Adverse Events of Common Psychiatric Medications: An Umbrella Review

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General Abstract

Title: Adverse events of common psychiatric medications: an umbrella review

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Abstract:

BACKGROUND: Psychiatric medications were the second most prescribed therapeutic class in the United States in 2015 with 547 million prescriptions. Adverse events of medications are very common, can be distressing to patients and are often underreported in the primary studies. The purpose of this thesis is to systematically review the scientific literature to estimate the prevalence and burden of adverse events among the most common psychiatric medications.

METHODS: The 23 most commonly prescribed psychiatric medications in the United States as well as eight psychiatric medications from the World Health Organization's Essential Medicine List were included. A systematic and comprehensive search was conducted to retrieve all published and unpublished systematic reviews with meta-analyses to assess adverse events of individual psychiatric medications (this process of collecting secondary publications and not primary studies is called "umbrella review"). Seven databases (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Embase, Medline, PreMedline, PsycINFO and PubMed) were searched between 1946 and 2016. Prevalence rates and effect estimates were extracted by two independent reviewers and summarised. A quality analysis was performed on included reviews using the AMSTAR (assessing the methodological quality of systematic reviews) tool and all were rated as medium or high quality reviews.

RESULTS: 69 systematic reviews and meta-analyses published were eligible for data extraction, quality appraisal and quantitative synthesis. Antipsychotic medications (60%) accounted for the majority of the findings, followed by antidepressants (16%), stimulants (13%), mood stabilisers (8%) and anxiolytics (3%). The strongest associations were between amitriptyline and sexual dysfunction (N=442, odds ratio [OR] 16.6; 95% Confidence Intervals [CI] 4.6 to 60.6), aripiprazole and somnolence (N=569, OR 25.8; 95% CI 1.3 to 112.3) and olanzapine and weight gain (N=249, OR 32.0; 95% CI 1.7 to 98.4). Overall, neurological adverse events were reported most frequently for antidepressant, antipsychotic and anxiolytic medication classes. Patient characteristics, particularly age and diagnosis, explained differences in adverse events across and within medication classes.

DISCUSSION & CONCLUSION:
To my knowledge, this is the first umbrella review on the tolerability profiles of 31 common psychiatric medications worldwide. Many medications were linked to adverse events through a weak or moderate strength of association and additional factors contributed to the variability in adverse outcome reporting aside from patient characteristics. Findings from this review need to be examined with the efficacy profiles of the medications and the clinical circumstances of the individual patients.

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Abbreviations and Symbols Used

- AE = Adverse event
- CI = Confidence interval
- OR = Odds ratio
- RR = Risk ratio
- ES = Effect size
- SMD = Standardised mean difference
- SMR = Standardised mortality ratio
- ARR = Absolute risk reduction
- ARI = Absolute risk increase
- * = Data not found
- N = Study size
- k = Number of reviews
- PO = Per oral
- IM = Intramuscular
- mg/d = Milligrams per day
- ms = Milliseconds
- x = Mean
- AMSTAR = Assessing the methodological quality of systematic reviews
- Q1 = Question one
- EPS = Extrapyramidal symptoms
- GI = Gastrointestinal
- PD = Panic disorder
- ADD = Attention deficit disorder
- ADHD = Attention deficit hyperactivity disorder
- OCD=Obsessive compulsive disorder
- ASD = Autism spectrum disorder
- ID = Intellectual disability
- PDD = Pervasive developmental disorder
- BMI = Body Mass Index
- URTI = Upper respiratory tract infection
- AIMS = Abnormal Involuntary Movement Scale
- NOS = Not otherwise specified
- SAS = Sampson-Angus Scale
- BAS = Barnes Akathisia Scale
- DIEPSS = Drug Induced Extrapyramidal Symptom Scale
- ESRS = Extrapyramidal Symptom Rating Scale
- C&A = Children and adolescents
- Rx = Treatment

Chapter 1: Introduction

1.1 Background

Psychiatric medications are a key component of the healthcare of millions of people worldwide. Psychiatric medications were prescribed in the United States more than almost every other therapeutic class of medications in 2015 (547 million prescriptions), second only to antihypertensive medications (706 million).[1] Among these medications, antidepressants and anti-epileptic medications were two of the five medication classes that experienced the highest prescription growth in 2015. Adverse events are common among people taking psychiatric drugs. Their severity ranges from mild to severe and can even lead to death in the very rare cases.[2]

To date, systematic reviews investigating adverse events of psychiatric medications have often focused on one or two specific adverse events, such as mortality, akathisia, prolongation in the corrected QTc interval, weight gain, insomnia or somnolence.[3-7] Specifically, atypical antipsychotics were reported to be associated with a small increased risk of death compared to placebo for older people with Alzheimer's disease or dementia.[3] Certain atypical antipsychotics, such as aripiprazole, asenapine and lurasidone, were also associated with a higher risk of akathisia, anxiety and agitation compared to placebo and older atypical antipsychotics in individuals with schizophrenia.[4] Healthy volunteers taking aripiprazole had a significantly decreased QTc interval whereas participants taking risperidone and ziprasidone significantly increased the QTc interval.[5] Olanzapine, risperidone and aripiprazole were reported by Almandil et al. to be associated with statistically significant weight gain in children and adolescents with a range of psychiatric conditions.[6] The majority of second-generation antidepressants were found to be linked to insomnia, somnolence and suicidality in individuals with major depressive

disorder.[8] Additionally, there are reviews that analysed a pre-selected cluster of adverse events. For instance, DeHert et al. studied metabolic and endocrine adverse events and reported that atypical antipsychotics were associated with hyperprolactinaemia, weight gain and associated metabolic disturbances in children and adolescents with a wide range of psychiatric diagnoses.[9] All of the previously mentioned reviews had several limitations such as insufficient information on the baseline clinical characteristics, medical conditions or concurrent medications of the study population, publication bias, different and inconsistent cut-offs for the reporting of adverse events, high levels of heterogeneity or a lack of details on the methodology implemented. These systematic reviews also reported a small number of included studies, included studies with small sample sizes or included studies that were too short to adequately measure all of their primary research outcomes.

Due to the significance of adverse events for patients, more clarity on the prevalence and strength of associations between medications and specific adverse events is necessary, and this lends itself to an umbrella review. Unlike a traditional systematic review or meta-analysis that are restricted to individual studies, a single treatment comparison or a single adverse event, an umbrella review (also referred to as a meta-review) can assess multiple psychiatric medications and multiple adverse events in the same review.[10] Such research can benefit patients, clinicians and researchers' understanding of tolerability outcomes. It can also provide an overview of adverse effects that can be weighed more easily with their established efficacy profiles to facilitate clinical decision-making.

This umbrella review will summarise the evidence from reviews and meta-analyses on adverse events according to medication. The umbrella review research design is appropriate and has

many potential advantages. Specifically, it involves a transparent and reproducible systematic search strategy, which minimizes the risk of research error and bias that are often associated with narrative reviews. Additionally, the umbrella review methodology allows for the analysis of multiple treatments and multiple outcomes. Moreover, given the increasingly large volume of clinical literature, I wanted to provide a broad overview of the evidence landscape, which was conveniently facilitated by this research design.[11] To my knowledge, there is no pre-existing umbrella review on adverse events for such an extensive list of psychiatric medications across psychiatric diagnoses and age ranges. A good example of an umbrella review that had a focus similar to my own was completed by Correll et al. in 2015.[12] It reported the effect estimates of adverse events for antipsychotics, antidepressants and mood stabilisers in individuals with schizophrenia, depression and bipolar disorder. However, it was distinct from the umbrella review I conducted as it presented data for entire classes of medications (not individual medications), focused only on three psychiatric conditions, and exclusively looked at adverse events that related to the risk of physical diseases.

1.2 Aims

The aim of this review was to systematically analyse the adverse events of the most common psychiatric medications. I presented the extracted results first by class of medication, then by diagnosis of the population studied and finally by individual medication. Furthermore, I aimed to examine and compare the characteristics of the included systematic reviews as well as their methods and quality ratings.

Chapter 2: Methodology

2.1 Search Strategy

The following electronic databases were searched from inception to February 1st 2016: Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Embase, Medline, PreMedline, PsycINFO and PubMed. I consulted with an information scientist, Sarah Stockton, who optimized my search terms and suggested two of the databases used (Database of Abstracts of Reviews of Effects and PreMedline). A search for unpublished meta-analyses was also undertaken by searching through PROSPERO, contacting the authors of conference abstracts to retrieve the papers in full and checking the reference lists of relevant papers.[13] No date or language restrictions were applied.

The following subject index terms were used to target the medications of interest: *'antidepressive agents; antidepressive agents, second generation; antidepressive agents, tricyclic; serotonin uptake inhibitors; serotonin and noradrenaline reuptake inhibitors; amitriptyline; bupropion; citalopram; clomipramine; desvenlafaxine succinate; duloxetine hydrochloride; fluoxetine; paroxetine; sertraline; trazodone; venlafaxine hydrochloride; antipsychotic agents; aripiprazole; chlorpromazine; clozapine; fluphenazine; haloperidol; quetiapine fumarate; risperidone; anticonvulsants; carbamazepine; lithium carbonate; lithium; valproic acid; central nervous system stimulants; lisdexamfetamine dimesylate; methylphenidate; amphetamines; anti anxiety agents; buspirone; hydroxyzine; benzodiazepines; alprazolam; diazepam; lorazepam'*.

A separate search combining index terms for generic and specific adverse events was conducted. The following subject index terms were used: *'dizziness; nausea; suicide'; 'suicide, attempted';*

'suicidal ideation'; 'hostility'; 'mortality'; 'drug-related side effects and adverse reactions'; 'sleep initiation and maintenance disorders'; 'disorders of excessive somnolence'; 'accidental falls'; 'gastrointestinal haemorrhage'; 'cardiovascular diseases'. The following specific subject index terms were used to identify systematic reviews and meta-analyses: *'placebo; prevalence; randomized controlled trial'; 'randomized controlled trial (topic)'; 'meta-analysis as topic'; 'review literature as topic'.* These terms were combined with a study design limit for *systematic reviews* and *meta-analyses*.

