-up periods of the included studies were generally over several months, which is not recommended for the benzodiazepines. The common practice for prescribing benzodiazepines is switching to other medications (i.e. SSRIs) after 4 weeks. One included study (Ekinci, Ekinci 2022) compared the short-term (cumulative days of use 69.8±22.6) and long term (cumulative days of use 251.2±29.4) effects of benzodiazepines in schizophrenia, and short-term OR for suicide attempt was 0.67 (95% CI 0.43-1.04). Despite not reaching statistical significance these results provide evidence that benzodiazepines tend to associate with lower risks of suicidal behaviour when prescribed short-term. At the same time the OR for suicide attempt in the long-term exposure was 7.67 (95% CI 5.56-10.57), which shows a strong association with higher risks of suicide attempt. Therefore, while this review provides evidence that the benzodiazepines are associated with higher risks of suicide-related outcomes, there is also evidence that within the recommended periods of treatment benzodiazepines may be associated with lower risks of suicidal behaviour. Medication effects by diagnostic category provided a framework with which to analyse the main findings.

4.3.3 Between-individual studies' findings v. within-individual studies' findings

Some medications in the within-individual studies showed association with higher risks of suicide behaviour, while in the between-individual studies those medications were associated with the lower risks of suicidal behaviour. This difference was observed in the antidepressants and the second-generation antipsychotics.

As described in the introduction, between- and within-individual studies apply different principles for accounting for confounding. In between-individual studies, confounding is controlled via sample selection for controls and statistical methods, such as propensity score matching. In within-individual studies, study participants form their own control group, which should eliminate potential confounding by individual differences. However, the within-individual studies do not typically account for time-variant factors, such as the severity of the symptoms. Therefore, there is a possibility of an indication bias in the within-individual studies, where a person generally experiences worse mental health conditions when they are prescribed with the medication being studied compared to the non-exposure periods. This may explain the difference in the results between the study designs. Many within-individual studies used a long follow-up period (more than 6 months), particularly the non-exposure period, which could possibly create the indication bias. A patient would visit their healthcare provider when they experience the worsening of symptoms for several weeks, which was shown in the studies with monthly comparisons for a year before and

after initiation of the medication. According to studies conducted in patients prescribed with SSRIs (Lagerberg, Fazel et al. 2022) and a second-generation antipsychotic quetiapine (Hayes, Hardoon et al. 2022), the suicide behaviour risks were rising for a year before starting treatment, and the highest risk of suicide event was the month before starting treatment. After the start of treatment, the risk of suicide significantly dropped within the first month but remained higher than a year before treatment. Based on these data, the comparison between a month before and a month after treatment would result in the association of an approximately two-fold decrease in suicide risk.

There is also a principal difference in the outcomes that can be studied in these designs. Observational studies with the between-individual design can be used for any types of suicide-related outcomes, while within-individual studies are used for evaluating repetitive outcomes, such as suicide attempts and non-suicidal self-injury. Repetition of self-harm is a known risk-factor for the future suicidal behaviour and suicide mortality (Liu, Jia et al. 2022). Therefore, the inclusion of people with the prior history of suicide-related outcomes in the within-individual studies makes the suicidal behaviour more likely to occur during the study period compared to the between-individual cohort studies, where people are included without a prior history and this factor is often accounted for in the data analysis.

4.3.4 Suicide attempts v. suicide mortality

The findings for suicide attempts generally corresponded with those for suicide mortality. However, the larger variety of outcomes included in the suicide attempts category likely contributed to the higher heterogeneity of the results that are more inconclusive. While suicide mortality in observational studies is usually verified with nationwide mortality registers, suicide attempts can be defined and recorded in many ways. Although I excluded studies that relied on self-reports, healthcare standards in several countries do not separate self-harm behaviour with and without suicide intent and do not consider the differences in risk factors between different fatal and non-fatal outcomes. This makes the mortality data more reliable and more conclusive which was reflected in the results. Nevertheless, these results showed that psychopharmacological prevention strategies may be similar for both fatal non-fatal suicide events.

4.4 Heterogeneity and publication bias

The results presented were characterised by high heterogeneity in many studied medications, which complicates interpretation. There are several potential reasons for heterogeneity: some of them were explored and confirmed in this review, others are yet to be confirmed, which creates one of the directions for future research.

First, high heterogeneity in the results can be explained with clinical differences between patient samples. When the analysis was carried out in separate diagnostic groups, heterogeneity measures dropped for most of the medication classes. Excluding data in extremely severe conditions, such as treatment-resistant schizophrenia or depression, confirmed the hypothesis that heterogeneity may appear when groups of patients with different mental status are lumped together in the studies.

Second, it is important to consider temporal changes. This review covers over 45 years of observational research, and within this period diagnostic guidelines have changed drastically. The earliest known observation included in this review dates the year 1979 (Neutel, Patten 1997), a year when the ICD-9 was set to take effect and a year before an official publication of DSM-III. Hence, the observed events in the included papers have been covered by the three editions of international diagnostic manuals. Consequently, prescribing and treatment guidelines also changed considerably with time which could create significant clinical differences between patients in 1979 and 2023 who would be diagnosed with depression and prescribed antidepressants. Additionally, there could be temporal trends in what medications are preferred by the clinicians, which would also impact the naturalistic data. These factors should be investigated further.

Another temporal factor that should be considered is potential changes in how study protocols and datasets have changed over time. The development of the psychiatric and public health research field created new guidelines and standards for scientists, and the studies published within the span of 25 years may provide different estimates of suicide events, with older studies over- or underestimating effects.

Moreover, different country and regional areas may provide different data. For example, while Scandinavian countries tend to report suicide events accurately (Tøllefsen, Helweg-Larsen et al. 2015), there is evidence of underreporting suicide mortality in different Asian countries (Onie, Usman et al. 2024, Li, Yip 2020). There is also a possibility of different approaches to non-fatal suicide events that could be related to a higher stigmatisation of mental disorder and suicide in some cultures. Although over 80% (n = 58) of studies were

conducted in Europe, North America or Australia, socio-cultural differences could create additional heterogeneity in the data.

The leave-one-out sensitivity analysis provides more insight of heterogeneity in the included studies. In most of the cases, where the number of studies was over five, only one study would be the main influence on heterogeneity metrics. The exclusion of that study would not change the result for any of the pooled effects but sometimes would make the pooled effect statistically significant.

Finally, the observational study design itself carries a possibility of creating heterogeneous results. Most of the studies measure treatment by the number of prescriptions filled. This creates a possibility of misclassification of actual treatment, because for most of the medications it is not possible to accurately account for actual medication use, adherence and potential polypharmacy effects in the naturalistic data.

4.5 Strengths and limitations

This review included large, high-quality studies. By looking at both within-individual and between-individual designs, I was able to identify sources of heterogeneity. Limitations should be considered. Most of medications were only studied in few studies, which limited analysis of publication bias or between studies heterogeneity. Most of the effect sizes were pooled as the adjusted OR. Although in the majority of the studies the adjusted variables were similar: age, gender, clinical characteristics, and socioeconomic background; it could account for higher heterogeneity and lead to less accurate results, although unlikely to significantly impact the direction of OR. Many investigations were excluded because they did not report underlying diagnoses, and outcome definitions varied: some focused on suicide attempts or non-suicidal self-injury, while others included deaths. Suicide-related adverse effects may not have been captured due to healthcare registries rarely reporting them. Inclusion of such events would likely skew the data towards higher odds of suicide-related outcomes, especially non-fatal. Although there was a high level of agreement between reviewers regarding screening decisions, only 20% of studies were screened independently. Since I excluded the studies conducted in selected populations (e.g., people in prison, in specific age groups), this could potentially limit our findings, including for the suicide-related outcomes in children and adolescents. Future reviews should consider comparing suicide-related outcomes in different age and socio-demographic groups. All studies were conducted in cohorts from high- and upper-middle-income countries. As suicides were rare, and the differences between outcomes were minimal, this did not clearly influence findings.

4.6 Implications of the study

4.6.1 Clinical implications

These results have potential clinical implications for management of people with high risks of suicide-related outcomes. The findings, taken together, suggest that suicide prevention strategies should consider the appropriate use of prescribed medications in people with psychiatric disorders. In addition, individuals prescribed benzodiazepines require follow-up and periodic medication reviews to avoid chronicity and potential harms. At the same time, the review findings are not causal and need triangulation using other research designs. Trials with suicide outcomes may not be feasible, and proxy outcomes such as suicide attempts can be considered with caution. The review also highlights the importance of diagnosis in people with mental disorders – the effects of medication clearly differed by main diagnostic category.

Suicide attempts and deaths are relatively rare outcomes, including among individuals with diagnosed psychiatric disorders, and they typically are not the primary target of most treatments. Although certain medications show protective associations with suicide-related outcomes, they are unlikely to prevent all such events. Pharmacological interventions should therefore be implemented alongside psychosocial treatments and other risk management strategies for suicide prevention. Furthermore, the development and validation of robust prognostic risk models are necessary to identify individuals at highest risk (Seyedsalehi, Fazel 2024, Mughal, Cipriani et al. 2025), thereby enabling more effective targeting of preventive resources. Validated models include OxMIS (Fazel, Wolf et al. 2019) and OxSATS (Fazel, Vazquez-Montes et al. 2023), and were recently reviewed in a large meta-analysis (Seyedsalehi, Bailey et al. 2025).

4.6.2 Future research

Future studies should consider more targeted designs, especially within-individual comparisons and target trial emulations, with clearly defined outcomes. Pharmacoepidemiological studies for suicide prevention should avoid combining mental health diagnoses. More research is needed in substance use disorders, which were rarely included in the current review despite being at high risk, in low- and middle-income countries, and on medications where uncertainty remains due to potential biases or underrepresentation in observational studies, such as second-generation antipsychotics in bipolar disorder, or SNRIs in depression.

While RCTs are often considered as a golden standard of studying the effects of interventions, they provide limited validity in certain areas of studies, including suicide-related effects, due to recruitment criteria and short follow-up periods. As a result, observational data remain essential to study suicidal behavioural and other naturalistic events. However, researchers have been cautious about observational data referring to the limitations to prove causality in observational studies. Although this caution is justified, recent developments in causal inference frameworks (Li, Pearl 2023, Hernán 2018) provide evidence and methodology to establish causality from observational data. Future research should focus on maximising the value of real-world evidence through applications of such methodology, especially in the areas where RCTs are unfeasible.

Chapter 5. Conclusion

This systematic review and meta-analysis synthesised evidence from observational studies on the association between commonly prescribed psychotropic medications and suicide-related outcomes, including both suicidal attempts and suicide mortality. Since trial evidence is limited and often not generalisable in this field, this review synthesises real-world data across different diagnoses and study designs, providing broader insight.

The findings show that some medications, such as lithium, clozapine, SSRIs, and some valproate-related formulations, were associated with reduced risks of suicide-related outcomes depending on the diagnoses. Certain other psychotropic medications, mainly benzodiazepines, were associated with elevated risks of suicide. The direction and strength of associations varied across diagnoses, highlighting the importance of considering diagnostic subgroups when evaluating suicide risk. Moreover, methodological differences and the handling of time-varying confounders are likely to affect the results in different study designs. Therefore, it is important in the future studies to consider diagnostic context, study design and current prescribing practices.

While heterogeneity and potential confounding remain key limitations, this review demonstrates that high-quality observational studies may offer important insights into suicide prevention in psychiatric populations. It is important to consider the biopsychosocial complexity of suicidal behaviour when analysing effects of medications and other factors.

Overall, psychotropic medications are associated with suicide risk, but these effects vary between diagnoses, which highlights the importance of careful and accurate diagnostic procedures. These findings have potentially important implications for clinicians, policymakers, and researchers aiming to reduce suicide mortality and improve psychiatric care.

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Appendix

A1. PROSPERO protocol

Review title and basic details

Review title: Psychopharmacology for suicide prevention

Review objectives: What psychotropic medications show the most effectiveness in preventing suicide-related outcomes according to observational studies?

Searching and screening

Searches: Ovid (MEDLINE, Embase, APAPsychArticles, AMED, BIOSIS, Global Health, PsycINFO), Web of Science Core Collection.

No limitations on date of publication or language was used

The search had happened in the period until Feb 14 2024 and will be rerun before data synthesis

Study design

Inclusion criteria: We will include observational studies (including cohort and case-control studies) and focus on within-subject (or self-controlled) study designs.

Exclusion criteria: studies that measure suicidal ideation/thoughts.

Eligibility criteria

Condition or domain being studied: Suicide mortality, suicide attempts, self-harm

Population

Inclusion criteria: General population, humans.

Exclusion criteria: studies with unrepresentative population, i.e. exclusively children, or patient populations with non-psychiatric disorders (cardiac or cancer).

Intervention(s) or exposure(s)

Inclusion criteria: Taking prescribed conventional psychotropic medication (antidepressants, antipsychotics, addiction medication, mood stabilisers and ADHD medication) according to Stahl's Psychopharmacology Prescription Guide.

Exclusion criteria: studies that assess the effect of non-conventional and off-licence medications, i.e. psilocybin, cannabis, ketamine.

Comparator(s) or control(s)

Interventions will be compared between each other. Studies comparing the intervention with placebo, matched controls and the subjects themselves will be included.

Outcomes to be analysed

Main outcomes: Suicide mortality

Measures of effect: Odds ratios, hazard ratios, number of events

Additional outcomes: Self-harm events

Measures of effect: Odds ratios, hazard ratios, number of events

Data collection process

Data extraction (selection and coding)

The screening will be conducted using the Rayyan.ai software. Two researchers will be screening studies for eligibility. The researchers will be blind to each other's decisions. Disagreements will discussed and attempts to resolve them made, with the advice from supervisor.