The electronic database search was supplemented by a manual search of reference lists from relevant reviews. The protocol was registered in Prospero, the international prospective register of systematic reviews, on March 31st, 2016.

2.2 Study Eligibility

Eligible studies included: (a) systematic reviews (comprehensive, transparent and replicable reviews) and meta-analyses (statistical analyses of results from multiple studies that often calculate a single summary effect size) that examined the adverse events of one of the thirty-one medications; (b) reviews comprised of randomised or quasi-randomised placebo-controlled studies; (c) reviews that provided either a prevalence rate or an effect estimate with 95% confidence intervals; (d) both published and unpublished reviews were considered without any date or language restriction. The intervention inclusion criteria were based on the IMS' list of the most prescribed medications and the WHO Essential Medicine List so that this umbrella review would be clinically relevant in many different settings.[14-15]

Studies that used a research design different than that of a systematic review, such as randomized controlled trials, were excluded. Systematic reviews comprised of observational studies were

excluded. Due to the wide scope of the project, I decided to focus on participants with a psychiatric illness or healthy participants without any medical condition. Reviews that examined patients with a non-psychiatric illness were excluded. Reviews that included combination or adjunct therapy were excluded. Systematic reviews with more than 20% of the study population with medical comorbidities were excluded. The papers were independently screened by a second researcher, Tomasz Bajorek, a higher trainee (post-MRCPsych) psychiatrist with experience in clinical research. Any disagreements were arbitrated by a third researcher, Andrea Cipriani.

Inclusion Criteria	Exclusion Criteria
Design: Systematic reviews with meta-analysis of randomised or quasi-randomised controlled trials.	**Design:** Meta-analyses and systematic reviews of non-randomised trials, individual randomised controlled trials, observational studies, narrative reviews, and case studies.
Population: Individuals who were prescribed one of the medications of interest who are either healthy participants or have a psychiatric illness coded for in the DSM-IV.	**Population:** Individuals with a non-psychiatric illness (e.g. diabetes, chronic pain or cancer) or those prenatally exposed to a medication of interest.
Interventions: **Antidepressants:** Amitriptyline, bupropion, citalopram, clomipramine, desvenlafaxine, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, trazodone, venlafaxine. **Antipsychotics:** Aripiprazole, clozapine, fluphenazine, haloperidol, olanzapine, quetiapine, risperidone. **Anxiolytics:** Alprazolam, buspirone, diazepam, hydroxyzine, lorazepam. **Mood stabilisers:** Carbamazepine, lithium, valproate. **Stimulants:** Amphetamine salts, lisdexamfetamine, methylphenidate.	**Interventions:** Cognitive Behavioral Therapy, Dialectical Behavior Therapy, Mindfulness-based Therapy, other group therapies (e.g. Music Therapy, Art Therapy), homeopathic medication, St. John's Wort, non-psychotropic medication, combination or augmentation therapy, studies with active controls.
Outcomes: Clinical adverse events (e.g. suicidal ideation, tardive dyskinesia, sedation, weight gain, constipation, edema, tremor, diarrhea, rash, headaches, dizziness, dry mouth, abdominal pain, decreased appetite, psychosis, tics, dyspepsia, nasal congestion, sexual dysfunction or parkinsonism).	**Outcome:** Non-clinical adverse events that required brain imaging or genetic tests to identify (e.g. brain glutamate levels, reduced hippocampal volumes, gray matter abnormalities, serum levels of inflammatory cytokines), general dropout rates.

Other: Studies in any language and published at any date prior to the last date of the search (1st February, 2016). Unpublished studies, such as doctoral theses, were also considered.	**Other:** Studies that failed to provide either prevalence rates or effect sizes with 95% confidence intervals for specific adverse events, even after contact with the authors, were excluded.

Table 1 - Inclusion and Exclusion Criteria for Quantitative Synthesis

2.3 Data Extraction and Quality Assessment

Data was extracted onto a standardised form (Appendix D). The original prevalence rates and effect estimates with 95% confidence intervals were recorded. In addition, the number of reviews, total number of participants, year of publication, medication, dose, duration, patient setting, patient's illness, mode of diagnosis and adverse events examined were recorded. The data were cross-checked by a second extractor, Tomasz Bajorek.

Considerable effort was invested in retrieving included papers following the title and abstract screening. For example, whenever a corresponding author of an irretrievable paper was listed on PubMed or an alternative online platform, an e-mail was sent to retrieve the full paper. Thirty-one e-mails were sent in total and a response was received from 11 authors. Additionally, e-mails were sent to authors of abstracts that had been included in conference proceedings to retrieve the papers in full. Authors were also contacted in order to retrieve any relevant appendices, including tables and figures, if the full text did not clearly state the effect sizes, confidence intervals, study size or study characteristics.

Multiple papers that were retrieved in the search were published in foreign languages and no more than their abstracts, if that, were translated into English. Papers that were in Dutch, French, Italian, Spanish, Portuguese, Mandarin and German were translated with the help of colleagues who were also fluent in these languages.[16]

The 'Assessing the Methodological Quality of Systematic Reviews' ('AMSTAR') tool was leveraged to assess the quality of the included reviews. I selected this instrument as it is a standard tool in similar evidence synthesis project, it has good inter-rater agreement, test-retest reliability, face validity and construct validity.[17] The assessment is comprised of eleven items, which each score either a '1' if the item is present in the review or a '0' if the item is absent. Scores that were equal or less than 3 were considered low, between 4 to 7 were medium, and between 8 to 11 were high. The eleven questions of the tool were also outlined in Table 2.

AMSTAR scores were calculated for each review that met the final inclusion criteria. No distinction was made between medium or high scoring reviews in the forest plot diagrams. No reviews were excluded on the basis of having a lower AMSTAR score. Any concerns surrounding the quality of the eligible reviews are discussed further in the Discussion Section under Strengths and Limitations.

Question	Score '1' or '0'
1. Was an a priori design provided?	
2. Was there duplicate study selection and data extraction?	
3. Was a comprehensive literature search performed?	
4. Was 'grey' (unpublished) literature considered?	
5. Was a list of studies (included and excluded) provided?	
6. Were the characteristics of the included studies provided?	
7. Was the scientific quality of the included studies assessed and documented?	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	
9. Were methods used to combine the findings of studies appropriate?	
10. Was the likelihood of publication bias assessed?	
11. Were conflicts of interest stated?	
Total :	**/11**

Table 2 - Assessing the Methodological Quality of Systematic Reviews Scoring System

2.4 Statistical Analysis – Effect Estimates

Different methods of expressing effect estimates were used amongst the included reviews. The following effect estimates were reported: odds ratios (ORs), relative risks (RRs), Cohen's d and standardised mean differences (SMDs). Systematic reviews that presented Cohen's d, SMDs or sufficient prevalence data were included and these data were converted into ORs or RRs.

The medications with the most reported effect estimates were presented in forest plots. RRs and ORs were combined in the same forest plots although when possible the results were converted into comparable units of analysis. Effect sizes reported as Cohen's d or alternative standardised mean differences were converted into log transformed ORs.[18] The formulae used were outlined in Appendix A. Reviews that were lacking effect estimates occasionally reported prevalence rates. If data were reported for both the exposed group and the placebo group, I calculated the respective ORs. In total, I dichotomized data from nine different reviews, which resulted in more evidence for 13 of the included medications. When it was feasible ORs were converted into RRs in order for the entirety of the results for a medication to be in comparable units, such was the case for lisdexamfetamine and methylphenidate. Given that ORs and RRs are distinct effect estimates (with ORs typically providing higher effects than RRs), the RRs have been marked with an asterisk on the forest plots.

All analyses were performed using Stata 14.1.

The criteria in Table 3 that were based on the work of Rosenthal 1996 were utilised to analyse the ORs extracted.[19] ORs with values of 1.0 to 1.5 were considered weak, 1.6 to 2.5 were considered moderate, 2.6 to 9.9 were considered strong and 10.0 or greater were considered very strong. The above and below criteria only applied if the 95% CI didn't include the null value of

one. The criteria outlined in Table 4 were amalgamated from the works of Monson 1990 and Schoenbach 2000 and used to analyse the extracted RRs.[20,21] Therefore, an RR either between 0.7 and 1.0 (decreased risk) or 1.0 and 1.5 (increased risk) was considered to be weak and an RR either less than 0.9 or greater than 1.5 was considered moderate to strong. A value of 1.0 indicated no difference in the rate of the adverse event between the experimental and placebo study populations.

Odds Ratio (Increased Risk)	Odds Ratio (Decreased risk)	Strength of Association
1.0 – 1.5	0.67 – 1.0	Weak
1.6 – 2.5	0.40 - 0.66	Moderate
2.6 – 9.9	0.10 - 0.39	Strong
10.0 <	< 0.10	Very strong

Table 3 - Assessing the Strength of an Odds Ratio

Risk Ratio (Increased risk)	Risk Ratio (Decreased risk)	Strength of Association
1.0 – 1.5	0.7 – 1.0	Weak
1.5 - 3.0	0.3 – 0.7	Moderate
> 3.0	< 0.3	Strong

Table 4 - Assessing the Strength of a Relative Risk

I chose three categories of adverse events from the 28 that were listed in the NCI Common Terminology Criteria for Adverse Events.[22] These were three categories that were deemed the most relevant and a fourth category named 'Other' was added to group all the remaining adverse events (Table 5).

Category Name	Adverse Events Included
Constitutional	Fatigue, fever, hypothermia, insomnia, obesity, patient odour, rigors/chills, sweating, weight gain, weight loss, constitutional adverse events-other
Gastrointestinal	Anorexia, ascites, colitis, constipation, dehydration, dentures, periodontal, teeth, teeth development, diarrhoea, dehydration, hypotension, distension, dry mouth, dysphagia, enteritis, esophagitis, GI fistula, gastritis, heartburn, haemorrhoids, ileus, incontinence, GI leak, malabsorption, mucositis/stomatitis, nausea, GI necrosis, GI obstruction, GI perforation, proctitis, GI prolapse of stoma, salivary gland changes, GI stricture, taste alteration, typhlitis, GI ulcer, vomiting, GI-other
Neurology	Agitation, anxiety, apnea, ataxia, brachial plexopathy, CNS necrosis, cognitive depression, disturbance, confusion, dizziness, encephalopathy, involuntary movement, euphoria, extrapyramidal, restlessness, hydrocephalus, irritability, laryngeal nerve, CSF leak, leukoencephalopathy, memory impairment, mental status, mood alteration, myelitis, neuropathy-cranial, neuropathy-motor, neuropathy-sensory, personality, phrenic nerve, psychosis, pyramidal tract dysfunction, seizure, somnolence, speech impairment, syncope (fainting), tremor, neuralgia/peripheral nerve, neurology-other
Other	Other event not listed in the categories above

Table 5 – Common Terminology Criteria for Adverse Events

Chapter 3: Results

3.1 Main Results

3.1.1 Included studies

The original search yielded over 14,000 references and after de-duplication there were 13,282 papers for initial screening (Figure 1). 729 papers were selected for full paper screening based on their titles and abstracts. After further scrutiny, a final set of 69 papers was included. Sixty-three of these papers provided ORs or RRs and six papers solely provided prevalence data, Cohen's d or SMDs. The data and the study characteristics were extracted and the quality of these 69 papers was analysed. However, the 63 papers with ORs or RRs were the main focus of this analysis and I used the data in these papers to make the forest plots for each of the included medications. The remaining six papers were used to either validate or challenge the results found from the 63 systematic reviews.

The included systematic reviews were comprised of more than 100,000 participants overall. Twenty-six individual medications and 120 specific adverse events were included in the quantitative analysis. Appendix D defines the characteristics of the included reviews. The systematic reviews were comprised of at least 80% parallel studies. However, data were only extracted from meta-analyses that used the first period of cross-over studies to avoid any carry-over effects. The duration of the studies ranged from 1.5 hours to 4 years. The studies took place in a variety of settings including hospitals, ambulatory care, community centres and nursing homes. Many of the eligible reviews failed to report their own study characteristics such as dosages administered, number of participants, number of studies and patient setting. Numerous effect sizes reached statistical significance and occasionally reviews would contradict each other in terms of whether an adverse event was significantly associated with a medication or not.

However, I did not identify reviews with opposing directions of magnitude for any adverse event. Nearly all of the adverse event outcomes favoured the placebo rather than the study group with a few exceptions, which will be discussed in the Results under the heading of Decreased Risks.

In this chapter, I will first discuss the results by class of medication in order to give an overview of the literature. Then, I will discuss the results by diagnosis followed by individual medication in order to give a more detailed presentation of the results. Throughout the Results Section by Individual Medication I will indicate in parentheses the effect estimates and 95% confidence intervals extracted for the drugs with the strongest effect sizes. More detailed information on the study size and the number of studies can be found in Appendix D. In the subsection entitled Main Results by Class of Medication and Main Results by Diagnosis, the most significant results will not be indicated in the text as the data are presented in table format. Additionally, due to the large volume of adverse events reported, they are not explained in detail here but in Appendix E.

3.1.2 Excluded studies

660 reviews were excluded. Often the included trials were not randomised or the reviews were not comprehensive, for instance, only relying on one database to conduct their search. 25 systematic reviews focused on either pregnant women or individuals prenatally exposed to the medications of interest. 134 meta-analyses were based on selective reviews that had been conducted in a non-systematic manner. 74 systematic reviews were comprised of observational studies. Additionally, reviews that included an active comparator, augmentation strategies or participants with medical co-morbidities were excluded.

The DSM IV was used to make the list of diagnoses for the inclusion criteria, however, reviews based on studies using previous versions of the DSM and ICD were allowed. Examples of reviews that did not meet the inclusion criteria included "Treatment of fibromyalgia with antidepressants: A meta-analysis," "Impact of particular antiepileptic drugs on the survival of patients with glioblastoma multiforme" and "Efficacy and safety of low-dose tricyclic antidepressants in patients with irritable bowel syndrome: a meta-analysis."[23-25] A few reviews analysed pharmacogenetic outcomes or neurological outcomes that would require medical testing beyond the scope of an initial primary care visit to detect. Specifically, the following papers were examples of reviews that were excluded: "Brain glutamate levels measured by brain magnetic resonance spectroscopy in patients with bipolar disorder: A meta-analysis", "Reduced hippocampal volumes in bipolar disorders are masked by exposure to lithium: A meta-analysis", "Gray matter abnormalities in cocaine versus methamphetamine-dependent patients: A neuroimaging meta-analysis" and "The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: A meta-analysis."[26-29] Often papers discussed broad classes of medications, such as SSRIs or benzodiazepines, and provided effect estimates for the entire class as opposed to the individual agents. Similarly, reviews reported the total number of dropouts without investigating the incidence of specific adverse events that occurred. Approximately 26% of the systematic reviews retrieved inadequately reported the study size or total number of studies included.

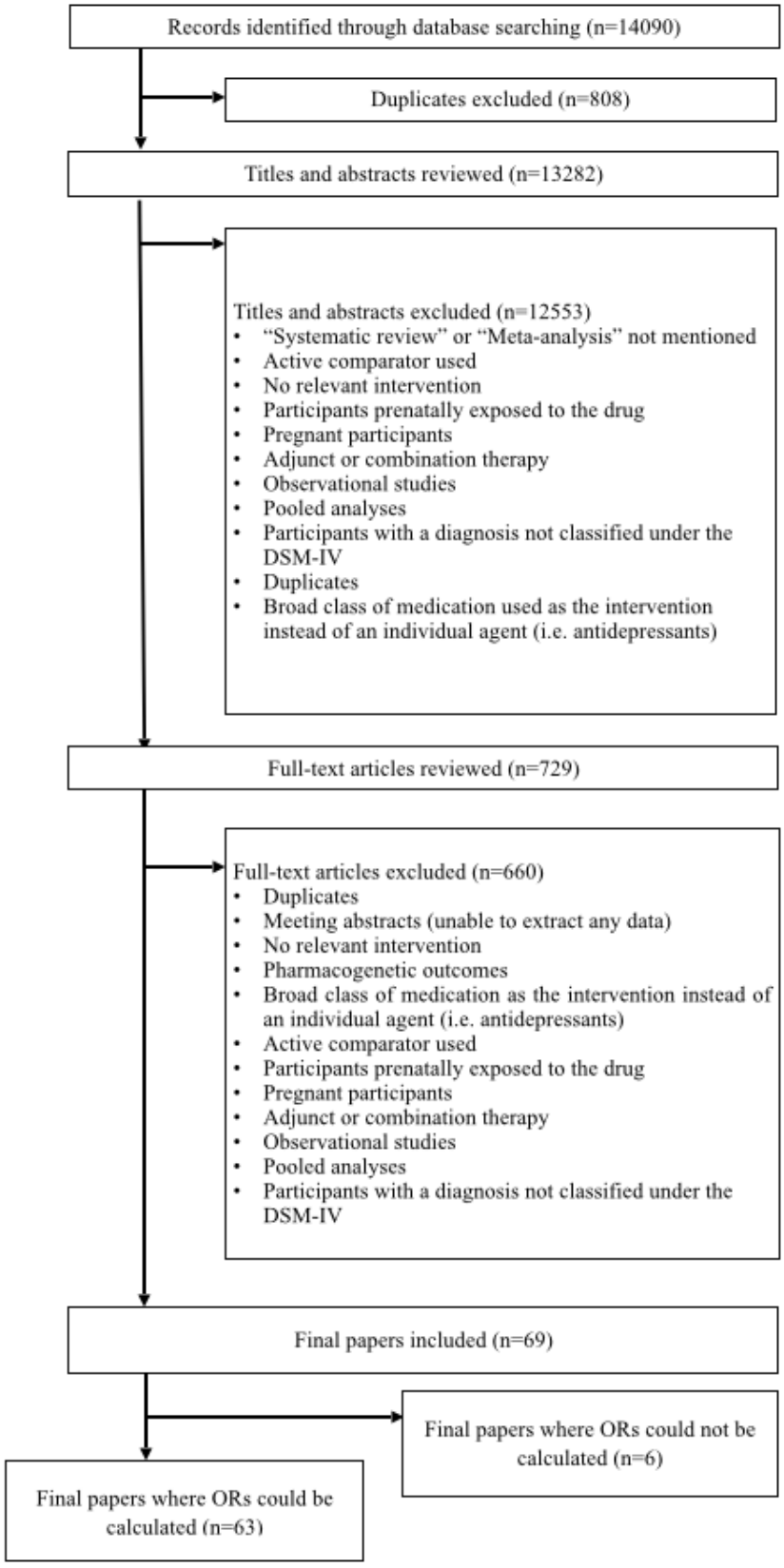

Figure 1 – Modified PRISMA flow diagram

3.2 Main Results by Class of Medication

In this section I discussed the results by class of treatment. The classes of psychiatric medications included antidepressants, antipsychotics, anxiolytics, mood stabilisers, and stimulants. Tables were generated to display the outcomes for each class of medications and the results were listed in descending order of strength of association. Additionally, I highlighted the three strongest associations to events extracted for each class of medication. First, I analysed antidepressants.