Data to be extracted: information about study design and methodology, time-to-event data, number of events.

Risk of bias (quality) assessment: The quality assessment will be conducted using the Ottawa-Newcastle Scale (ONS) for observational studies.

Planned data synthesis

Strategy for data synthesis

Data will be synthesised on all medications that have more than two studies with the relevant data. We will add all the information on the suicide mortality and suicide attempts. If feasible, meta-analysis of odds ratios and/or hazard ratios will be conducted. If not feasible due to high heterogeneity and/or too small number of studies included, data synthesis will be a formal narrative reporting odds ratios and/or hazard ratios.

Analysis of subgroups or subsets

Dependent on the amount of studies included, it will be either a subgroup or network meta-analysis (if meta-analysis is feasible). The groups to be compared are the following: lithium, antipsychotics, antiepileptics, SSRIs, MAOIs, TCAs, addiction medication, ADHD medication. The treatment outcomes are to be compared to each other. Studies with the within subject-design (i.e. mirror-image studies) are to be analysed separately to compare the result with other study designs.

A2. Search strategy

(((self-harm or self harm or selfharm or suicid*) and (antidepressant* or SSRI* or TCA* or SNRI* or NASSA* or SARI* or MAO* or anti-anxiety or tranquil* or benzodiazepin* or anxiolytic* or anxiolitic* or antipsychotic* or neuroleptic* or mood stabili* or antiepileptic* or acamprosate or agomelatine or alprazolam or amisulpride or amitriptyline or amoxapine or amphetamine or aripiprazole or armodafinil or asenapine or atomoxetine or benperidol or buprenorphine or bupropion or buspirone or cariprazine or chlordiazepoxide or chlorpromazine or citalopram or clomipramine or clonazepam or clonidine or clorazepate or clozapine or cyamemazine or desipramine or desvenlafaxine or dexamfetamine or diazepam or disulfiram or dosulepin or dothiepin or doxepin or duloxetine or escitalopram or fluoxetine or flupentixol or fluvoxamine or guanfacine or haloperidol or hydroxyzine or imipramine or isocarboxazid or lamotrigine or levomepromazine or lisdexamfetamine or lithium or lofepramine or lofexidine or loflazepate or lorazepam or loxapine or lurasidone or maprotiline or melatonin or methadone or methylphenidate or mianserin or mirtazapine or moclobemide or modafinil or nalmefene or naltrexone or nefazodone or nortriptyline or olanzapine or oxazepam or paliperidone or paroxetine or phenelzine or pimozide or prazosin or prochlorperazine or propranolol or quetiapine or reboxetine or risperidone or selegiline or sertraline or sulpiride or tianeptine or tranylcypromine or trazodone or trifluoperazine or trimipramine or valproate or varenicline or venlafaxine or vilazodone or vortioxetine or zuclopenthixol)).ab. and (observational or target trial or cohort or case-control or case control).af.) not (systematic review or meta-analysis or meta-review or umbrella review).ti. not (psilocybin* or ketamine or esketamine or psychodelic* or psylocibin*).ab

A3. Overall meta-analysis results

Table A3. Overall meta-analysis results. Bold text – the result is statistically significant.

	Suicide attempts										Suicide death				
	Within-individual					Between-individual									
Medication	k studies	OR	95% CI	I^2,%	Certainty (GRADE)	k studies	OR	95% CI	I^2, %	Certainty (GRADE)	k studies	OR	95% CI	I^2,%	Certainty (GRADE)
Antiepileptics (unspecified)	3	0.50	0.19-1.32	91	Moderate (imprecision)	2	1.74	0.78-3.90	85	Low	3	1.08	0.76-1.53	0	High
Antidepressants (unspecified)	3	0.93	0.73-1.17	60	Moderate (inconsistency)	10	1.17	0.67-2.02	88	Low	12	0.88	0.66-1.17	83	Moderate (inconsistency)
Antipsychotics (unspecified)	4	1.20	0.68-2.14	98	Low	10	1.40	0.97-2.01	86	Moderate (inconsistency)	9	1.15	0.98-1.34	19	Moderate (imprecision)
Anxiolytics (unspecified)	2	**1.42**	**1.06-1.90**	77	Moderate (inconsistency)	3	1.41	0.82-2.42	68	Moderate (inconsistency)					
Benzodiazepines	3	**2.12**	**1.51-2.97**	98	Moderate (inconsistency)	5	**2.94**	**1.31-6.60**	85	Moderate (imprecision)	9	2.14	1.49-3.06	42	High
Mood stabilisers (unspecified)						2	1.44	0.93-2.21	95	Moderate (inconsistency)	4	0.75	0.59-0.95	58	Moderate (imprecision)
Lithium	7	**0.60**	**0.44-0.81**	82	Moderate (inconsistency)	5	0.61	0.30-1.27	96	Moderate (inconsistency)	10	0.49	0.37-0.64	13	High
Stimulants	4	**0.66**	**0.54-0.81**	10	High	2	**0.69**	**0.66-0.72**	0	High	2	**0.57**	**0.36-0.91**	8	High
Carbamazepine, oxcarbazepine	3	0.50	0.14-1.81	79	Low	4	0.76	0.41-1.41	75	Moderate (imprecision)	2	0.53	0.18-1.55	60	Low
Divalproex						2	**0.49**	**0.40-0.61**	0	High					
Gabapentin	3	0.60	0.16-2.27	91	Low										
Lamotrigine	3	0.70	0.37-1.34	88	Moderate (inconsistency)	2	0.86	0.65-1.14	0	High					
Topiramate	3	0.96	0.56-1.65	26	Low										

Sodium valproate	2	0.93	0.73-1.18	58	Low	4	**1.09**	**1.00-1.19**	0	High	2	**0.64**	**0.58-0.71**	0	High
Valproic acid	2	0.77	0.49-1.20	87	Low						2	**0.66**	**0.49-0.89**	0	High
SSRIs	2	0.90	0.42-1.93	95	Low	6	1.26	0.73-2.17	67	Low	5	0.80	0.56-1.13	36	Moderate (imprecision)
NaSSa, SNRI, SARI	2	**1.30**	**1.14-1.49**	8	Moderate (inconsistency)	3	1.10	0.92-1.31	0	Moderate (imprecision)	6	**1.71**	**1.20-2.44**	23	High
TCA						3	0.60	0.21-1.70	44	Moderate (imprecision)	2	0.96	0.58-1.59	0	Moderate (imprecision)
Amitriptyline	2	1.36	0.94-1.97	0	Moderate (imprecision)										
Citalopram	3	0.97	0.71-1.32	80	Moderate (inconsistency)	2	1.16	0.89-1.51	0	High	3	0.69	0.27-1.76	71	Low
Duloxetine	2	**1.39**	**1.17-1.63**	0	Moderate (imprecision)										
Escitalopram	2	0.97	0.46-2.02	83	Low										
Fluoxetine	3	1.02	0.57-1.85	93	Low	2	1.10	0.80-1.59	37	High	3	0.79	0.33-1.90	38	Low
Paroxetine	3	1.07	0.59-1.93	75	Low	2	1.25	0.84-1.84	23	Moderate (imprecision)					
Sertraline	3	0.93	0.56-1.54	90	Low	2	**0.65**	**0.44-0.96**	0	High	2	**0.21**	**0.05-0.87**	0	High
FGA											2	**1.72**	**1.21-2.43**	0	High
SGA											3	**0.76**	**0.59-0.98**	0	High
Aripiprazole	3	**1.40**	**1.19-1.65**	0	High	4	0.96	0.56-1.65	86	Moderate (inconsistency)	3	**0.61**	**0.37-1.00**	0	High
Chlorprothixene											2	1.51	0.41-5.56	92	Low
Clozapine	3	**0.66**	**0.53-0.82**	0	High	7	0.62	0.37-1.02	88	Moderate (imprecision)	8	**0.48**	**0.30-0.76**	61	Moderate (inconsistency)
Flupentixol						2	0.72	0.53-1.01	0	High	3	0.67	0.35-1.32	24	Moderate (imprecision)
Haloperidol	3	**1.53**	**1.18-1.98**	0	Moderate (imprecision)	5	1.16	0.73-1.83	85	Moderate (inconsistency)	4	0.88	0.52-1.50	37	Moderate (imprecision)

Levomepromazine	3	1.25	0.83-1.87	81	Moderate (inconsistency)						2	1.21	0.52-2.80	80	Low
Olanzapine	3	**1.23**	**1.08-1.40**	0	High	6	0.76	0.52-1.10	88	Moderate (inconsistency)	5	**0.56**	**0.39-0.81**	29	High
Perphenazine						4	0.86	0.72-1.03	15	Moderate (imprecision)	5	**0.73**	**0.59-0.92**	49	High
Quetiapine	4	1.08	0.92-1.27	51	Moderate (inconsistency)	5	1.12	0.81-1.53	88	Moderate (inconsistency)	4	**0.75**	**0.58-0.96**	0	High
Risperidone	3	1.06	0.75-1.48	57	Low	5	**0.67**	**0.55-0.82**	64	Moderate (imprecision)	4	**0.57**	**0.37-0.87**	66	Moderate (inconsistency)
Zuclopenthixol	3	**1.53**	**1.13-2.09**	32	Moderate (imprecision)	4	0.98	0.84-1.16	0	Moderate (imprecision)	3	**0.43**	**0.29-0.65**	4	High

A4. Results by diagnosis

Table A4.1 Effects of medications when used in individuals with schizophrenia spectrum disorders. Bold text – the result is statistically significant.

Outcomes	Suicide attempts					Suicide mortality				
Study design	Between-individual studies									
	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence
Antidepressants (unspecified)	2	**1.40**	**1.19-1.66**	0%	High	3	0.77	0.25-2.37	90%	Moderate (inconsistency)
SSRIs						4	**0.59**	**0.38-0.89**	12%	High
Citalopram						2	0.50	0.15-1.65	77%	Moderate (inconsistency)
Fluoxetine						2	0.49	0.18-1.31	0%	Moderate (imprecision)
Antipsychotics (unspecified)	2	**0.90**	**0.81-0.99**	0%	High	2	0.95	0.65-1.37	0%	High
First-generation antipsychotics (unspecified)						2	**2.16**	**1.39-3.35**	0%	High
Second-generation antipsychotics (unspecified)						3	0.65	0.27-1.53	73%	Moderate (inconsistency)
Aripiprazole	2	0.81	0.45-1.48	87%	Moderate (inconsistency)	3	0.61	0.37-1.01	0%	Moderate (imprecision)
Chlorprothixene						2	1.44	0.42-4.97	90%	Moderate (inconsistency)
Clozapine	6	0.62	0.37-1.02	94%	Moderate (inconsistency)	7	**0.40**	**0.26-0.60**	60%	Moderate (inconsistency)
Flupentixol	2	0.73	0.53-1.01	0%	High	3	0.66	0.35-1.25	28%	Moderate (imprecision)
Haloperidol	4	1.16	0.73-1.83	89%	Moderate (inconsistency)	4	0.82	0.49-1.38	65%	Moderate (inconsistency)
Olanzapine	4	**0.76**	**0.60-0.98**	84%	Moderate (inconsistency)	5	**0.53**	**0.39-0.71**	34%	High
Perphenazine	2	0.84	0.69-1.01	20%	High	4	0.72	0.45-1.16	65%	Moderate (inconsistency)
Risperidone	3	**0.61**	**0.52-0.72**	57%	Moderate (inconsistency)	4	**0.55**	**0.38-0.79**	64%	Moderate (inconsistency)
Levomepromazine						2	1.14	0.54-2.43	71%	Moderate (inconsistency)
Quetiapine	3	1.12	0.74-1.70	93%	Moderate (inconsistency)	4	**0.75**	**0.58-0.96**	0%	High

Zuclopenthixol	3	0.98	0.84-1.16	0%	High	3	**0.44**	**0.30-0.63**	0%	High
Benzodiazepines	3	2.78	0.91-8.47	93%	Moderate (inconsistency)	3	**2.93**	**1.57-5.47**	14%	High
Lithium						2	0.78	0.36-1.66	100%	Moderate (inconsistency)

Table A4.2. Effects of individual medications when used in individuals with bipolar disorder. Bold text – the result is statistically significant.

Outcomes	Suicide attempt										Suicide mortality				
Study design	Within-individual studies					Between-individual studies									
	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence
Mood stabilisers (unspecified)											2	**0.68**	**0.56-0.83**	61%	Moderate (inconsistency)
Lithium	6	**0.60**	**0.44-0.82**	92%	Moderate (inconsistency)	5	0.86	0.67-1.11	89%	Moderate (inconsistency)	6	**0.38**	**0.28-0.50**	67%	Moderate (inconsistency)
Antipsychotics (unspecified)	3	1.38	0.69-2.73	97%	Moderate (inconsistency)	2	**1.53**	**1.36-1.74**	0%	High	2	1.13	0.76-1.68	48%	Moderate (imprecision)
Antidepressants (unspecified)	2	0.71	0.42-1.20	85%	Moderate (inconsistency)										
Antiepileptics (unspecified)	2	0.39	0.10-1.59	97%	Moderate (inconsistency)	2	1.76	0.40-7.71	90%	Moderate (inconsistency)					
Carbamazepine	2	0.42	0.14-1.29		Moderate (imprecision)	3	1.23	0.59-2.56	72%	Moderate (inconsistency)					
Divalproex															
Gabapentin	2	0.98	0.36-2.66												
Lamotrigine	2	0.56	0.21-1.52	89%	Moderate (inconsistency)	2	0.86	0.65-1.14	0%	Moderate (imprecision)					
Topiramate	2	0.60	0.26-1.40	0%	Moderate (imprecision)										
Sodium Valproate	2	0.87	0.60-1.25	81%	Moderate (inconsistency)	4	**1.16**	**1.03-1.31**	13%	High					
Valproic Acid											3	**0.66**	**0.59-0.75**	0%	High
Benzodiazepines											2	**3.03**	**1.72-5.34**	0%	High

Table A4.3. Effects of medications when used in individuals with depression. Bold text – the result is statistically significant.