3.2.1 Adverse Events for Antidepressants

Over the last 50 years, increased research efforts and reporting schemes have shaped the development and improvement of antidepressant medications. As mentioned in the Methodology Section, I analysed the prevalence and types of adverse events for each class. 43% of the results reported in the antidepressant class of medications were neurological adverse events and 44% of these neurological adverse events were found to be statistically significant. Examples of neurological adverse events investigated in this umbrella review included suicidality, somnolence, dizziness, confusion and mood alterations, such as agitation and anxiety. The second most commonly reported category of adverse events for antidepressant medications was constitutional (20%), followed by gastrointestinal (19%) and 'Other' (18%). The table below (Table 6) illustrates the strongest associations between antidepressant medications and adverse events. Over half (55%) of the results with strong effect sizes were reported by a single review.[30] A wide range of ages were investigated; certain reviews focused solely on children and adolescents while others focused on the adult population or a mix of all both. The three strongest associations were between amitriptyline and sexual dysfunction, venlafaxine and suicide-related events and amitriptyline and dry mouth. Numerous adverse events for antidepressants in this

umbrella review have previously been reported or flagged in ongoing debates. For instance, suicidality has been a concern of second-generation antidepressants since 2003 and as a result, regulatory bodies such as the Food and Drug Administration have cautioned physicians in the prescribing of such medications, particularly for children and adoelscents.[31]

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N
Leucht, 2012 [30]	Amitriptyline	Major Depression	Sexual Dysfunction	15-93 years	OR	*	16.6	4.5 - 60.6	442
Whittington, 2004 [32]	Venlafaxine	Major Depression	Suicide-related Events	8-18 years	*	RR	13.8	1.8 - 103.6	*
Leucht, 2012	Amitriptyline	Major Depression	Dry Mouth	15-93 years	OR	*	13.5	9.4 - 19.4	1414
Leucht, 2012	Amitriptyline	Major Depression	Urinary Problems	15-93 years	OR	*	8.7	2.0 - 39.1	418
Leucht, 2012	Amitriptyline	Major Depression	Dyspepsia	15-93 years	OR	*	6.8	2.5 - 18.5	859
Leucht, 2012	Amitriptyline	Major Depression	Anticholinergic AE	15-93 years	OR	*	6.3	3.4 - 11.7	279
Leucht, 2012	Amitriptyline	Major Depression	Tremor	15-93 years	OR	*	5.7	3.2 - 10.1	1230
Leucht, 2012	Amitriptyline	Major Depression	Sedation/Sleepiness/ Somnolence/ Drowsiness	15-93 years	OR	*	5.5	3.7 - 8.2	1690
Leucht, 2012	Amitriptyline	Major Depression	Increased appetite	15-93 years	OR	*	4.0	2.0 - 8.2	460
Leucht, 2012	Amitriptyline	Major Depression	Tachycardia	15-93 years	OR	*	3.9	1.7 - 8.8	384
Leucht, 2012	Amitriptyline	Major Depression	Blurred Vision and Ambloyopia	15-93 years	OR	*	3.7	2.4 - 5.8	1055
Leucht, 2012	Amitriptyline	Major Depression	Constipation	15-93 years	OR	*	3.4	2.4 - 4.9	1255
Alberti, 2015 [7]	Citalopram	Major Depression	Somnolence	=>18 years	OR	*	3.0	1.9 - 4.9	3034
Coleman, 2012 [33]	Desvenlafaxine	Major Depression	Nausea	=>18 years	OR	*	3.0	1.4 – 6.4	*
Coleman, 2012	Venlafaxine	Major Depression	Nausea	=>18 years	OR	*	3.0	1.6 - 5.8	*
Leucht, 2012	Amitriptyline	Major Depression	Low blood pressure/ Dizziness/ Syncope	15-93 years	OR	*	2.9	2.1 - 4.1	1246
Alberti, 2015	Duloxetine	Major Depression	Somnolence	=>18 years	OR	*	2.9	2.2 - 3.8	5612
Alberti, 2015	Desvenlafaxine	Major Depression	Somnolence	=>18 years	OR	*	2.9	2.5 - 3.4	9593
Alberti, 2015	Paroxetine	Major Depression	Somnolence	=>18 years	OR	*	2.8	2.4 - 3.4	6181
Alberti, 2015	Venlafaxine	Major Depression	Somnolence	=>18 years	OR	*	2.8	2.3 - 3.4	9327

Alberti, 2015	Escitalopram	Major Depression	Somnolence	=>18 years	OR	*	2.6	1.8 - 3.8	5276
Barbui, 2008 [70]	Paroxetine	Major Depression	Suicidal Tendencies	>=18 years	OR	*	2.6	1.2 - 5.5	3739

Table 6 – Significant associations between antidepressants and adverse events

3.2.2 Adverse Events for Antipsychotics

The tolerability profiles, especially the neurological adverse events, for antipsychotic medication have sparked increased research in this area. 53% of the adverse events in this umbrella review were classified as neurological and a majority (57%) were statistically significant. Extrapyramidal symptoms such as akathisia, dystonia, parkinsonism, tremor and dyskinesia were often reported. They were mostly reported in individual categories instead of under the umbrella term of extrapyramidal symptoms, which has been useful for data analysis purposes in the past. For instance, acute extrapyramidal symptoms, such as muscular spasms of the jaw, back and extremities, were flagged as risk factors for tardive dyskinesia.[35] Different directions of evidence were found for numerous adverse events in this class, especially for extrapyramidal symptoms. A more detailed explanation of the differences found among results was outlined in the Variation in Results Section. The second most commonly reported category of adverse events for antipsychotic medications was 'Other' (27%), followed by constitutional (14%) and gastrointestinal (6%). The table below (Table 7) illustrates the 50 strongest associations between adverse events and antipsychotics agents. There were many strong links found between antipsychotics and adverse events (Appendices D and E for full results) and more than any other class of medication. The three strongest effect sizes were between olanzapine and weight gain (twice) as well as between haloperido1 and dystonia.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N
Rendell, 2003 [36]	Olanzapine	Bipolar or Schizoaffective Disorder	Weight gain	18-86 years	OR	*	32.0	1.7 - 98.4	249
Cohen, 2012 [37]	Olanzapine	Schizophrenia or Bipolar Disorder	Weight Gain (kg)	8-17 years	OR	*	15.1	6.6 - 31.1	242
Adams, 2013 [38]	Haloperidol	Schizophrenia	Dystonia	<18-65 years	*	RR	11.5	3.2 - 40.9	471
Kishi, 2012 [39]	Olanzapine	Anorexia Nervosa	Drowsiness/ Sedation/ Somnolence	12-37 years	*	RR	11.5	2.9 - 44.5	
Ching, 2012 [40]	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Tremor	6-17 years	*	RR	10.3	1.4 - 76.6	313
Ching, 2012	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Drooling	6-17 years	*	RR	9.6	1.3 - 72.1	313
Cohen, 2013 [41]	Risperidone	Pervasive Developmental Disorder or Intellectual Disability	Somnolence	7-14 years	OR	*	9.6	3.5 - 22.8	569
Cohen, 2012	Olanzapine	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	8.5	4.0 - 16.6	1291
Leucht, 2009 [42]	Olanzapine	Schizophrenia	Sedation	38 years (median)	*	RR	8.3	1.2 - 59.6	408
Gao, 2008 [35]	Haloperidol	Bipolar Mania	Overall EPS	Unclear	OR	*	7.8	4.5 - 13.4	484
Cohen, 2013	Risperidone	Pervasive Developmental Disorder or Intellectual Disability	Significant weight gain	7-14 years	OR	*	7.8	1.9 - 25.2	470
Cohen, 2012	Risperidone	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	7.3	4.6 - 11.2	1827
Tan, 2015 [43]	Olanzapine	Dementia	Urinary infection	77-84 years	OR	*	6.9	1.3 – 36.0	*
Powney, 2012 [44]	Haloperidol	Psychosis-induced Aggression or Agitation	EPS During 24 Hours	18-73 years	*	RR	6.8	2.2 - 21.1	398
Stoffers, 2010 [45]	Olanzapine	Borderline Personality Disorder	Body weight change in kg	23-33 years	OR	*	6.7	5.1 - 8.8	752
Cohen, 2012	Olanzapine	Schizophrenia or Bipolar Disorder	EPS	8-17 years	OR	*	6.4	2.4 - 13.8	1014
Cohen, 2013	Aripiprazole	Pervasive Developmental Disorder or Intellectual	Significant Weight Gain	8-10 years	OR	*	6.3	1.6 - 17.1	507

		Disability							
Cohen, 2012	Quetiapine	Schizophrenia or Bipolar Disorder	Significant weight gain	8-17 years	OR	*	6.2	2.6 - 13.6	1343
Cohen, 2012	Aripiprazole	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Somnolence	8-17 years	OR	*	6.1	2.8 - 12.2	1632
Adams, 2014 [46]	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Photosensitivity	18-64 years	*	RR	6.0	3.2 - 11.3	799
Cohen, 2012	Risperidone	Schizophrenia or Bipolar Disorder	Significant weight gain	8-17 years	OR	*	6.0	3.0 - 11.4	1756
Tan, 2015	Quetiapine	Dementia	Somnolence	77-84 years	OR	*	5.9	2.4 - 14.5	*
Komossa, 2010 [47]	Quetiapine	Major Depression	Sedation	18-70 years	OR	*	5.8	2.3	2118
De Fruyt, 2012 [48]	Aripiprazole	Bipolar Depression	Akathisia	18-65 years	*	RR	5.6	3.4 - 9.3	727
Adams, 2013	Haloperidol	Schizophrenia	Parkinsonism	<18-65 years	*	RR	5.5	2.7 - 11.2	485
Cohen, 2012	Quetiapine	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	5.4	2.9 - 9.3	1424
Ballard, 2006 [49]	Risperidone	Alzheimer's Disease	Abnormal gait	>60 years	OR	*	5.3	2.2 - 12.6	1100
Maher, 2011 [50]	Quetiapine	Dementia	Sedation	Unclear	OR	*	5.2	2.9 - 9.5	799
Adams, 2013	Haloperidol	Schizophrenia	Rigidity	<18-65 years	*	RR	5.0	2.7 - 9.0	461
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weight Increase	18-64 years	*	RR	4.9	2.3 - 10.4	165
Adams, 2013	Haloperidol	Schizophrenia	Weight gain (kg)	<=65 years	*	RR	4.9	1.4 – 17.0	441
Gao, 2008	Aripiprazole	Bipolar Mania	Akathisia	Unclear	OR	*	4.8	2.3 - 10.1	523
Ballard, 2006	Olanzapine	Alzheimer's Disease	Abnormal Gait	>60 years	OR	*	4.8	1.7 - 13.6	450
Ballard, 2006	Olanzapine	Alzheimer's Disease	Weight Gain	>60 years	OR	*	4.7	1.1 - 20.4	685
Maher, 2011	Olanzapine	Dementia	Increased appetite or weight increase	Unclear	OR	*	4.7	1.9 - 14.1	808
Maher, 2011	Olanzapine	Dementia	Sedation	Unclear	OR	*	4.6	2.9 - 7.6	1218

Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Dry Mouth	18-64 years	*	RR	4.6	2.4 - 8.9	1015
Ballard, 2006	Olanzapine	Alzheimer's Disease	Fever	>60 years	OR	*	4.6	1.0 - 19.8	450
Tan, 2015	Risperidone	Dementia	Stroke	77-84 years	OR	*	4.5	1.8 - 11.7	*
DeFruyt, 2012	Quetiapine	Bipolar Depression	Sedation	18-65 years	*	RR	4.5	2.6 - 4.7	1732
Depping, 2010 [51]	Quetiapine	Generalised Anxiety Disorder	Sedation in short term	=>18 years	OR	*	4.9	2.7 - 7.6	2262
Cohen, 2012	Aripiprazole	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Weight Gain	8-17 years	OR	*	4.4	2.0 - 8.9	1615
Gao, 2008	Risperidone	Bipolar Disorder	Anticholinergic Use	Unclear	OR	*	4.4	2.7 - 7.3	549
McQuire, 2015 [52]	Risperidone	Autism Spectrum Disorder or Intellectual Disability	Weight change in kg	=<18 years	OR	*	4.4	2.8 - 6.8	*
Ching, 2012	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Sedation	6-17 years	*	RR	4.3	1.6 - 11.6	313
Gao, 2008	Risperidone	Bipolar Disorder	Overall EPS	Unclear	OR	*	4.2	2.6 - 7.1	584
Ballard, 2006	Haloperidol	Alzheimer's Disease	Drowsiness	>60 years	OR	*	4.2	1.8 - 9.9	229
Cipriani, 2006 [53]	Haloperidol	Bipolar or Schizoaffective Disorder	Extrapyramidal Disorder	18-68 years	*	RR	4.2	2.9 - 6.0	474
Adams, 2013	Haloperidol	Schizophrenia	Blurred Vision	<18-65 years	*	RR	4.0	1.2 - 12.9	240
Adams, 2013	Haloperidol	Schizophrenia	Tremor	<18-65 years	*	RR	3.9	2.0 - 7.9	447

Table 7 – Significant associations between antipsychotics and adverse events

3.2.3 Adverse Events for Anxiolytics

This umbrella review investigated the adverse events for anxiolytic medication. Only systematic reviews for hydroxyzine and buspirone were retrieved in my search. These systematic reviews

comprised of adults and older adults with generalised anxiety disorder. 42% of the total results constituted of neurological adverse events and 19% of these neurological adverse events were found to be statistically significant. The next most commonly reported category of adverse events for anxiolytic medications were gastrointestinal (25%) and 'Other' (25%). I generated the table below (Table 8) to illustrate the statistically strong links between adverse events and anxiolytics. Buspirone was shown to be strongly associated with dizziness. However, the paucity of data overall in the table suggests there are limitations of my search methodology or an absence of good quality systematic reviews on anxiolytics.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N
Chessick, 2006 [60]	Buspirone	Generalised Anxiety Disorder	Dizziness	=>18 years	*	RR	3.2	1.8 - 5.6	635

Table 8 – Significant associations between anxiolytics and adverse events

3.2.4 Adverse Events for Mood Stabilisers

The adverse events for mood stabilisers were explored. My search retrieved three eligible systematic reviews for lithium, which was the most widely used mood stabiliser for years.[61-63] However, the evidence has reported a narrow therapeutic index for the drug as well as concerns regarding its effect on renal function and the risk of teratogenicity.[64] 20% to 40% of patients may not respond to lithium and may be prescribed valproate or carbamazepine, which have become the best adjunctive and alternative treatments for the treatment of bipolar disorder. My search retrieved no eligible reviews for carbamazepine and seven systematic reviews for valproate. Valproate has demonstrated its effectiveness in treating acute mania or for maintenance treatment of bipolar disorder. However, the evidence has previously linked this anticonvulsant with a range of adverse events ranging from alopecia and lethargy to rarer and fatal adverse events such as pancreatitis and hepatotoxicity.[65] Among the total results extracted in this

umbrella review 35% were classified as 'Other' types of adverse events, such as hypothyroidism, skin disorders, headaches urinary tract infection, thrombocytopenia and falls. 31% of these 'Other' adverse events were statistically significant. The second most commonly reported category of adverse events was gastrointestinal (26%), followed by neurological (24%) and constitutional (15%). A table was generated (Table 8) to illustrate the strong associations in this class. The three strongest associations for mood stabilisers were all for valproate. Specifically, the drug was associated with thrombocytopenia, gastrointestinal problems, and dizziness.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N
Lonergan, 2009 [66]	Valproate	Dementia	Thrombocytopenia	=> 49 years	OR	*	7.9	1.9 - 32.6	186
Lonergan, 2009	Valproate	Dementia	GI problems	=> 49 years	OR	*	7.1	1.7 - 29.0	208
Macritchie, 2003 [65]	Valproate	Bipolar Disorder	Dizziness	18-75 years	*	RR	3.2	1.1 - 8.9	279
Lonergan, 2009	Valproate	Dementia	Urinary tract infection	=> 49 years	OR	*	3.0	1.0 - 8.8	227

Table 9 – Significant associations between mood stabilisers and adverse events

3.3.5 Adverse Events for Stimulants

This umbrella review analysed the adverse events for stimulants. 44% of the total results were categorised in the 'Other' category of adverse events and included headaches, feeling jittery, abdominal pain, skin disorders, injury, pyrexia, pharyngitis, influenza, nasal congestion, change in the QT interval and nasal congestion. 20% of these 'Other' results were statistically significant. The next most commonly reported category of adverse events was gastrointestinal (21%) and neurological (21%), which were followed by constitutional adverse events (14%). Table 10 highlights the statistically strong links between adverse events and stimulant medications. The three strongest associations were between lisdexamfetamine and feeling jittery, lisdexamfetamine and decreased appetite, and methylphenidate and weight gain (decreased risk).

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N
Citrome, 2015 [67]	Lisdexamfetamine	Binge Eating Disorder	Feeling jittery	18-55 years	*	RR	11.4	2.4 - 40.6	1004
Punja, 2016 [68]	Lisdexamfetamine	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	9.8	5.1 - 19.0	1081
Punja, 2016	Amphetamine salts	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	6.4	1.6 - 26.5	1124
Punja, 2016	Lisdexamfetamine	Attention Deficit Hyperactivity Disorder	Insomnia/trouble sleeping	6-17 years	*	RR	5.9	2.8 - 12.3	1081
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Dry mouth	18-55 years	*	RR	4.9	3.8 - 6.2	1004
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Constipation	18-55 years	*	RR	4.5	1.9 - 9.8	1004
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Decreased appetite	18-55 years	*	RR	4.1	2.4 - 6.8	1004
Storebo, 2015 [69]	Methylphenidate	Attention Deficit Hyperactivity Disorder	Decreased weight	6-17 years	*	RR	3.9	1.4 - 10.6	859
Storebo, 2015	Methylphenidate	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	3.7	2.6 - 5.2	2962
Schacter, 2001 [70]	Methylphenidate	Attention Deficit Disorder	Dizziness	=<18 years	*	RR	3.5	1.2 - 9.3	383
Punja, 2016	Amphetamine salts	Attention Deficit Hyperactivity Disorder	Insomnia/trouble sleeping	6-17 years	*	RR	3.3	1.3 – 9.0	1280
Schacter, 2001	Methylphenidate	Attention Deficit Disorder	Decreased appetite	=<18 years	*	RR	3.1	2.5 - 3.7	675
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Insomnia	18-55 years	*	RR	2.9	1.9 - 4.4	1004
Storebo, 2015	Methylphenidate	Attention Deficit Hyperactivity Disorder	Weight gain	6-17 years	OR	*	0.13	0.1 - 0.3	805

Table 10 – Significant associations between stimulants and adverse events

3.3 Main Results by Diagnosis

After providing an overview of the adverse events by medication class, I will now examine adverse effects grouped by diagnosis. Diagnoses were classified under the following broader categories: schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, eating disorders, cognitive disorders and developmental disorders. An additional category labeled 'Other' was used to include non-diagnostic problems such as erectile dysfunction and aggression or agitation. Additionally, a subcategory was made in the 'Other' category to group together all of reviews not classified elsewhere. The reason for this was that numerous reviews included participants with wide-ranging psychiatric conditions, which made comparability

between data not feasible. The most commonly reported diagnoses among the included reviews were schizophrenia spectrum disorders, as well as mood disorders, specifically major depression and bipolar disorder. Tables were generated to display the results for each diagnosis and the results were listed in descending order of strength of association to facilitate analysis. Additionally, I identified the three strongest associations reported in each diagnosed population.

3.3.1 Adverse Events in Populations with Schizophrenia and Other Psychotic Disorders

3.3.1.1 Schizophrenia Spectrum Disorders

Seven reviews and six medications were included in this category. Six of the reviews focused on populations with a diagnosis of schizophrenia, schizoaffective disorder or acute relapse of schizophrenia. One review looked at individuals with either schizophrenia or non-affective, serious mental illness. Among the significant results listed below in Table 11, the three strongest were between haloperidol and dystonia, olanzapine and sedation as well as between chlorpromazine and photosensitivity. There were more results reported for individuals with schizophrenia spectrum disorders than any other diagnosis.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Adams, 2013 [38]	Haloperidol	Schizophrenia	Dystonia	18-65 years	*	RR	11.5	3.2 - 40.8	471	5
Leucht, 2009 [42]	Olanzapine	Schizophrenia	Sedation	38 years (median)	*	RR	8.3	1.2 - 59.6	408	3
Adams, 2014 [46]	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Photosensitivity	18-64 years	*	RR	6.0	3.2 - 11.3	799	6
Adams, 2013	Haloperidol	Schizophrenia	Parkinsonism	18-65 years	*	RR	5.5	2.7 - 11.2	485	5
Adams, 2013	Haloperidol	Schizophrenia	Rigidity	18-65 years	*	RR	5.0	2.7 - 9.1	461	5
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weight Increase	18-64 years	*	RR	4.9	2.3 - 10.4	165	5
Adams, 2013	Haloperidol	Schizophrenia	Weight gain (kg)	<=65 years	*	RR	4.9	1.4 – 17.0	441	2
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental	Dry Mouth	18-64 years	*	RR	4.6	2.4 - 8.9	1015	7