Outcomes	Suicide attempt					Suicide mortality				
Study design	Between-individual studies									
	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence
Antidepressants unspecified	2	1.02	0.81-1.28	0%	Moderate (imprecision)	3	0.69	0.33-1.47	92%	Moderate (imprecision)
SSRIs	4	0.91	0.72-1.16	0%	High	**2**	**0.61**	**0.47-0.81**	23%	High
New non-SSRIs	2	1.07	0.82-1.40	0%	Moderate (imprecision)	**2**	**0.71**	**0.43-1.17**	43%	Moderate (imprecision)
Older antidepressants	4	0.60	0.21-1.70	64%	Moderate (imprecision)	2	**0.68**	**0.59-0.78**	0%	High
Antipsychotics overall	3	**2.43**	**1.37-4.33**	72%	Moderate (inconsistency)					
Benzodiazepines						2	2.00	0.94-4.22	71%	Moderate (imprecision)

Table A4.4 Effects of individual medications when used in individuals with personality disorders. Bold text – the result is statistically significant.

Outcomes	Suicide attempt					Suicide mortality				
Study design	Within-individual studies									
	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence
Methylphenidate	2	0.59	0.28 -1.28	86%	Low (inconsistency, imprecision)					
Antipsychotics overall	3	0.97	0.67-1.40	99%	Moderate (inconsistency)					
Quetiapine	2	1.05	0.92 -1.19	14%	High					
Benzodiasepines						2	**4.29**	**3.28-5.60**	0%	High

Table A4.5. Effects of medications used in individuals with epilepsy. Bold text – the result is statistically significant.

Outcomes	Suicide attempts									
Study design	Within-individual studies					Between-individual studies				
	k studies	OR	CI 95%	I^2	Certainty of evidence	k studies	OR	CI 95%	I^2	Certainty of evidence
Antiepileptics (unspecified)						3	1.02	0.76-1.36	28	Moderate (inconsistency)
Carabamazepine, oxcarbazepine	2	**0.52**	**0.31-0.90**	0%	High					
Gabapentin	3	1.05	0.91-1.22	0%	Moderate (imprecision)					
Lamotrigine	2	**2.60**	**1.24-5.43**	0%	Moderate (imprecision)					
Sodium valproate	2	1.03	0.25-4.34	84%	Low					

A5. Studies excluded at the full-text screening stage

Table A5. All excluded studies with the exclusion reason, sorted by the first author in an alphabetical order. Some of the papers would be excluded with multiple reasons, they appear in either a more appropriate category or the one that was noticed first.

First author	Year	Title	DOI or link
Study design			
Amendola	2021	Did the introduction and increased prescribing of antidepressants lead to changes in long-term trends of suicide rates?	https://dx.doi.org/10.1093/eurpub/ckaa204
Angst	2005	Suicide in 406 Mood-Disorder Patients With and Without Long-Term Medication: A 40 to 44 Years' Follow-Up.	https://dx.doi.org/10.1080/13811110590929488
Bagley	2017	Association between psychostimulant agents and suicide related events in individuals with Attention-Deficit Hyperactivity Disorder.	
Baldessarini	2003	Lithium treatment and suicide risk in major affective disorders: Update and new findings	
Bell	2008	Health care utilization and morbidity associated with methadone and buprenorphine treatment	http://www.atforum.com/pdf/europad/HeroinAdd10-2.pdf
Bocchetta	1998	Suicidal Behavior On and Off Lithium Prophylaxis in a Group of Patients With Prior Suicide Attempts	
Born	2005	Newer prophylactic agents for bipolar disorder and their influence on suicidality	https://dx.doi.org/10.1080/13811110590929541
Brodersen	2000	Sixteen-year mortality in patients with affective disorder commenced on lithium	https://dx.doi.org/10.1192/bjp.176.5.429
Caplehorn	1996	Methadone maintenance and addicts' risk of fatal heroin overdose	http://dx.doi.org/10.3109/10826089609045806
Carvalho	2024	Mortality and lithium-protective effects after first-episode mania diagnosis in bipolar disorder: A nationwide retrospective cohort study in Taiwan.	https://dx.doi.org/10.1159/000535777
Castelpietra	2016	Diagnoses and prescriptions of antidepressants in suicides: Register findings from the Friuli Venezia Giulia Region, Italy, 2002-2008	https://dx.doi.org/10.3109/13651501.2016.1149196

Castelpietra	2008	Antidepressant use and suicide prevention: a prescription database study in the region Friuli Venezia Giulia, Italy	
Chan	2024	Mortality risk and mood stabilizers in bipolar disorder: a propensity-score-weighted population-based cohort study in 2002-2018.	https://dx.doi.org/10.1017/S2045796024000337
Chawla	2022	Assessment of lethality and its clinical correlates in suicide attempters with mood disorders	10.4103/ipj.ipj_251_21
Cheung	2015	Antidepressant use and the risk of suicide: A population-based cohort study	https://dx.doi.org/10.1016/j.jad.2014.12.032
Collazo	2022	A Retrospective Cohort Study on the Increasing Trend of Suicide Ideations and Risks in an Opioid-Dependent Population of Puerto Rico 2015-2018	https://dx.doi.org/10.1007/s10903-021-01310-8
Collins	2008	Divalproex, lithium and suicide among Medicaid patients with bipolar disorder.	https://dx.doi.org/10.1016/j.jad.2007.07.014
Conner	2007	Suicide attempts among individuals with opiate dependence: The critical role of belonging	https://dx.doi.org/10.1016/j.addbeh.2006.09.012
Connery	2018	Microscopes and telescopes: The societal impact of substance use disorder treatment.	https://dx.doi.org/10.1176/appi.ajp.2018.18060694
Coryell	2001	Lithium and suicidal behavior in major affective disorder: A case-control study	https://dx.doi.org/10.1034/j.1600-0447.2001.00338.x
Cougnard	2009	Impact of antidepressants on the risk of suicide in patients with depression in real-life conditions: a decision analysis model	
Coull	2000	Post-mortem studies of brain phosphatidylinositol hydrolysis in depression and the effect of antidepressant treatment	10.1017/S1461145700001851
Coupland	2015	Antidepressant use and risk of suicide and attempted suicide or self harm in people aged 20 to 64: cohort study using a primary care database	
Courtet	2010	Suicidality: risk factors and the effects of antidepressants. The example of parallel reduction of suicidality and other depressive symptoms during treatment with the SNRI, milnacipran	https://dx.doi.org/10.2147/NDT.S11774
Courtet	2017	Antidepressants and suicide risk in depression.	https://dx.doi.org/10.1002/wps.20460

Crocq	2010	Suicide attempts in a prospective cohort of patients with schizophrenia treated with sertindole or risperidone	https://dx.doi.org/10.1016/j.euroneuro.2010.09.001
De Hert	2010	Do antipsychotic medications reduce or increase mortality in schizophrenia? A critical appraisal of the FIN-11 study.	https://dx.doi.org/10.1016/j.schres.2009.12.029
De la Fuente-Sandoval	2019	P.614 Depression and suicidal ideation in treatment-resistent depression patients in latam: cross-sectional analysis from the multicentre, prospective, observational TRAL study	https://dx.doi.org/10.1016/j.euroneuro.2019.09.598
Delapaz	2021	An emulation of randomized trials of administrating antipsychotics in ptsd patients for outcomes of suicide-related events	https://dx.doi.org/10.3390/jpm11030178
Denee	2024	Impact of moderate-to-high-suicide-intent in major depressive disorder: a retrospective cohort study on patient characteristics and healthcare resource utilisation in England.	https://dx.doi.org/10.1186/s12888-024-05961-3
Fedyszyn	2014	Suicidal behaviours during treatment for first-episode psychosis: Towards a comprehensive approach to service-based prevention	https://dx.doi.org/10.1111/eip.12084
Fernandez-Miranda	2016	Clinical and functional outcomes of patients with severe schizophrenia undergoing comprehensive treatment: A 6-year follow-up	https://dx.doi.org/10.1016/j.eurpsy.2016.01.629
Fernandez-Miranda	2020	High Doses of Second-Generation Long-Acting Antipsychotics in the Treatment of Patients with Severe Resistant Schizophrenia: A Six-Year Mirror-Image Study	https://dx.doi.org/10.5455/PCP.20201011042823
Fernandez-Miranda	2022	The Use of Second-Generation Antipsychotics in Patients with Severe Schizophrenia in the Real World: The Role of the Route of Administration and Dosage-A 5-Year Follow-Up.	https://dx.doi.org/10.3390/biomedicines11010042
Fleischhacker	2014	Completed and attempted suicides among 18,154 subjects with schizophrenia included in a large simple trial	https://dx.doi.org/10.4088/jcp.13m08563
Fond	2023	How can we improve the care of patients with schizophrenia in the real-world? A population-based cohort study of 456,003 patients	https://dx.doi.org/10.1038/s41380-023-02154-4
Garcia-Carmona	2020	Long-Acting Injectable Antipsychotics: Analysis of Prescription Patterns and Patient Characteristics in Mental Health from a Spanish Real-World Study	https://dx.doi.org/10.1007/s40261-020-00913-7

Garcia-Carmona	2021	Evaluation of long-acting injectable antipsychotics with the corresponding oral formulation in a cohort of patients with schizophrenia: a real-world study in Spain	10.1097/YIC.0000000000000339
Goldstein	1995	Heroin addicts and methadone treatment in Albuquerque: A 22-year follow-up	https://dx.doi.org/10.1016/0376-8716%2895%2901205-2
Gonzalez-Pinto	2006	Suicidal risk in bipolar I disorder patients and adherence to long-term lithium treatment	
Goodwin	2003	Suicide Risk in Bipolar Disorder during Treatment with Lithium and Divalproex	https://dx.doi.org/10.1001/jama.290.11.1467
Haukka	2009	Antidepressant use and mortality in Finland: A register-linkage study from a nationwide cohort	https://dx.doi.org/10.1007/s00228-009-0616-9
Hayes	2016	Self-harm, Unintentional Injury, and suicide in bipolar disorder during maintenance mood stabilizer treatment a UK population-based electronic health records study	ttps://dx.doi.org/10.1001/jamapsychiatry.2016.0432
Henriksson	2011	Suicides are seldom prescribed antidepressants: findings from a prospective prescription database in Jamtland county, Sweden, 1985-95	
Hesdorffer	2016	Occurrence and recurrence of attempted suicide among people with epilepsy	https://dx.doi.org/10.1001/jamapsychiatry.2015.2516
Huang	2016	Comparison of Long-Acting Injectable Antipsychotics with Oral Antipsychotics and Suicide and All-Cause Mortality in Patients with Newly Diagnosed Schizophrenia	https://dx.doi.org/10.1001/jamanetworkopen.2021.8810
Isaacson	2009	Decrease in suicide among the individuals treated with antidepressants: A controlled study of antidepressants in suicide, Sweden 1995-2005.	https://dx.doi.org/10.1111/j.1600-0447.2009.01344.x
Jalbert	2016	Channeling bias in a comparative effectiveness study of a newly launched antipsychotic	https://dx.doi.org/10.1002/pds.4070
Jiang	2021	Suicide prediction among men and women with depression: A population-based study	https://dx.doi.org/10.1016/j.jpsychires.2021.08.003
Jick	2004	Antidepressants and the Risk of Suicidal Behaviors	
Joffe	2004	Does lithium save lives?	
Joseph	2022	Association between mirtazapine use and serious self-harm in people with depression: an active comparator cohort study using UK electronic health records	https://dx.doi.org/10.1136/ebmental-2021-300355

Kamat	2014	Association between antidepressant prescribing and suicide rates in OECD countries: An ecological study.	https://dx.doi.org/10.1055/s-0033-1357183
Kapur	1992	Antidepressant medications and the relative risk of suicide attempt and suicide	https://dx.doi.org/10.1001/jama.268.24.3441
Kelty	2018	Morbidity and mortality in opioid dependent patients after entering an opioid pharmacotherapy compared with a cohort of non-dependent controls	https://dx.doi.org/10.1093/pubmed/fdx063
Kim	2024	Risk factors of reattempt among suicide attempters in South Korea: A nationwide retrospective cohort study.	https://dx.doi.org/10.1371/journal.pone.0300054
Leith	2019	The association between gabapentin and suicidality in bipolar patients	https://dx.doi.org/10.1097/YIC.0000000000000242
Leppein	2023	Newer Antiseizure Medications and Suicidality: Analysis of the Food and Drug Administration Adverse Event Reporting System (FAERS) Database	https://dx.doi.org/10.1007/s40261-023-01272-9
Machado	2011	Suicidal risk and suicide attempts in people treated with antiepileptic drugs for epilepsy	https://dx.doi.org/10.1016/j.seizure.2010.12.010
Martinez	2005	Antidepressant treatment and the risk of fatal and non-fatal self harm in first episode depression: Nested case-control study.	https://dx.doi.org/10.1136/bmj.330.7488.389
Maust	2023	Benzodiazepine Discontinuation and Mortality Among Patients Receiving Long-Term Benzodiazepine Therapy.	10.1001/jamanetworkopen.2023.48557
McGirr	2006	Risk factors for completed suicide in schizophrenia and other chronic psychotic disorders: A case-control study	10.1016/j.schres.2006.02.025
Miller	2014	Antidepressant class, age, and the risk of deliberate self-harm: A propensity score matched cohort study of SSRI and SNRI users in the USA.	https://dx.doi.org/10.1007/s40263-013-0120-8
Miller	2014	Antidepressant Dose, Age, and the Risk of Deliberate Self-harm	10.1001/jamainternmed.2014.1053
Montastruc	2019	Association of Aripiprazole with the risk of psychiatric hospitalization, self-harm, or suicide	https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2722562
Moon	2020	Premature mortality and causes of death of people with epilepsy in South Korea	
Moore	2023	Association between psychotropic drug prescription and suicide rates in Scotland: population study	https://dx.doi.org/10.1192/bjb.2021.88

Mulleroerlinghausen	1992	SUICIDES AND PARASUICIDES IN A HIGH-RISK PATIENT GROUP ON AND OFF LITHIUM LONG-TERM MEDICATION	10.1016/0165-0327(92)90084-J
Nakagawa	2007	Association of suicide and antidepressant prescription rates in Japan, 1999-2003.	https://dx.doi.org/10.4088/JCP.v68n0613
Nettelbladt	2007	Suicide rates in the Lundby cohort before and after the introduction of tricyclic antidepressant drugs	
Newhouse	2021	Using an Observational Dataset to Study the Association of Antidepressant Treatment Use with Suicidal Ideation, Self-Harm and Death by Suicide : a Retrospective Study of Patients, Who Received a Clinical Diagnosis of Depression, in Secondary Psychiatric Care	
Nielsen	2018	Second-generation LAI are associated to favorable outcome in a cohort of incident patients diagnosed with schizophrenia	https://dx.doi.org/10.1016/j.schres.2018.07.020
Lahteenvuo	2022	Association of opioid agonist treatment with all-cause mortality and specific causes of death among people with opioid dependence: A systematic review and meta-analysis	
Novick	2010	Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia	https://dx.doi.org/10.1016/j.psychres.2009.05.00
Osler	2019	P.219 Antidepressant medication, suicidal behaviour and violent crime in a cohort of Danish patients with affective disorders	https://dx.doi.org/10.1016/j.euroneuro.2019.09.262
Ouazana-Vedrines	2022	Outcomes associated with antidepressant treatment according to the number of prescriptions and treatment changes: 5-year follow-up of a nation-wide cohort study	https://dx.doi.org/10.3389/fpsyt.2022.923916
Park	2016	Suicidal thoughts/acts and clinical correlates in patients with depressive disorders in Asians: Results from the REAP-AD study.	https://dx.doi.org/10.1017/neu.2016.27
Perucci	1991	MORTALITY OF INTRAVENOUS-DRUG-USERS IN ROME - A COHORT STUDY	10.2105/AJPH.81.10.1307
Reselan	2006	Relationship between antidepressant sales and secular trends in suicide rates in the Nordic countries	
Ridout		Computational Strategies to Tailor Existing Interventions for First Major Depressive Episodes to Inform and Test Personalized Interventions	

Rihman	2015	Treatment of bipolar disorder with lamotrigine -- relapse rate and suicidal behaviour during 6 month follow-up	
Rissanen	2014	ANTIPSYCHOTICS AND ANTIDEPRESSANTS AND THEIR ASSOCIATIONS WITH SUICIDAL IDEATION - THE NORTHERN FINLAND BIRTH COHORT 1966	10.1016/S0920-9964(14)71013-8
Rohde	2024	A target trial emulation comparing the antidepressant effectiveness of Selective Serotonin Reuptake Inhibitors (SSRIs) highlighting the importance of patent-related confounding by indication.	https://dx.doi.org/10.1111/acps.13729
Rubino	2007	Risk of suicide during treatment with venlafaxine, citalopram, fluoxetine, and dothiepin: Retrospective cohort study	https://dx.doi.org/10.1136/bmj.39041.445104.BE
Sacchi	2021	Impact of antidepressant prescriptions on suicidal behavior in times of severe financial strain	https://dx.doi.org/10.1097/NMD.0000000000001336
Sani	2011	Suicide in a large population of former psychiatric inpatients.	10.1111/j.1440-1819.2011.02205.x
Schneeweiss	2010	Variation in the Risk of Suicide Attempts and Completed Suicides by Antidepressant Agent in Adults: A Propensity Score-Adjusted Analysis of 9 Years' Data.	
Simon	2007	Suicide Attempts Among Patients Starting Depression Treatment With Medications or Psychotherapy	
Smith	2009	Association between consistent purchase of anticonvulsants or lithium and suicide risk: A longitudinal cohort study from Denmark, 1995-2001	https://dx.doi.org/10.1016/j.jad.2009.01.013
Sondergard	2006	Temporal changes in suicide rates for persons treated and not treated with antidepressants in Denmark during 1995-1999.	
Su	2019	Comparisons of the risk of medication noncompliance and suicidal behavior among patients with depressive disorders using different monotherapy antidepressants in Taiwan: A nationwide population-based retrospective cohort study	https://dx.doi.org/10.1016/j.jad.2019.03.039
Sung	2019	Concurrent use of benzodiazepines, antidepressants, and opioid analgesics with zolpidem and risk for suicide: a case-control and case-crossover study	https://dx.doi.org/10.1007/s00127-019-01713-x
Taipale	2024	Attention-Deficit/Hyperactivity Disorder Medications and Work Disability and Mental Health Outcomes	https://dx.doi.org/10.1001/jamanetworkopen.2024.2859

Tang	2022	Risks of all-cause death and completed suicide in patients with schizophrenia/schizoaffective disorder treated with long-acting injectable or oral antipsychotics: A population-based retrospective cohort study in Taiwan	https://dx.doi.org/10.1192/j.eurpsy.2021.2258
Tiihonen	2006	Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study.	10.1136/bmj.38881.382755.2F
Torrents	2020	Methadone poisonings: a seven-year retrospective study of the French poison center network focusing on suicide attempts vs. misuses	10.1111/fcp.12506
Ulcickas Yood	2010	Epidemiologic study of aripiprazole use and the incidence of suicide events	https://dx.doi.org/10.1002/pds.2047
Valuck	2009	Antidepressant discontinuation and risk of suicide attempt: A retrospective, nested case-control study	https://dx.doi.org/10.4088/JCP.08m04943
Van der Zalm	2021	Clozapine and mortality: A comparison with other antipsychotics in a nationwide Danish cohort study	https://dx.doi.org/10.1111/acps.13267
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Liang	2018	Relationship between mortality in people with mental disorders and suicide mortality in China during 2000 to 2014 An observational study	10.1097/MD.0000000000013359
Li	2023	Factors Influencing Suicide Deaths in Patients With Schizophrenia Based on Cohort Data: An Empirical Study of a Sample of 170006 Patients in Sichuan Province	https://dx.doi.org/10.12182/20230160302 PT - Article
Madsen	2021	Cause-specific life years lost in individuals with treatment-resistant depression: A Danish nationwide register-based cohort study	https://dx.doi.org/10.1016/j.jad.2020.11.042
Merrall	2012	Mortality of those who attended drug services in Scotland 1996-2006: Record-linkage study	10.1016/j.drugpo.2011.05.010
Meyer	2014	Self-harm in people with epilepsy: A retrospective cohort study	https://dx.doi.org/10.1111/epi.12723

Molero	2023	Associations between β-blockers and psychiatric and behavioural outcomes: A population-based cohort study of 1.4 million individuals in Sweden	10.1371/journal.pmed.1004164
Niederkrotenthaler	2020	Healthcare utilization, psychiatric medication and risk of rehospitalization in suicide-attempting patients with common mental disorders.	https://dx.doi.org/10.1177/0004867419895112
Osborn	2008	Suicide and severe mental illnesses. Cohort study within the UK general practice research database	https://dx.doi.org/10.1016/j.schres.2007.11.025
Oyefeso	1999	Suicide among drug addicts in the UK.	
Pan	2014	Excessive suicide mortality and risk factors for suicide among patients with heroin dependence	10.1016/j.drugalcdep.2014.10.021
Pavarin	2023	Epidemiology and Clinical-Demographic Characteristics of Suicide Attempts in Alcohol Use Disorders in an Italian Population	https://dx.doi.org/10.1080/02791072.2022.2107464
Penttinen	2001	Risk of suicide and accidental death among subjects visiting a doctor because of mental disorder: A matched case-control study in Finnish farmers	10.1539/joh.43.107
Plans	2019	Completed suicide in bipolar disorder patients: A cohort study after first hospitalization	https://dx.doi.org/10.1016/j.jad.2019.07.048
Porras-Segovia	2023	Factors associated with transitioning from suicidal ideation to suicide attempt in the short-term: Two large cohorts of depressed outpatients	10.1016/j.jad.2023.05.018
Qin	2006	Trends in suicide risk associated with hospitalized psychiatric illness: A case-control study based on Danish longitudinal registers	10.4088/JCP.v67n1214
Reutfors	2021	Risk Factors for Suicide and Suicide Attempts Among Patients With Treatment-Resistant Depression: Nested Case-Control Study	10.1080/13811118.2019.1691692
Reutfors	2016	Suicide risk and antipsychotic side effects in schizophrenia: nested case-control study	10.1002/hup.2536
Sherry	2023	A National Retrospective Study of Antidepressants' Effects on Overdose and Self-Harm Among Adults Treated With Opioid Analgesics	https://dx.doi.org/10.1176/appi.ps.20220070
Stromme	2024	Risk factors for mortality in patients admitted to a psychiatric acute ward: A prospective cohort study	10.1111/acps.13657

Vold	2022	Prevalence and correlates of suicide attempts in high-risk populations: a cross-sectional study among patients receiving opioid agonist therapy in Norway	https://dx.doi.org/10.1186/s12888-022-03829-y
von Greiff	2018	Mortality and Cause of DeathA 30-Year Follow-Up of Substance Misusers in Sweden	10.1080/10826084.2018.1452261
Xin	2021	Relationship between suicide rate and antidepressant prescription: An ecological study in the People's Republic of China.	https://dx.doi.org/10.1002/hup.2760
Population			
Beckman	2016	Mental illness and suicide after self-harm among young adults: Long-term follow-up of self-harm patients, admitted to hospital care, in a national cohort.	https://dx.doi.org/10.1017/S0033291716002282
Chen	2020	Suicide attempts and death among heroin-involved women seeking methadone treatment in Taiwan	https://dx.doi.org/10.1016/j.drugalcdep.2020.108277
Gottlieb	2023	A comparison of mortality rates for buprenorphine versus methadone treatments for opioid use disorder	https://dx.doi.org/10.1111/acps.13477
Hamina	2024	Fatal drug overdoses in individuals treated pharmacologically for chronic pain: a nationwide register-based study	https://dx.doi.org/10.1016/j.bja.2023.10.016
Larney	2014	Opioid substitution therapy as a strategy to reduce deaths in prison: retrospective cohort study	10.1136/bmjopen-2013-004666
Lee	2018	Clinical epidemiology of long-term suicide risk in a nationwide population-based cohort study in South Korea	https://dx.doi.org/10.1016/j.jpsychires.2018.01.018
Linden	2013	Risk of suicide and suicide attempt associated with atomoxetine compared to central nervous system stimulant treatment	https://dx.doi.org/10.1002/pds.3512
Man	2017	Association of Risk of Suicide Attempts With Methylphenidate Treatment.	10.1001/jamapsychiatry.2017.2183
McCarthy	2009	Mortality associated with attention-deficit hyperactivity disorder (ADHD) drug treatment: A retrospective cohort study of children, adolescents and young adults using the general practice research database	https://dx.doi.org/10.2165/11317630-000000000-00000
Rohde	2018	Real-world effectiveness of clozapine for intellectual disability: Results from a mirror-image and a reverse-mirror-image study.	10.1177/0269881118783322

Rush	2024	A framework for inferring and analyzing pharmacotherapy treatment patterns.	https://dx.doi.org/10.1186/s12911-024-02469-4
Sondergard	2006	Do antidepressants prevent suicide?	https://dx.doi.org/10.1097/00004850-200607000-00003
Sorensen	2001	Risk of suicide in users of β-adrenoceptor blockers, calcium channel blockers and angiotensin converting enzyme inhibitors	10.1046/j.0306-5251.2001.01442.x
Stralin	2019	Medication, hospitalizations and mortality in 5 years after first-episode psychosis in a Swedish nation-wide cohort	https://dx.doi.org/10.1111/eip.12697
Teferra	2011	Five-year mortality in a cohort of people with schizophrenia in Ethiopia.	https://dx.doi.org/10.1186/1471-244X-11-165
Thomas	2024	Suicide, Stimulants, and Selective Serotonin Reuptake Inhibitors: A Retrospective Chart Review.	https://dx.doi.org/10.1089/cap.2023.0068
Wimberley	2017	Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia	https://dx.doi.org/10.1176/appi.ajp.2017.16091097
Woody	2007	Premature Deaths After Discharge from Methadone Maintenance: A Replication.	10.1097/ADM.0b013e318155980e
Duplicated samples and other background papers			
Andersohn	2009	Use of antiepileptic drugs in epilepsy and the risk of self harm and suicidal behaviour	https://dx.doi.org/10.1002/pds.1806
Bralet	2000	[Cause of mortality in schizophrenic patients: prospective study of years of a cohort of 150 chronic schizophrenic patients].	
Brodersen	2001	Mortality in patients with affective disorder who commenced treatment with lithium. A 16-year follow-up	
Chang	2015	Estimation of life expectancy and the expected years of life lost among heroin users in the era of opioid substitution treatment (OST) in Taiwan	10.1016/j.drugalcdep.2015.05.033
Fernandez Miranda	2019	Suicide prevention with second-generation long-acting-injectable antipsychotics among people with severe schizophrenia	https://doi.org/10.1080/24750573.2019.1603432
Fernandez-Miranda	2021	Oral versus long-acting injectable antipsychotic treatment for people with severe schizophrenia: A 5-year follow-up of effectiveness.	https://dx.doi.org/10.1097/NMD.0000000000001299