		Illness								
Adams, 2013	Haloperidol	Schizophrenia	Blurred Vision	18-65 years	*	RR	4.0	1.2 - 12.9	240	2
Adams, 2013	Haloperidol	Schizophrenia	Tremor	18-65 years	*	RR	3.9	2.0 - 7.9	447	5
Gao, 2008 [35]	Haloperidol	Schizophrenia	Overall EPS	Unclear	OR	*	3.7	2.1 - 6.4	450	3
Adams, 2013	Haloperidol	Schizophrenia	Akathisia	18-65 years	*	RR	3.7	2.2 – 6.0	695	6
Matar, 2013 [57]	Fluphenazine	Schizophrenia	Rigidity	16-58 years	*	RR	3.5	1.8 - 7.1	227	2
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Acute Movement Disorders (Dystonia)	18-64 years	*	RR	3.5	1.5 - 8.0	942	5
Matar, 2013	Fluphenazine	Schizophrenia	Akathisia	16-58 years	*	RR	3.4	1.2 - 9.6	227	2
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Salivation	18-64 years	*	RR	3.4	1.1 - 10.6	830	3
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weakness	18-64 years	*	RR	3.3	1.0 - 10.9	92	3
Adams, 2013	Haloperidol	Schizophrenia	Needing Antiparkinson Medication	18-65 years	*	RR	3.2	2.2 - 4.7	480	4
Matar, 2013	Fluphenazine	Schizophrenia	Tremor	16-58 years	*	RR	3.2	1.3 - 8.1	227	2
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Fits/Loss of Consciousness	18-64 years	*	RR	3.1	1.1 - 9.2	695	3
Adams, 2014	Chlorpromazine	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Eye Opacity/Eye Pigment Problems	18-64 years	*	RR	3.1	1.9 - 5.1	657	2
Adams, 2013	Haloperidol	Schizophrenia	Sleepiness	<=65 years	*	RR	3.1	1.5 - 6.3	686	7
Hutton, 2015 [59]	Quetiapine	Schizophrenia	Significant weight change	>12 years	OR	*	3.0	2.1 - 4.4	2083	10
Gao, 2008	Haloperidol	Schizophrenia	Akathisia	Unclear	OR	*	2.9	1.7 - 4.9	450	3
Gao, 2008	Haloperidol	Schizophrenia	Anticholinergic Use	Unclear	OR	*	2.5	1.7 - 3.8	450	3

Table 11 – Significant effect sizes for adverse events in study populations with schizophrenia spectrum disorder

3.3.2 Adverse Events in Populations with Mood Disorders

3.3.2.1 Major Depressive Disorder

There were 13 reviews and 12 medications included in this category. Eleven reviews analysed populations with major depression, one review involved participants with either major depression or bipolar disorder and the last review analysed participants who either had major

depression or who were healthy subjects. Komossa was the only review to report a statistically strong adverse event in people with major depression taking an antipsychotic agent.[47] This review indicated a strong link between aripiprazole and sedation. The three strongest were between amitriptyline and sexual dysfunction, venlafaxine and suicide-related events as well as amitriptyline and dry mouth (Table 12).

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Leucht, 2012 [30]	Amitriptyline	Major Depression	Sexual Dysfunction	15-93 years	OR	*	16.6	4.5 - 60.6	442	2
Whittington, 2004 [32]	Venlafaxine	Major Depression	Suicide-related Events	8-18 years	*	RR	13.8	1.8 - 103.6	*	2
Leucht, 2012	Amitriptyline	Major Depression	Dry Mouth	15-93 years	OR	*	13.5	9.4 - 19.4	1414	11
Leucht, 2012	Amitriptyline	Major Depression	Urinary Problems	15-93 years	OR	*	8.7	2.0 - 39.1	418	3
Leucht, 2012	Amitriptyline	Major Depression	Dyspepsia	15-93 years	OR	*	6.8	2.5 - 18.5	859	5
Leucht, 2012	Amitriptyline	Major Depression	Anticholinergic AE	15-93 years	OR	*	6.3	3.4 - 11.7	279	2
Komossa, 2010 [47]	Aripiprazole	Major Depression	Sedation	18-70 years	OR	*	5.8	2.3 – 14.3	2118	4
Leucht, 2012	Amitriptyline	Major Depression	Tremor	15-93 years	OR	*	5.7	3.2 – 10.1	1230	10
Leucht, 2012	Amitriptyline	Major Depression	Sedation/ Sleepiness/ Somnolence/ Drowsiness	15-93 years	OR	*	5.5	3.7 – 8.2	1690	13
Leucht, 2012	Amitriptyline	Major Depression	Increased appetite	15-93 years	OR	*	4.0	2.0 – 8.2	460	3
Leucht, 2012	Amitriptyline	Major Depression	Tachycardia	15-93 years	OR	*	3.9	1.7 – 8.8	384	5
Leucht, 2012	Amitriptyline	Major Depression	Blurred Vision and Ambloyopia	15-93 years	OR	*	3.7	2.4 – 5.8	1055	10
Leucht, 2012	Amitriptyline	Major Depression	Constipation	15-93 years	OR	*	3.4	2.4 – 4.9	1255	9
Alberti, 2015 [7]	Citalopram	Major Depression	Somnolence	=>18 years	OR	*	3.0	1.9 - 4.9	3034	*
Coleman, 2012 [33]	Desvenlafaxine	Major Depression	Nausea	=>18 years	OR	*	3.0	1.4 – 6.4	644	27
Coleman, 2012	Venlafaxine	Major Depression	Nausea	=>18 years	OR	*	3.0	1.6 - 5.8	*	*
Leucht, 2012	Amitriptyline	Major Depression	Lowblood pressure/ Dizziness/Syncope	15-93 years	OR	*	2.9	2.1 - 4.1	1246	8
Alberti, 2015	Duloxetine	Major Depression	Somnolence	=>18 years	OR	*	2.9	2.2 - 3.8	5612	*
Alberti, 2015	Desvenlafaxine	Major Depression	Somnolence	=>18 years	OR	*	2.9	2.5 - 3.4	9593	*
Alberti, 2015	Paroxetine	Major Depression	Somnolence	=>18 years	OR	*	2.8	2.4 - 3.4	6181	*
Alberti, 2015	Venlafaxine	Major Depression	Somnolence	=>18 years	OR	*	2.8	2.3 - 3.4	9327	*
Alberti, 2015	Escitalopram	Major Depression	Somnolence	=>18 years	OR	*	2.6	1.8 - 3.8	5276	*
Barbui, 2008 [34]	Paroxetine	Major Depression	Suicidal Tendencies	>=18 years	OR	*	2.6	1.2 - 5.5	3739	15

Table 12 – Significant effect sizes for adverse events in study populations with major depressive disorder

3.3.2.2 Bipolar Disorder

There were 13 reviews and 12 medications included in this category. Reviews in this category investigated populations with either bipolar depression, bipolar mania, bipolar I or bipolar II. Macritchie was the only review to report a strong link between a mood stabiliser and an adverse event for individuals with bipolar disorder.[65] The three strongest effect sizes were all for aripiprazole (Table 13). Specifically, they included extrapyramidal symptoms and akathisia (twice). Many reviews did not study individuals with bipolar disorder but instead studied individuals who experienced acute mania.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Gao, 2008 [35]	Aripiprazole	Bipolar Mania	Overall EPS	Unclear	OR	*	7.8	4.5 - 13.4	484	2
De Fruyt, 2012 [48]	Aripiprazole	Bipolar Depression	Akathisia	18-65 years	*	RR	5.6	3.4 - 9.3	727	2
Gao, 2008	Aripiprazole	Bipolar Mania	Akathisia	Unclear	OR	*	4.8	2.3 - 10.1	523	3
De Fruyt, 2012	Quetiapine	Bipolar Depression	Sedation	18-65 years	*	RR	4.5	2.6 - 4.7	1732	5
Gao, 2008	Quetiapine	Bipolar Disorder	Anticholinergic Use	Unclear	OR	*	4.4	2.7 - 7.3	549	2
Gao, 2008	Quetiapine	Bipolar Disorder	Overall EPS	Unclear	OR	*	4.2	2.6 - 7.1	584	2
De Fruyt, 2012	Quetiapine	Bipolar Depression	Somnolence	18-65 years	*	RR	3.9	2.8 - 5.5	1732	5
Suttajit, 2014 [55]	Quetiapine	Acute Bipolar Depression	Somnolence	10-65 years	*	RR	3.7	2.9 - 4.9	*	5
Meduri, 2016 [56]	Aripiprazole	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Akathisia	6-65 years	*	RR	3.7	2.5 - 5.4	1807	6
Suttajit, 2014	Quetiapine	Acute Bipolar Depression	Dry mouth	10-65 years	*	RR	3.7	3.0 - 4.4	*	6
Suttajit, 2014	Quetiapine	Acute Bipolar Depression	Sedation	10-65 years	*	RR	3.3	2.7 - 4.1	*	6
Macritchie, 2003	Valproate	Bipolar Disorder	Dizziness	18-75 years	*	RR	3.2	1.1 - 8.9	279	2
De Fruyt, 2012	Aripiprazole	Bipolar Depression	EPS	18-65 years	*	RR	3.2	2.3 - 4.5	727	2

Table 13 – Significant effect sizes for adverse events in study populations with bipolar disorder

3.3.2.3 Acute Mania

Mania is primarily treated with medication with the intent to decrease agitation, aggression and dangerous behaviour.[71] There were six reviews and four medications included in this category.

Reviews grouped into this category often looked at populations with acute mania with a diagnosis of either bipolar disorder or schizoaffective disorder. There were two reviews that analysed individuals with either bipolar disorder or schizophrenia. The three strongest were between olanzapine and weight gain (twice) as well as between olanzapine and somnolence (Table 14).