Haukka	2006	Antidepressants and the risk of suicide, attempted suicide and overall mortality in a nation-wide cohort	
Katz	2018	Suicide risk in bipolar disorder: Comparing lithium, divalproex, and carbamazepine.	
Kelty	2012	Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic opiate use	10.1111/j.1360-0443.2012.03910.x
Rahman	2022	Disability pension due to common mental disorders: Subsequent psychiatric morbidity and suicidal behaviour.	
Ruengorn	2011	Incidence and risk factors of suicide reattempts within 1 year after psychiatric hospital discharge in mood disorder patients	https://www.dovepress.com/getfile.php?fileID=11435
Song	2017	Suicidal behavior during lithium and valproate treatment: A within-individual 8-year prospective study of 50,000 patients with bipolar disorder.	https://dx.doi.org/10.1176/appi.ajp.2017.16050542
Sun	2015	Zolpidem and the risk of suicide: A nationwide population-based case-control study	https://dx.doi.org/10.1016/j.jns.2015.08.649
Tiihonen	2009	11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study)	10.1016/S0140-6736(09)60742-X
Tondo	2024	Prevention of suicidal behavior with lithium treatment in patients with recurrent mood disorders.	https://dx.doi.org/10.1186/s40345-024-00326-x
Tournier	2022	Risk of suicidal behavior associated with benzodiazepines: A nationwide case-crossover study	
Tournier	2016	Outcomes of three treatment strategies in bipolar disorder using conventional mood stabilizers and antipsychotic drugs	https://dx.doi.org/10.1002/pds.4070
Valuck	2005	Antidepressant treatment and risk of suicide attempt by adults with major depressive disorder: A propensity-adjusted retrospective cohort study	
Yager	2016	Do Statins Improve Antidepressant Effectiveness?	10.1056/nejm-jw.NA41161
Ziemba	2010	Do Antiepileptic Drugs Increase the Risk of Suicidality in Adult Patients With Epilepsy?: A Critically Appraised Topic.	10.1097/NRL.0b013e3181f79f37
Publication type (conference abstracts, research proposals, etc.)			

Abdullah	2010	National mental health registry - Schizophrenia one year outcome study	http://www.e-mjm.org/2010/CRC_2010_supA.pdf
Arana	2011	"Suicide-related Events in Patients Treated With Antiepileptic Drugs"	10.1097/EDE.0b013e31823198fc
Astrup	2013	Impact of censoring at or truncating risk time of hospitalizations on the association between antiepileptic drugs and suicide attempt	https://dx.doi.org/10.1007/s10654-013-9820-0
Barbui	2014	Antidepressant dose and the risk of deliberate self-harm	https://dx.doi.org/10.1017/S2045796014000456
Bellivier	2013	Wave-BD, an ambispective multinational observational study on bipolar I and II disorder (BDI, BDII): French cohort clinical outcomes (nct01062607)	
Berardelli	2024	The role of long-acting antipsychotics in illness relapse: an observational study	https://dx.doi.org/10.1192/j.eurpsy.2024.805
Bjorkholm	2021	P.0871 Epidemiology of major depression and intentional self-harm from a total-population cohort in the greater Stockholm region	https://dx.doi.org/10.1016/j.euroneuro.2021.10.727
Cano	2015	Clinical outcomes in schizophrenia patients during first years of diagnosis, a cohort study	https://dx.doi.org/10.1017/S1092852914000765
Chang	2022	Use of central nervous system drugs in combination with selective serotonin reuptake treatment: A Bayesian screening study for risk of suicidal behavior	https://dx.doi.org/10.1002/pds.5518
Coon	2022	Risk for Suicidal Ideation with Atomoxetine And Bupropion In Attention-Deficit/Hyperactivity Disorder: A Cohort Study	https://dx.doi.org/10.1002/jac5.1661
Crocq	2010	Suicide attempts in the SCoP study	https://dx.doi.org/10.1016/j.schres.2010.02.692
De Hert	2009	"Mortality in patients with schizophrenia": Comment.	https://dx.doi.org/10.1016/S0140-6736%2809%2961943-7
Denee	2022	POSA152 Characterising Patients with Major Depressive Disorder with Moderate-to-High Suicide Intent and Their Healthcare Resource Utilisation in England	https://dx.doi.org/10.1016/j.jval.2021.11.293
Diaz-Fernandez	2018	Clinical and rehabilitation treatment outcomes of patients with severe schizophrenia in a comprehensive, case managed programme. A 7-year follow-up	https://dx.doi.org/10.1016/j.eurpsy.2017.12.022
Dubovsky	2016	Lithium: Still the One.	10.1056/nejm-jw.NA41376

Fernandez Miranda	2015	Treatment outcomes of patients with severe schizophrenia undergoing specific severe mental illness programme. A 6-year follow-up	
Fructuoso	2014	Suicide attempt and medications. A retrospective case-control study	https://dx.doi.org/10.1111/bcpt.12301
Garcia-Carmona	2018	Paliperidone long-acting injectable (LAI) is associated with a lower intake of benzodiazepines and a lower number of admissions compared with other lais in a cohort of patients with schizophrenia	https://dx.doi.org/10.1093/schbul/sby016.507
Gasse	2013	Impact of previous suicide attempts and family history of psychiatric disease on the size of the association between antiepileptic drugs and suicide related events	https://dx.doi.org/10.1002/pds.3512
Grabner	2024	HSD70 Characteristics of Medicare Patients Initiating Long-Acting Injectable Antipsychotic Medications	https://dx.doi.org/10.1016/j.jval.2024.03.1293
Granbichler	2012	Causes of death in epilepsy patients	
Granbichler	2011	Cause-specific mortality among patients with epilepsy: Results of a 40-year cohort study	https://dx.doi.org/10.1111/j.1528-1167.2011.03206.x
Hamina	2022	Fatal overdoses in a cohort of chronic pain patients	https://dx.doi.org/10.1002/pds.5518
Hoier	2022	The association between benzodiazepine and nonbenzodiazepine and suicide: a nationwide cohort study	https://dx.doi.org/10.1192/j.eurpsy.2022.478
Hopkins	1998	Duration of untreated psychosis and outcome in a 10 year follow-up cohort of schizophrenic subjects	
Isohanni	2014	Outcomes of schizophrenia from a lifespan perspective. The Northern Finland 1966 birth cohort study (NFBC 1966)	
Jalbert	2014	Disease progression, treatment patterns, and outcomes in schizophrenia over a 3-year period: Results from the cohort for the general study of schizophrenia (CGS)	https://dx.doi.org/10.1002/pds.3701
Kanner	2012	Psychiatric comorbidities and epilepsy: Is it the old story of the chicken and the egg?	https://dx.doi.org/10.1002/ana.23679
Karadima	2010	Reasons and patterns of hospitalization among schizophrenic patients in Greece: The Grace study	https://dx.doi.org/10.1186/1744-859X-9-S1-S95

Lagerberg	2022	Reply to Ploderl and Hengartner: Learning about the course of suicidal behavior but not about the effects of SSRIS.	https://dx.doi.org/10.1038/s41386-021-01254-5
Li	2021	Meth use is associated with overdoses, high-risk practices, and adverse social determinants	https://dx.doi.org/10.1097/ADM.0000000000000902
Lindmark	2020	P.303 Treatment outcomes in patients with prescription narcotic use disorder (TAPE)	https://dx.doi.org/10.1016/j.euroneuro.2019.12.066
Lovejoy	2017	Suicidal ideation and behaviors following clinician-initiated prescription opioid discontinuation among long-term opioid users	
Lovrecic	2016	Overdoses and other drug related deaths: Comparison between outpatient treatment registered and not-registered patients	http://www.heroinaddictionrelatedclinicalproblems.org/harcp-archives.php
Manchon	2013	Psychotropics and suicidal behaviour-a case-control study	
Murru	2017	One-year course of illness and clinical management in a cohort of patients affected with schizoaffective and bipolar disorders	
Neligan	2010	Antiepileptic medications and the risk of suicide.	https://dx.doi.org/10.1001/jama.2010.1067
Nieto	2021	Completed suicide in bipolar i patients after their first hospitalisation	https://dx.doi.org/10.1192/j.eurpsy.2021.1656
Ohlund	2021	Self-injurious behaviour in patients with bipolar disorder and attention deficit hyperactivity disorder after central stimulant start- a retrospective study based on the lisie cohort	https://dx.doi.org/10.1192/j.eurpsy.2021.239
Peuskens	2010	Principal outcomes of the Sertindole Cohort Prospective (SCOP) study	https://dx.doi.org/10.1016/j.schres.2010.02.428 PT - Conference Abstract
Pompili	2022	Routine treatment pathways of patients with major depression and active suicidal ideation with intent in Italy: interim results from the ARIANNA observational study	https://dx.doi.org/10.1192/j.eurpsy.2022.397
Reutfors	2017	All-cause mortality in treatment-resistant depression: A register-based cohort study in Sweden	
Reutfors	2015	Suicide risk and side effects from antipsychotics in schizophrenia: A nested case-control study	https://dx.doi.org/10.1002/pds.3838

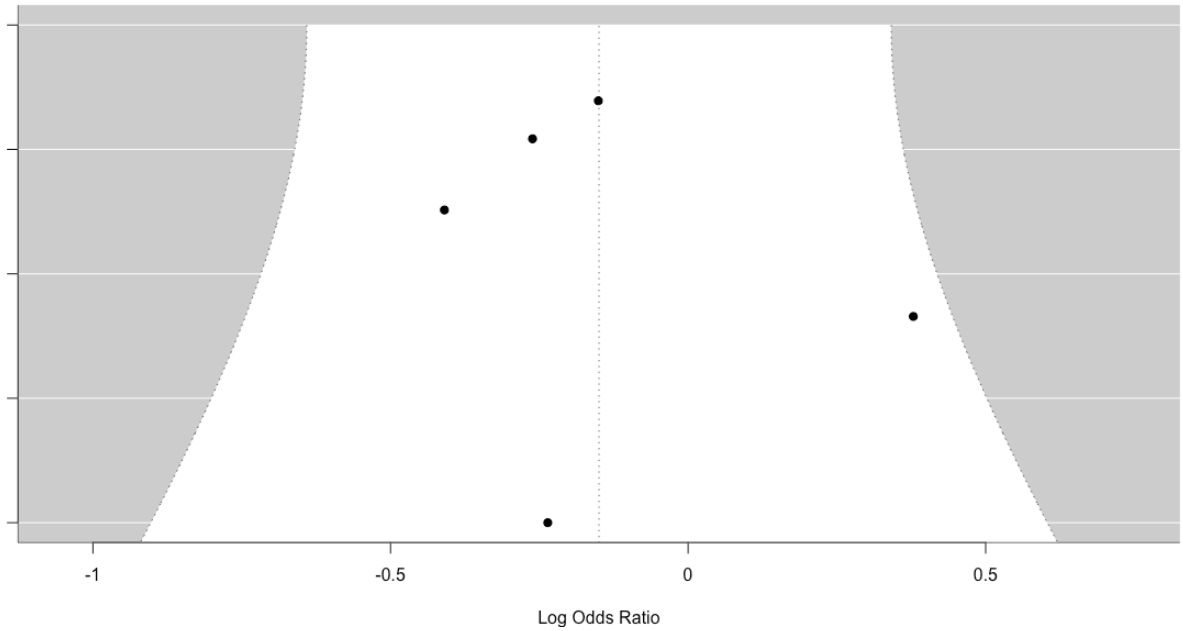
Rihmer	2015	Pharmacologial prevention of suicide	
Rihmer	2012	Depression, suicide and suicide prevention in Hungary	https://dx.doi.org/10.1016/S0924-9338%2812%2975674-2
Rissanen	2011	Use of antipsychotic medication and suicidality-the Northern Finland Birth Cohort 1966 Study	https://dx.doi.org/10.1097/01.yic.0000399969.31830.3f
Roy	2021	Disease Prevalence, Comorbid Conditions, and Medication Utilization Among Patients with Schizophrenia in the United States.	10.1017/S1092852920002515
Seppala	2017	Treatment-resistant and difficult-to treat schizophrenia as a challenge for clinical practices. Data from Finnish samples: Northern Finland birth cohort 1966 and Perfect-project	https://dx.doi.org/10.1007/s00406-017-0824-8
Stephansson	2010	Prescribed antipsychotic drugs and risk of re-hospitalization among incident patients with schizophrenia-related diagnosis	https://dx.doi.org/10.1002/pds.2019
Strom	2010	The ziprasidone observational study of cardiac outcomes (ZODIAC): Findings from a large simple trial of ziprasidone vs. olanzapine in real-world use among 18154 patients with schizophrenia	https://dx.doi.org/10.1016/j.schres.2010.02.523
Sung	2018	Risk of suicide with concurrent use of benzodiazepine, antidepressant, opioid analgesic, and zolpidem: A population based case-control and case-crossover study	https://dx.doi.org/10.1002/pds.4629
Terao	2018	Mixed features in bipolar I disorder and the effect of lithium on suicide.	https://dx.doi.org/10.1176/appi.ajp.2017.17070759
Tiihonen	2018	What does epidemiological data tell us about clozapine's effectiveness?	https://dx.doi.org/10.1093/schbul/sby014.170
Tiihonen	2018	Response to the editorial on antipsychotics and mortality in a nationwide cohort of 29,823 patients with schizophrenia	https://dx.doi.org/10.1016/j.schres.2018.06.035
Tiihonen	2006	Antidepressant use and the risk of suicide, attempted suicide and overall mortality in a nation-wide cohort	10.1016/S0924-977X(06)70350-9
Valenstein	2006	Antidepressants, Concurrent Treatments, and Completed Suicide in VA Registry Data	

Valuck	2009	General population risk of suicide attempt compared to depressed untreated and antidepressant treated populations	https://dx.doi.org/10.1002/pds.1806
Vieta	2011	Health care resource utilization among patients with bipolar disorder: Retrospective data from a large multinational longitudinal study (WAVE-BD)	
Wen	2009	Is antiepileptic drug use associated with suicidality in patients with epilepsy?	

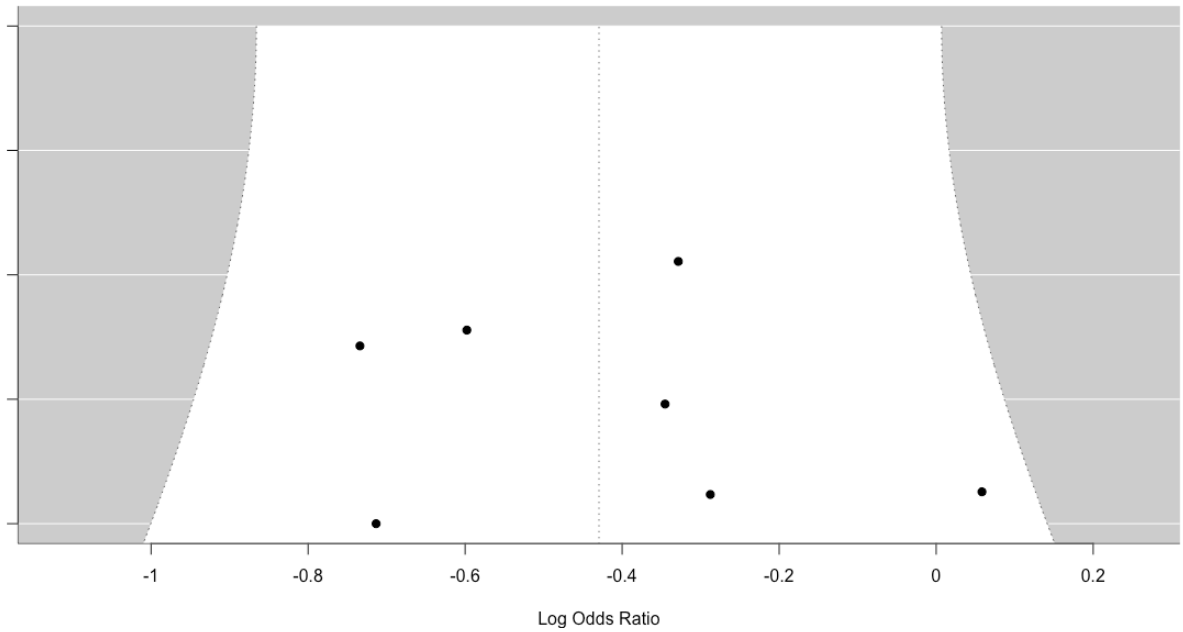
A6. Funnel plots

All visualised analyses synthesised the between-individual studies

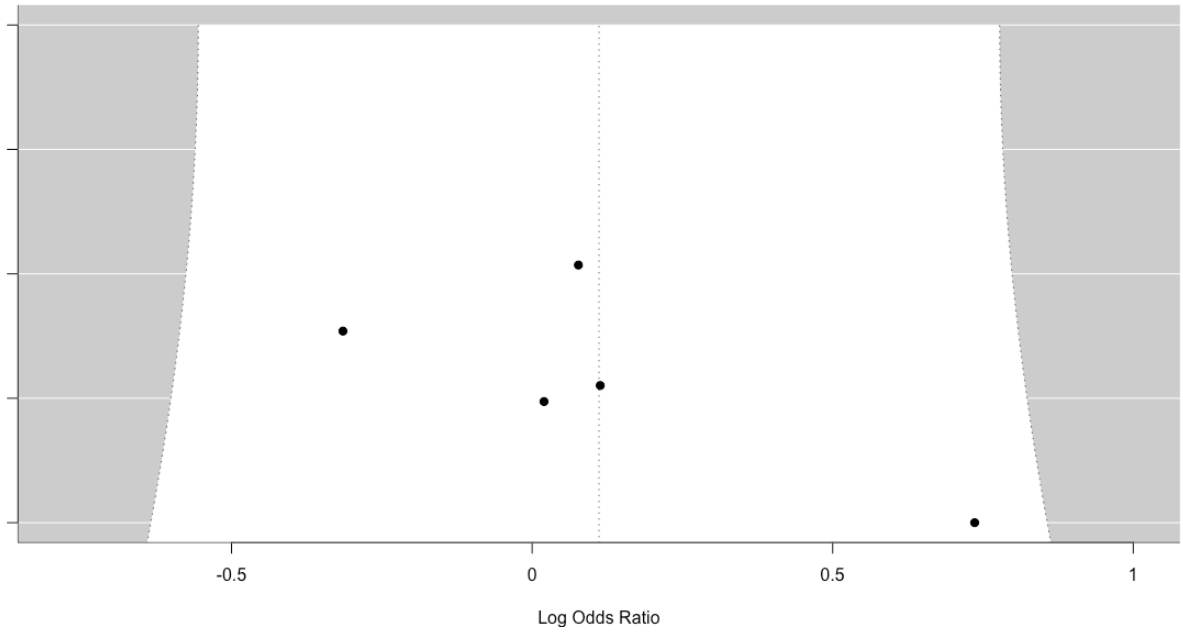
A6.1 Funnel plot for risks of suicide attempts in people with bipolar disorder treated with lithium



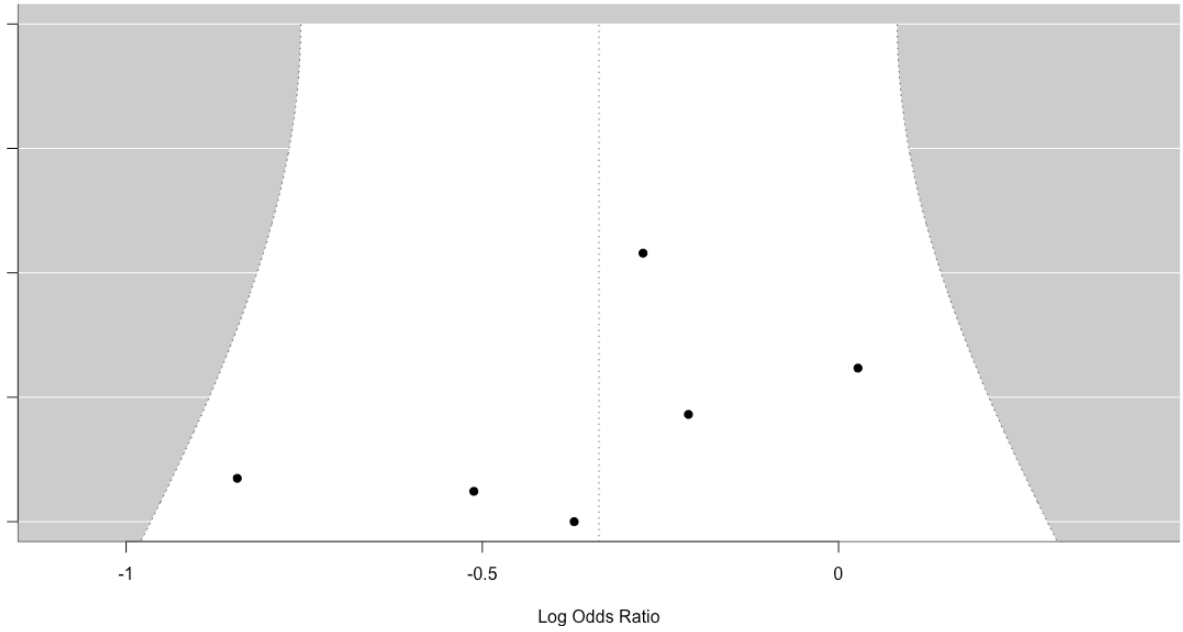
A6.2 Funnel plot for risks of suicide attempts in people treated with risperidone



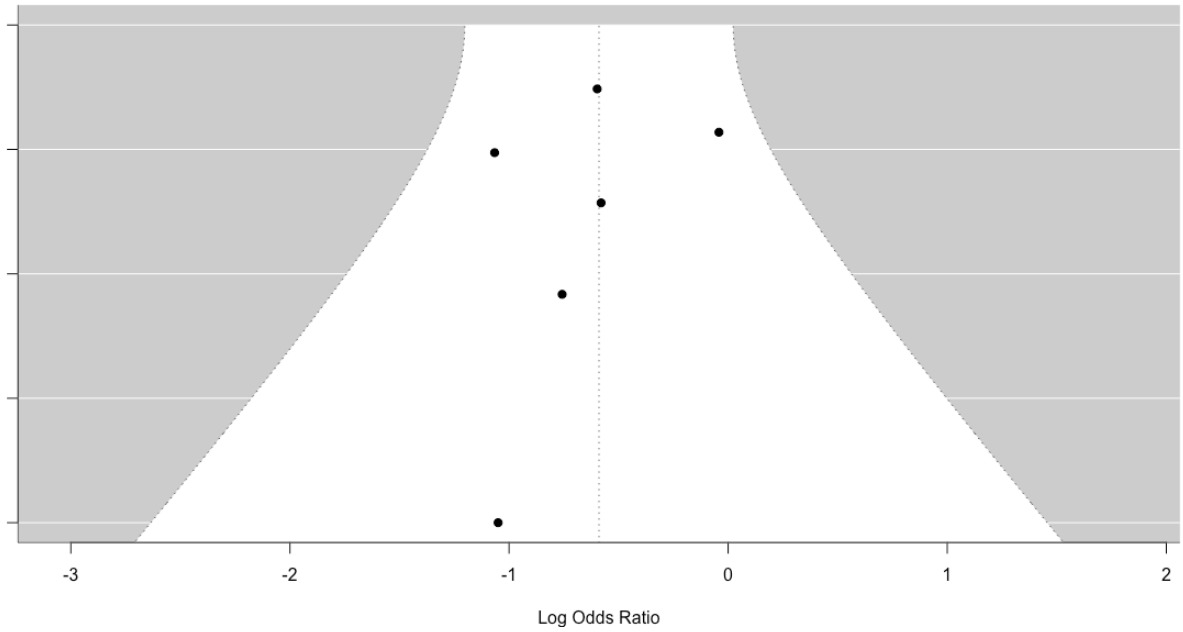
A6.3 Funnel plot for risks of suicide attempts in people treated with quetiapine



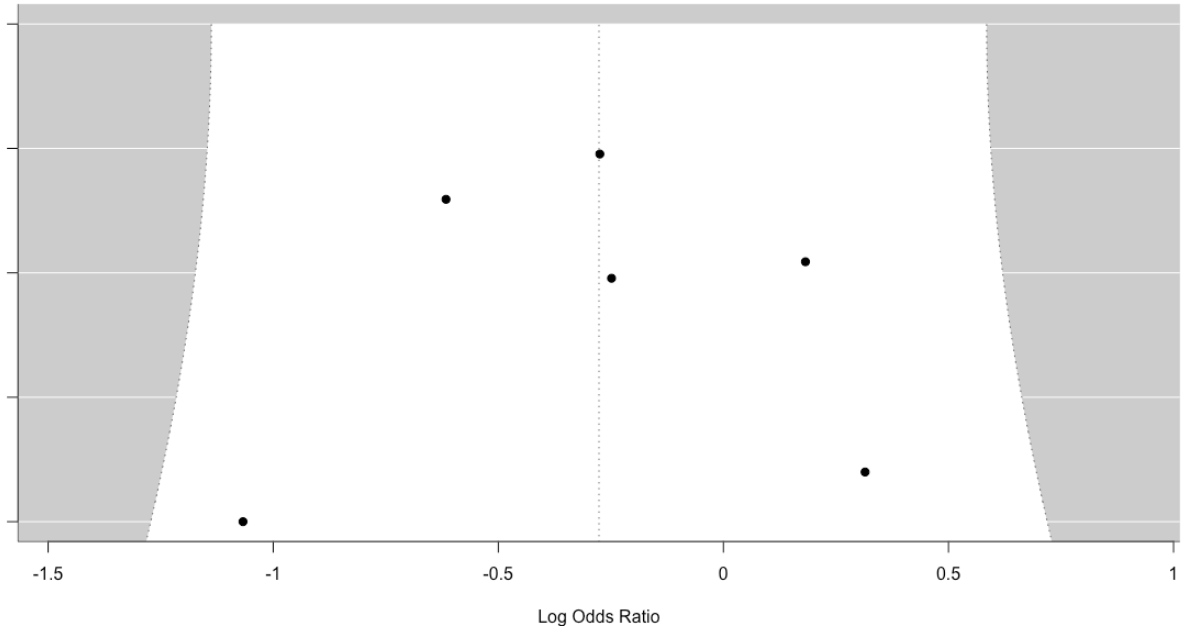
A6.4 Funnel plot for risks of suicide death in people treated with perphenazine