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Rendell, 2003 [36]	Olanzapine	Bipolar or Schizoaffective Disorder	Weight gain	18-86 years	OR	*	32.0	1.7 - 98.4	249	2
Cohen, 2012 [37]	Olanzapine	Schizophrenia or Bipolar Disorder	Weight Gain (kg)	8-17 years	OR	*	15.1	6.6 - 31.1	242	9
Cohen, 2012	Olanzapine	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	8.5	4.9 - 16.6	1291	*
Cipriani, 2006 [53]	Haloperidol	Bipolar or Schizoaffective Disorder	Extrapyramidal Disorder	18-68 years	*	RR	4.2	2.9 - 6.0	474	2
Scherk, 2007 [54]	Olanzapine	Acute Mania	Weight gain in kg	37-40 years (mean)	OR	*	3.9	2.4 - 6.3	246	2
Brown, 2013 [71]	Aripiprazole	Bipolar or Schizoaffective Disorder	EPS(Requiring Anticholinergic Medication)	8-74 years	*	RR	3.3	1.8 - 5.9	730	2
Cipriani, 2006	Haloperidol	Bipolar or Schizoaffective Disorder	Tremor	18-68 years	*	RR	3.3	1.9 - 5.8	484	2
Brown, 2013	Aripiprazole	Bipolar or Schizoaffective Disorder	Akathisia	8-74 years	*	RR	3.2	2.3 - 4.4	2305	7
Rendell, 2003	Olanzapine	Bipolar or Schizoaffective Disorder	Dry mouth	18-86 years	*	RR	3.1	1.5 - 6.2	254	2

Table 14 – Significant effect sizes for adverse events in study populations with mania

3.3.2.4 Borderline Personality Disorder

There was one review in this category and it analysed olanzapine. Stoffers reported a strong link between olanzapine and body weight change in 23- to 33-year olds with borderline personality disorder (Table 15).[45]

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Stoffers, 2010 [45]	Olanzapine	Borderline Personality Disorder	Body weight change in kg	23-33 years	OR	*	6.7	5.1 - 8.8	752	6

Table 15 – Significant effect sizes for adverse events in study populations with borderline personality disorder

3.4.2.5 Any Mood Disorder

The systematic review on lithium by Burgess was the sole review included in this category. No significant difference was found in hypothyroidism.[61]

3.3.3 Adverse Events in Populations with Anxiety Disorders

3.3.3.1 Generalised Anxiety Disorder

There were four reviews and three medications included in this category. Depping reported a statistically strong link between quetiapine and sedation in the short term for adults with generalised anxiety disorder (Table 16).[51] Chessick indicated a strong association between buspirone and dizziness.[60] Approximately the same number of outcomes that were reported for generalised anxiety disorder were reported for obsessive compulsive disorder, which is the next category to be discussed. However, few significant associations were found for individuals with obsessive compulsive disorder or seasonal affective disorder.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Depping, 2010 [51]	Quetiapine	Generalised Anxiety Disorder	Sedation in short term	=>18 years	OR	*	4.5	2.7 - 7.6	2262	4
Chessick, 2006 [60]	Buspirone	Generalised Anxiety Disorder	Dizziness	=>18 years	*	RR	3.2	1.8 - 5.6	635	3

Table 16 – Significant effect sizes for adverse events in study populations with generalised anxiety disorder

3.3.3.2 Obsessive Compulsive Disorder

There were two reviews and three medications included in this category. No statistically strong associations were found for fluoxetine, paroxetine or sertraline.

3.3.3.3 Seasonal Affective Disorder

There was one review in this category that studied the effects of bupropion. No strong associations were found between bupropion and headache, insomnia, nausea or diarrhoea.

3.3.3.4 Anxiety Disorder (Non-OCD)

There was one review and one medication included in this category. Bridge found no significant association between venlafaxine and suicidal behaviour.[72]

3.3.4 Adverse Events in Populations with Eating Disorders

3.3.4.1 Anorexia Nervosa

There was one systematic review in this category that studied olanzapine in individuals with anorexia nervosa. Kishi reported a statistically strong association between the drug and drowsiness, sedation or somnolence for individuals between the ages of 12 and 37 (Table 17).[39] Anorexia nervosa and binge eating disorder were the two types of eating disorders analysed by this umbrella review.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Kishi, 2012 [39]	Olanzapine	Anorexia Nervosa	Drowsiness/ Sedation/ Somnolence	12-37 years	*	RR	11.5	2.9 - 44.5	*	3

Table 17 – Significant effect sizes for adverse events in study populations with anorexia nervosa

3.3.4.2 Binge Eating Disorder

There was one systematic review in this category and it studied the effects of lisdexamfetamine on adults with binge eating disorder. Citrome had a study population of 1,004 participants and included three separate studies.[67] The three strongest were between lisdexamfetamine and feeling jittery, dry mouth and constipation (Table 18).

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Citrome, 2015 [67]	Lisdexamfetamine	Binge Eating Disorder	Feeling jittery	18-55 years	*	RR	11.4	2.4 - 40.6	1004	3
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Dry mouth	18-55 years	*	RR	4.9	3.8 - 6.2	1004	3
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Constipation	18-55 years	*	RR	4.5	1.9 - 9.8	1004	3
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Decreased appetite	18-55 years	*	RR	4.1	2.4 - 6.8	1004	3
Citrome, 2015	Lisdexamfetamine	Binge Eating Disorder	Insomnia	18-55 years	*	RR	2.9	1.9 - 4.4	1004	3

Table 18 – Significant effect sizes for adverse events in study populations with binge eating disorder

3.3.5 Adverse Events in Populations with Cognitive Disorders

3.3.5.1 Dementia and Delirium

There were six reviews and five medications included in this category. Three reviews focused on populations with dementia alone, one review focused on a population with dementia or delirium and the last two reviews looked at populations that had dementia with aggression. The three strongest associations were between valproate and thrombocytopenia, olanzapine and urinary infection as well as between quetiapine and somnolence (Table 19). There were fewer results reported for individuals with Alzheimer's disease than for individuals with dementia and delirium.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Lonergan, 2009 [66]	Valproate	Dementia	Thrombocytopenia	=> 49 years	OR	*	7.9	1.9 - 32.6	186	2
Tan, 2015 [43]	Olanzapine	Dementia	Urinary infection	77-84 years	OR	*	6.9	1.3 – 36.0	*	*
Tan, 2015	Quetiapine	Dementia	Somnolence	77-84 years	OR	*	5.9	2.4 - 14.5	*	*
Maher, 2011 [50]	Quetiapine	Dementia	Sedation	Unclear	OR	*	5.2	2.9 - 9.5	799	4
Maher, 2011	Olanzapine	Dementia	Increased appetite or weight increase	Unclear	OR	*	4.7	1.9 - 14.1	808	3
Maher, 2011	Olanzapine	Dementia	Sedation	Unclear	OR	*	4.6	2.9 - 7.6	1218	5
Tan, 2015	Risperidone	Dementia	Stroke	77-84 years	OR	*	4.5	1.8 - 11.7	*	4
Tan, 2015	Olanzapine	Dementia	Abnormal gait	77-84 years	OR	*	3.8	1.6 – 9.0	*	3
Tan, 2015	Olanzapine	Dementia	Somnolence	77-84 years	OR	*	3.6	1.8 - 7.1	*	*

Tan, 2015	Risperidone	Dementia	Somnolence	77-84 years	OR	*	3.6	2.7 - 4.7	*	*
Tan, 2015	Aripiprazole	Dementia	Somnolence	77-84 years	OR	*	3.5	1.6 - 7.5	*	*
Maher, 2011	Risperidone	Dementia	Increased appetite or weight increase	Unclear	OR	*	3.4	1.1 - 12.8	517	2
Maher, 2011	Risperidone	Dementia	Cerebrovascular accident	Unclear	OR	*	3.1	1.3 - 8.2	1852	4
Lonergan, 2009	Valproate	Dementia	Urinary tract infection	=> 49 years	OR	*	3.0	1.0 - 8.8	227	2
Maher, 2011	Risperidone	Dementia	EPS	Unclear	OR	*	3.0	2.0 - 4.7	2477	5

Table 19 – Significant effect sizes for adverse events in study populations with dementia or delirium

3.3.5.2 Alzheimer's Disease

There were two reviews and two medications included in this category. One review looked at participants with either dementia or Alzheimer's disease while the other focused on individuals with Alzheimer's disease.[49] All three of the strongest associations were reported by the latter review. These strong effect estimates were between risperidone and abnormal gait, haloperidol and drowsiness as well as between risperidone and cerebrovascular events (Table 20).

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Ballard, 2006 [49]	Risperidone	Alzheimer's Disease	Abnormal gait	>60 years	OR	*	5.3	2.2 - 12.6	1100	3
Ballard, 2006	Haloperidol	Alzheimer's Disease	Drowsiness	>60 years	OR	*	4.2	1.8 - 9.9	229	4
Ballard, 2006	Risperidone	Alzheimer's Disease	Cerebrovascular events	>60 years	OR	*	3.6	1.7 - 7.7	1954	5
Ballard, 2006	Risperidone	Alzheimer's Disease	Peripheral edema	>60 years	OR	*	2.8	1.5 - 5.0	938	3

Table 20 – Significant effect sizes for adverse events in study populations with Alzheimer's disease

3.3.6 Adverse Events in Populations with Developmental Disorders

3.3.6.1 Attention Deficit Hyperactivity Disorder and Attention Deficit Disorder

There were three reviews and two medications included in this category. The three adverse events with the strongest associations were extracted from two reviews. Punja reported strong links between amphetamine salts and decreased appetite in children and adolescents with attention deficit hyperactivity disorder.[68] Storebo studied the same population in terms of age

range and diagnosis. They found strong associations between methylphenidate and weight loss (Table 21).[69] The link between methylphenidate and weight loss can be supported by medication's association with decreased appetite as well. An equal number of eligible systematic reviews were retrieved by this umbrella review for the study of populations with autism spectrum disorders, intellectual disability and pervasive developmental disorder as for attention deficit (hyperactivity) disorder.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Punja, 2016 [68]	Amphetamine salts	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	6.4	1.6 - 26.5	1124	5
Storebo, 2015 [69]	Methylphenidate	Attention Deficit Hyperactivity Disorder	Decreased weight	6-17 years	*	RR	3.9	1.4 - 10.6	859	6
Storebo, 2015	Methylphenidate	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	3.7	2.6 - 5.2	2962	16
Schacter, 2001 [70]	Methylphenidate	Attention Deficit Disorder	Dizziness	=<18 years	*	RR	3.5	1.2 - 9.3	383	4
Punja, 2016	Amphetamine salts	Attention Deficit Hyperactivity Disorder	Insomnia/trouble sleeping	6-17 years	*	RR	3.3	1.3 – 9.0	1280	5
Schacter, 2001	Methylphenidate	Attention Deficit Disorder	Decreased appetite	=<18 years	*	RR	3.1	2.5 - 3.7	675	10
Storebo, 2015	Methylphenidate	Attention Deficit Hyperactivity Disorder	Weight gain	6-17 years	OR	*	0.13	0.1 - 0.3	805	5