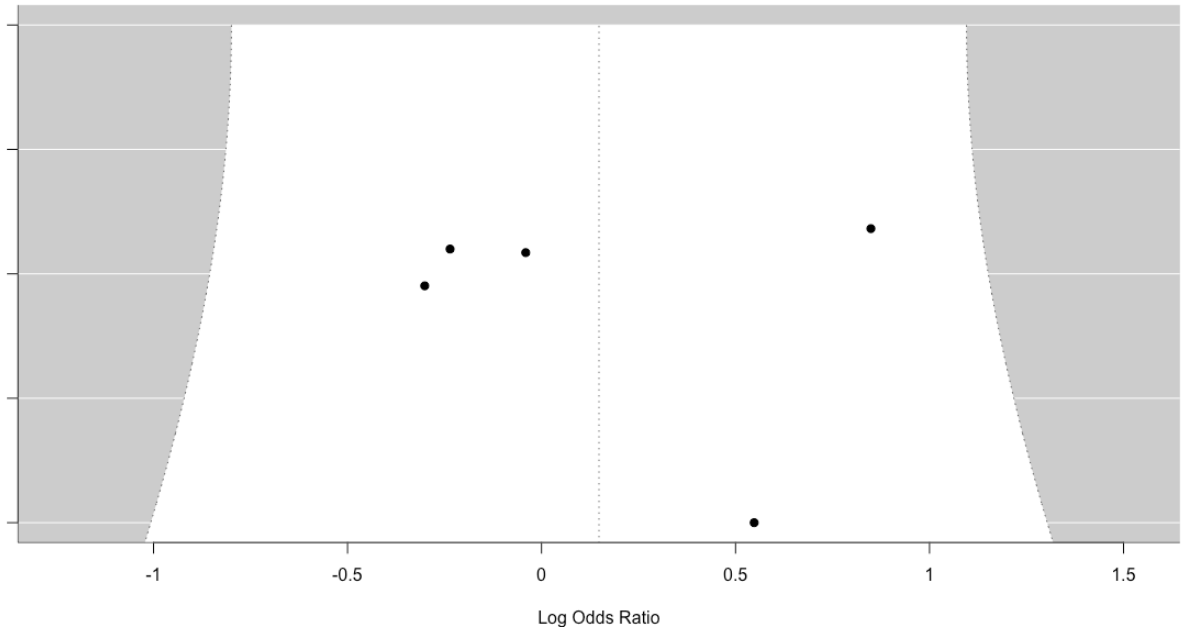
A6.5 Funnel plot for risks of suicide death in people treated with olanzapine



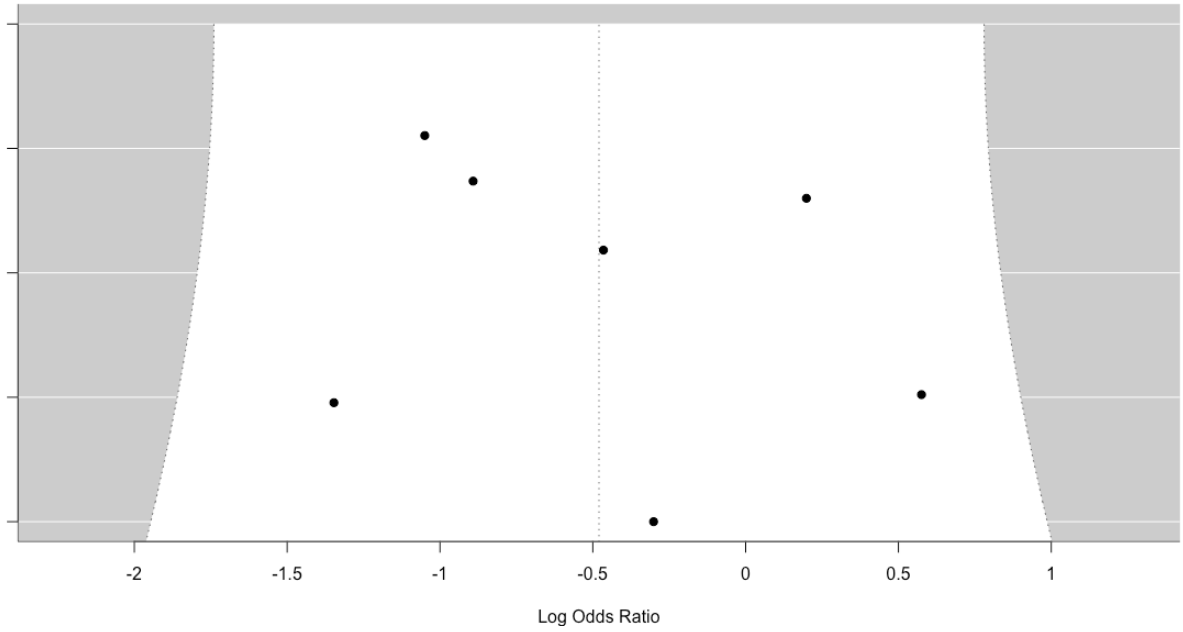
A6.6 Funnel plot for risks of suicide attempts in people treated with olanzapine



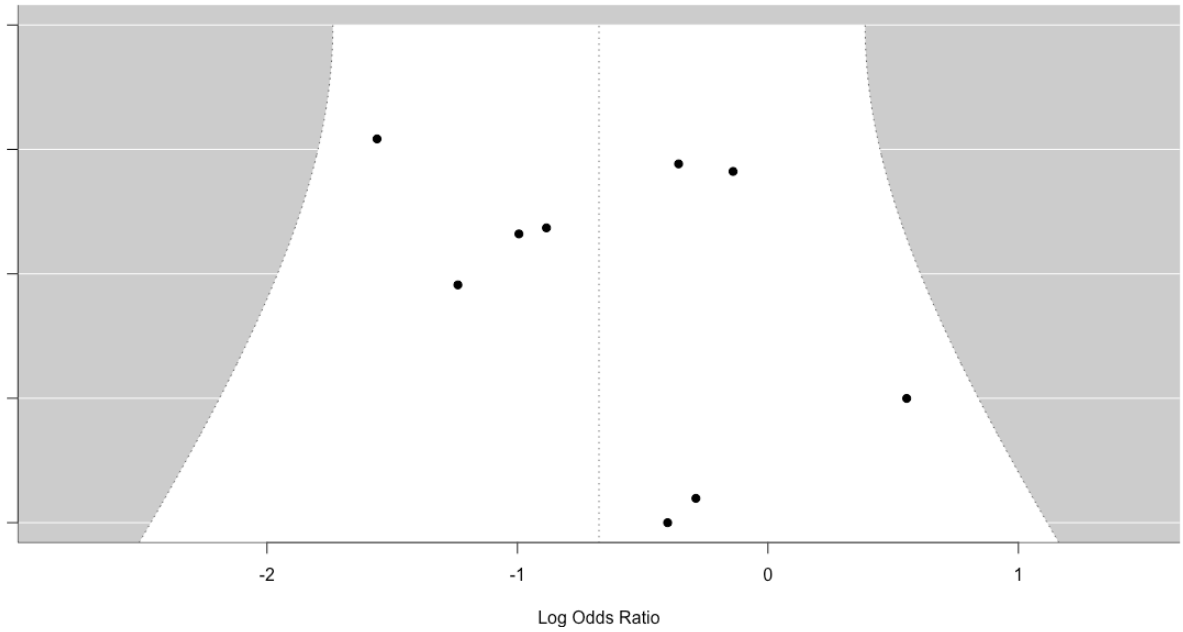
A6.7 Funnel plot for risks of suicide attempts in people treated with haloperidol



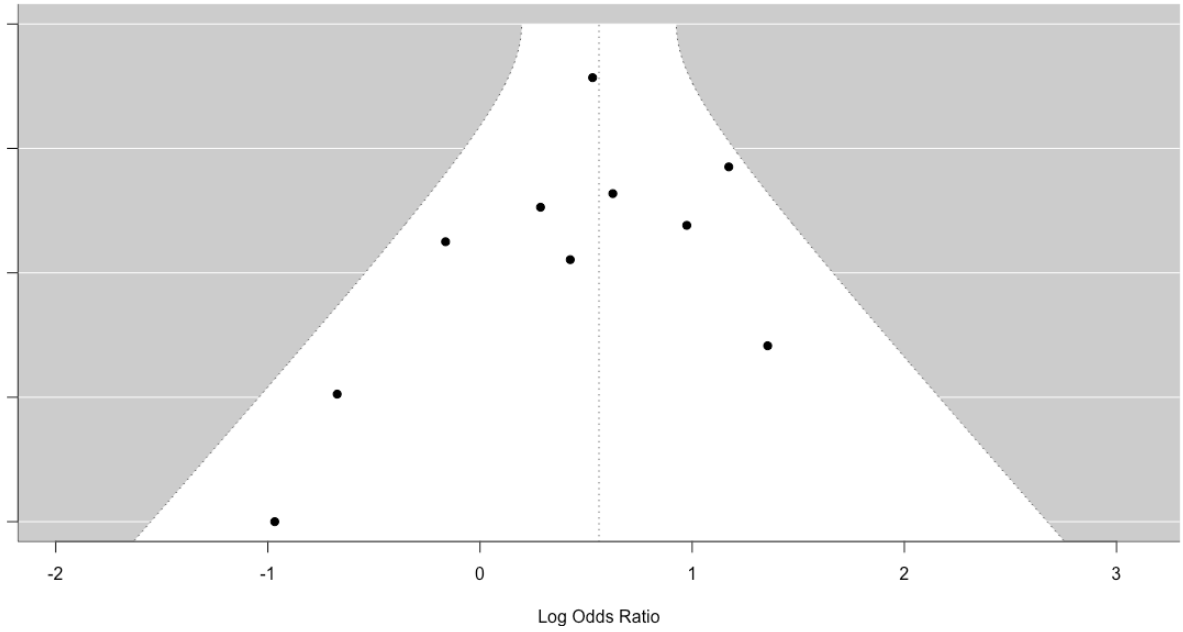
A6.8 Funnel plot for risks of suicide attempts in people treated with clozapine



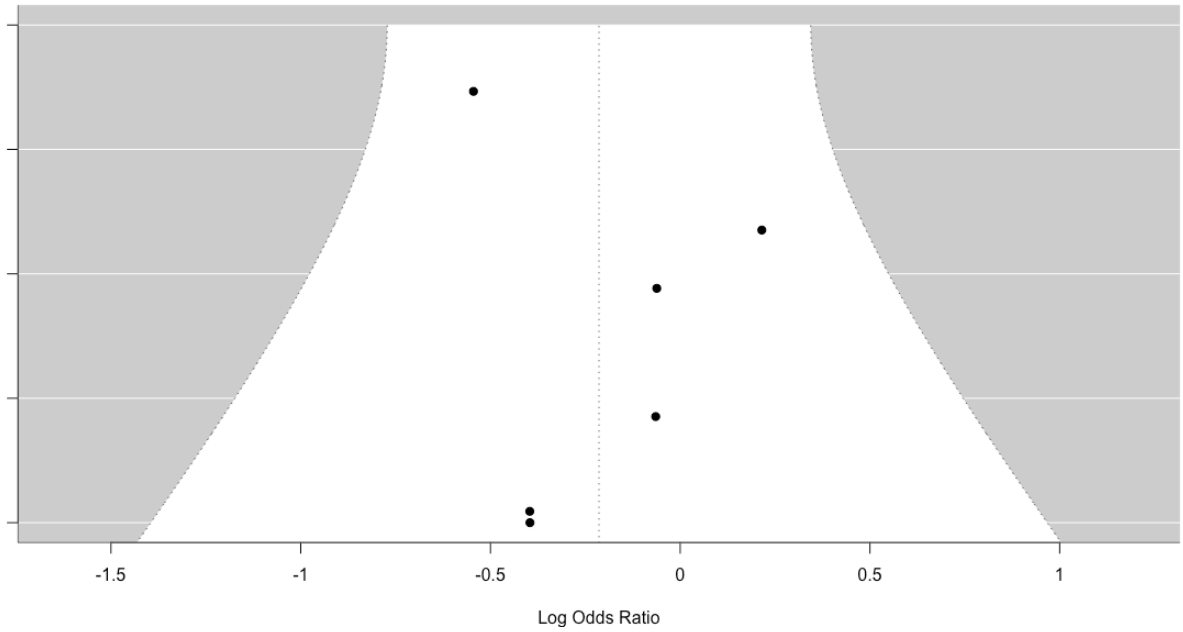
A6.9 Funnel plot for risks of suicide death in people treated with clozapine



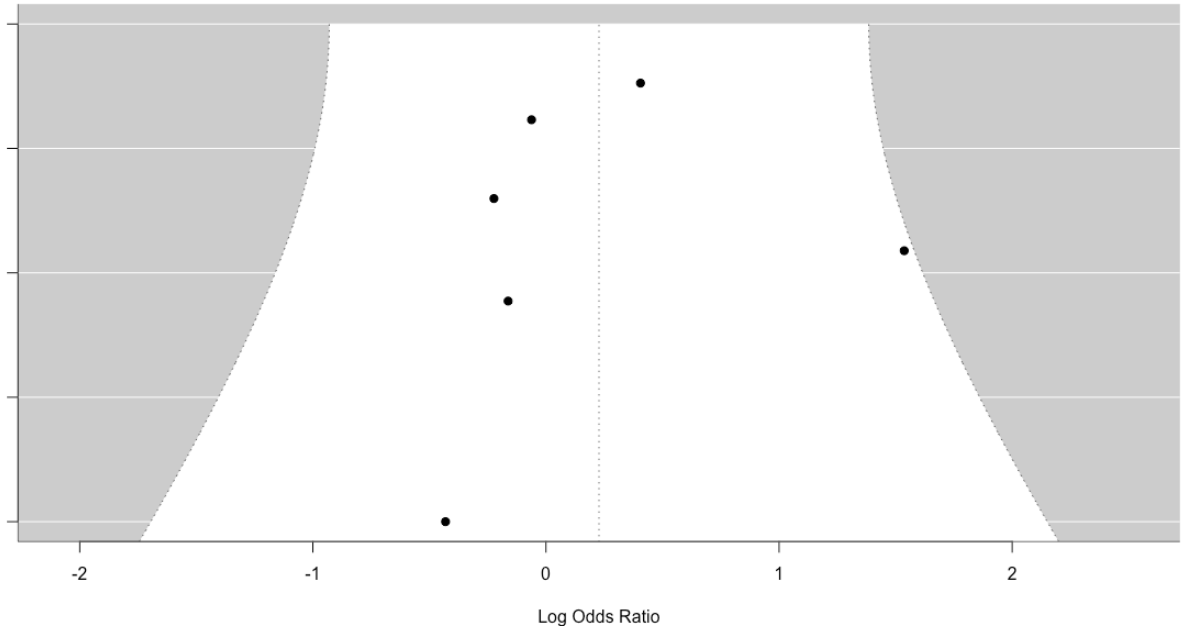
A6.10 Funnel plot for risks of suicide death in people treated with NaSSA and SNRI



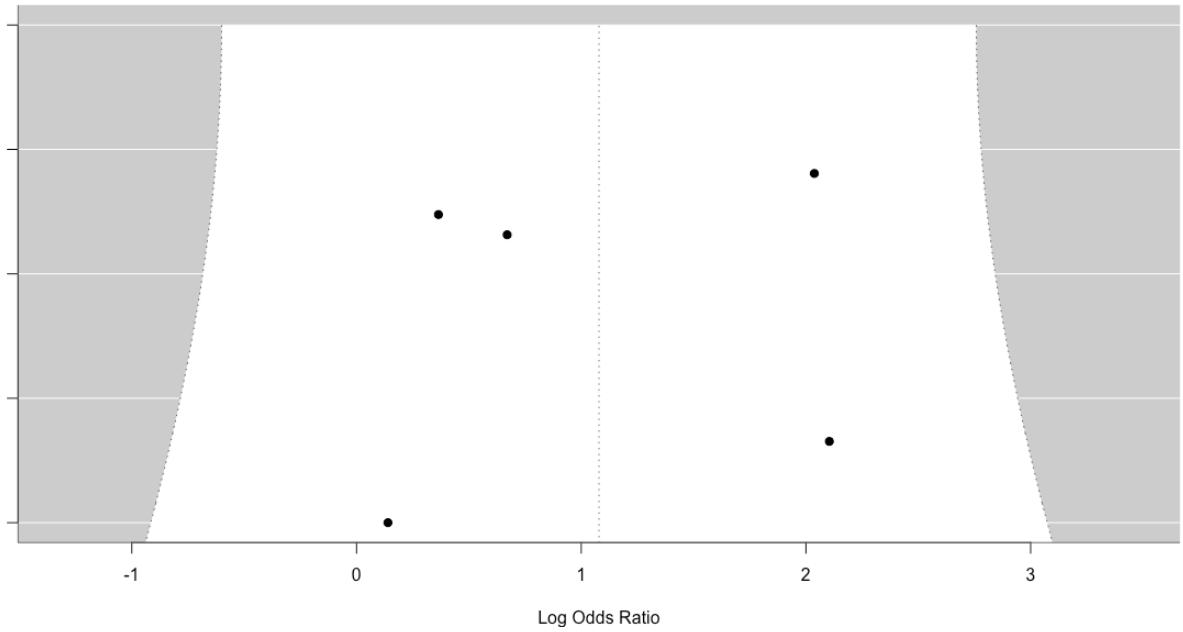
A6.11 Funnel plot for risks of suicide death in people treated with SSRIs



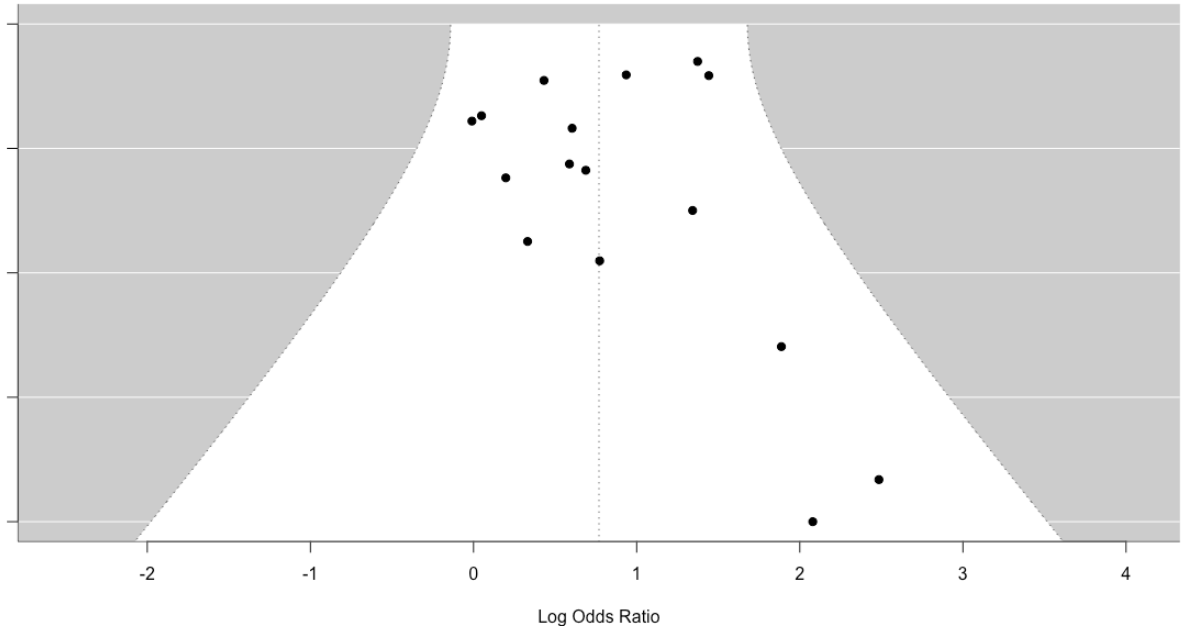
A6.12 Funnel plot for risks of suicide attempts in people treated with SSRIs



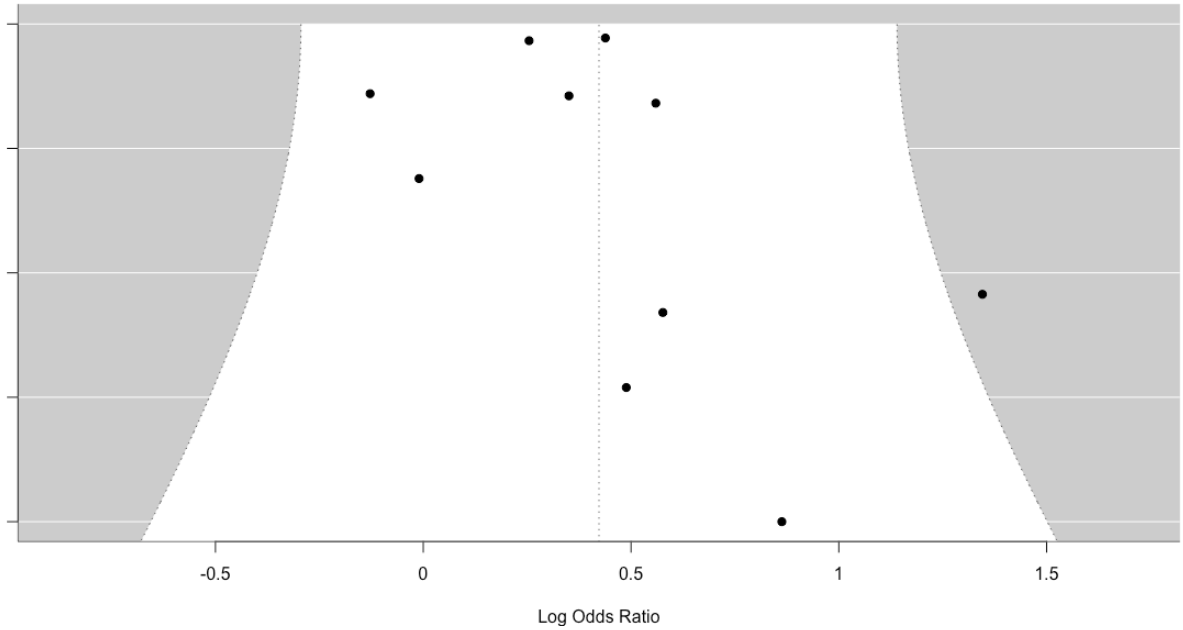
A6.13 Funnel plot for risks of suicide attempts in people treated with benzodiazepines



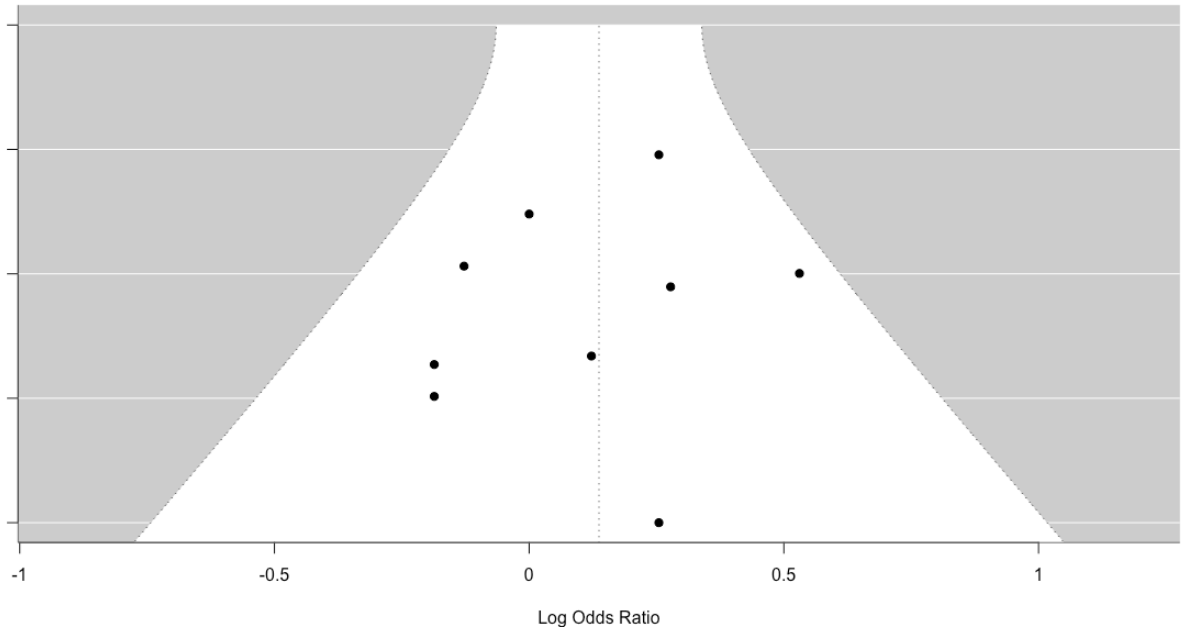
A6.14 Funnel plot for risks of suicide death in people treated with benzodiazepines



A6.15 Funnel plot for risks of suicide attempts in people treated with unspecified antipsychotics



A6.16 Funnel plot for risks of suicide death in people treated with unspecified antipsychotics



A7. PRISMA reporting checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	General abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Sect 1.2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Sect 1.3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Sect 2.3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Sect 2.2.
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Sect 2.2, A2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Sect 2.3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Sect 2.4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Sect 2.4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Sect 2.4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Sect 2.4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Sect 2.5.1 par 1
Synthesis	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention	Sect 2.5

Section and Topic	Item #	Checklist item	Location where item is reported
methods		characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Sect 2.5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Sect 2.6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Sect 2.6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Sect 2.4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Sect 3.1.1, 3.2.1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	Table 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	A3, A4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Available by request
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	A3, A4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3.1.2-3.1.6; 3.2.2-3.2.6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	3.4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	3.4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	3.5 par 1; A6
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	3.5 par 2;

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			A3, A4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	4.2-4.4
	23b	Discuss any limitations of the evidence included in the review.	4.5
	23c	Discuss any limitations of the review processes used.	
	23d	Discuss implications of the results for practice, policy, and future research.	4.6