Table 21 – Significant effect sizes for adverse events in study populations with ADD or ADHD

3.3.6.2 Autism Spectrum Disorder, Intellectual Disability and Pervasive Developmental Disorder

There were three reviews and three medications included in this category. The three strongest associations were extracted from two separate reviews. One review looked at children and adolescents with autism spectrum disorder or pervasive development disorder. They found strong links between aripiprazole and drooling and tremor. Cohen included 10- to 12-year-olds with pervasive developmental disorder or intellectual disability and reported a link between aripiprazole and somnolence (Table 22).[37] This umbrella review retrieved eligible systematic

reviews that did use a medical diagnosis for its population inclusion criterion. For instance, in the next section I discuss reviews that studied individuals with aggression or agitation.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Cohen, 2013 [41]	Aripiprazole	Pervasive Developmental Disorder or Intellectual Disability	Somnolence	8-10 years	OR	*	25.8	1.3 - 112.3	569	*
Ching, 2012 [40]	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Tremor	6-17 years	*	RR	10.3	1.4 - 76.6	313	2
Ching, 2012	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Drooling	6-17 years	*	RR	9.7	1.3 - 72.1	313	2
Cohen, 2013	Aripiprazole	Pervasive Developmental Disorder or Intellectual Disability	Significant Weight Gain	8-10 years	OR	*	6.3	1.6 - 17.1	507	*
McQuire, 2015 [52]	Aripiprazole	Autism Spectrum Disorder or Intellectual Disability	Weight change in kg	=<18 years	OR	*	4.4	2.8 - 6.8	*	3
Ching, 2012	Aripiprazole	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Sedation	6-17 years	*	RR	4.3	1.6 - 11.6	313	2

Table 22 – Significant effect sizes for adverse events in study populations with ASD, ID or PDD

3.3.7 Adverse Events in Populations with Other Conditions

3.3.7.1 Aggression and Agitation

There were four reviews and one medication included in this category. Belgamwar studied individuals who were acutely disturbed or agitated people with suspected serious mental illnesses.[73] They found no significant differences between olanzapine and extrapyramidal symptoms. Huband studied individuals experiencing recurrent aggressive outbursts or episodes. They reported a moderate link between valproate and weight gain (Table 23).[74] The other half of the reviews studied reported that individuals experienced aggression or agitation that was psychosis-induced. There were only two strong associations found in this category. Specifically,

Powney reported strong links between haloperidol and sedation and extrapyramidal symptoms within a 24-hour period.[44]

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Powney, 2012 [44]	Haloperidol	Psychosis-induced Aggression or Agitation	EPS During 24 Hours	18-73 years	*	RR	6.8	2.2 - 21.1	398	3
Powney, 2012	Haloperidol	Psychosis-induced Aggression or Agitation	Over Sedated	18-73 years	*	RR	3.4	1.4 – 8.0	313	2

Table 23 – Significant effect sizes for adverse events in study populations with psychosis-induced aggression or agitation

3.3.7.2 Erectile Dysfunction

There was one review in this category and it studied the medication trazodone. Fink reported no significant differences between the drug and sedation, dry mouth or nausea in adult males with erectile dysfunction.[75]

3.3.7.3 Variety of Conditions

There were seven reviews and four medications included in this category. These reviews were not able to be classified in a previously listed category as they often included participants with wide-ranging psychiatric conditions. For instance, Cohen studied individuals with either attention deficit hyperactivity disorder, schizophrenia, bipolar disorder, behavioral disorder, pervasive developmental disorder, Tourette syndrome, conduct disorder or intellectual disability (Table 24).[37] The three strongest associations were between clozapine and weight gain, aripiprazole and somnolence as well as between aripiprazole and weight gain. In addition to analysing the adverse events by class of medication and type of diagnosis, this umbrella review sorted the results by individual medication, which will be explored further in the next section.

Author & Year	Medication	Diagnosis	Adverse Events	Age	OR	RR	Effect	95% CI	N	k
Cohen, 2012 [37]	Clozapine	Schizophrenia, Bipolar Disorder, Behavioral Disorders, Autism, Intellectual Disability, Tourette Syndrome or Conduct Disorder	Weight Gain (kg)	8-17 years	OR	*	13.8	2.2 - 49.2	915	*
Cohen, 2012	Aripiprazole	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Somnolence	8-17 years	OR	*	6.1	2.8 - 12.2	1632	*
Cohen, 2012	Aripiprazole	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Weight Gain	8-17 years	OR	*	4.4	2.0 - 8.9	1615	*
Cohen, 2012	Aripiprazole	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	EPS	8-17 years	OR	*	3.8	2.2 - 6.2	1500	*
Pringsheim, 2011 [58]	Risperidone	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Extrapyramidal Disorder	=<18 years	OR	*	3.4	2.0 - 5.5	773	7

Table 24 – Significant effect sizes for adverse events in study populations with a condition or a combination thereof not otherwise specified

The aim of the Main Results by Diagnosis Section was to discuss the adverse events of significance and the strongest associations reported in relation to the populations studied. Among individuals with schizophrenia and other psychotic disorders the strongest link was between haloperidol and dystonia. For participants with mood disorders, the strongest association was reported for olanzapine and weight gain. Among individuals with anxiety disorders, the strongest link was found between quetiapine and short-term sedation. For individuals with eating disorders, the strongest association was for lisdexamfetamine and feeling jittery. Among populations with cognitive disorders the strongest association was found between valproate and thrombocytopenia. In relation to individuals with developmental disorders, the strongest association was between aripiprazole and somnolence. In individuals with other conditions, the

strongest link reported was for clozapine and weight gain. Although the focus of this section was the results of significance, non-significant and conflicting results were explored in great detail later in the Results as well as in in the Discussion.

3.4 Main Results by Individual Medication

Results were retrieved for 11 antidepressants, eight antipsychotics, two anxiolytics, two mood stabilisers and three psychostimulants. The frequency distribution of adverse events per medication is outlined in Table 6. As discussed in the Methodology Section, the outcomes were sorted into broader categories of adverse events. The category that was most commonly reported was neurological adverse events, which represented 45% of the results. The 'Other' category was the second most relevant with 29% of the adverse events reporting an outcome that was neither constitutional, gastrointestinal or neurological. Constitutional adverse events were the third most reported with 15% of the results reporting either weight change, fever, fatigue, asthenia, insomnia or sweating. The least reported category was gastrointestinal with 11% of the results reporting either anorexia, constipation, diarrhoea, dry mouth, dyspepsia, nausea or vomiting.

Types of Adverse Events:	**Constitutional**		**Gastrointestinal**		**Neurological**		**Other**		**Total**	
≈	+	-	+	-	+	-	+	-	+	-
Antidepressants										
Paroxetine	2	0	0	0	3	3	0	1	5	4
Fluoxetine	1	1	0	1	1	6	0	1	2	9
Citalopram	1	0	0	0	1	0	0	0	2	0
Venlafaxine	1	0	1	0	2	2	0	0	3	2
Sertraline	2	0	2	1	1	3	0	2	5	6
Bupropion	2	0	1	1	1	0	1	0	4	1
Desvenlafaxine	1	0	1	0	1	0	0	0	2	0
Escitalopram	1	0	0	0	1	1	0	0	2	1

Types of Adverse Events:	**Constitutional**		**Gastrointestinal**		**Neurological**		**Other**		**Total**	
≈	+	-	+	-	+	-	+	-	+	-
Amitriptyline	1	2	3	2	3	3	6	3	10	10
Duloxetine	1	0	0	0	1	0	0	0	2	0
Trazodone	0	0	0	2	0	1	0	0	0	3
Total:	16%	4%	10%	9%	19%	24%	9%	9%	51%	49%
Antipsychotics										
Aripiprazole	3	9	1	1	20	16	2	8	20	33
Risperidone	2	3	0	0	19	8	10	11	29	22
Olanzapine	8	3	2	3	13	25	6	10	29	41
Quetiapine	4	3	2	3	16	14	4	10	22	30
Haloperidol	1	3	0	2	20	8	4	6	21	19
Chlorpromazine	1	1	4	0	4	1	5	7	9	7
Clozapine	1	0	0	0	0	0	0	0	0	0
Fluphenazine	0	0	0	0	2	0	1	1	0	1
Total:	7%	7%	3%	3%	30%	23%	10%	17%	46%	54%
Anxiolytics										
Buspirone	0	0	1	1	1	1	0	3	2	5
Hydroxyzine	0	1	0	1	0	3	0	0	0	5
Total:	0%	8%	8%	17%	8%	34%	0%	25%	17%	83%
Mood stabilisers										
Valproate	3	2	1	7	4	3	4	7	12	19
Lithium	1	0	2	0	1	1	0	2	4	3
Total:	10%	5%	8%	18%	13%	11%	11%	24%	42%	58%
Stimulants										
Lisdexamfetamine	2	1	5	1	0	1	2	2	9	5
Methylphenidate	3	2	2	5	1	11	3	20	9	38
Amphetamine Salts	1	0	1	0	0	0	1	1	3	1
Total:	9%	5%	12%	9%	2%	19%	9%	35%	32%	68%
Grand Total:	**9%**	**6%**	**5%**	**6%**	**23%**	**22%**	**10%**	**19%**	**44%**	**56%**

Table 25 – Frequency distribution of adverse events per medication
+ = statistically significant, - = not statistically significant

Antipsychotics were the most commonly reported for adverse outcomes with 60% of all results. Antidepressants constituted 16% of the total results, followed by stimulants with 13%, mood stabilisers with 8% and anxiolytics with a mere 3% of the total results. A summary of the statistically strongest associations for the agents with the most reported outcomes will be discussed first. Subsequently, I will discuss the results by class of medication and finally by diagnosis. The order of the results is presented by class of psychiatric medication and alphabetically. Therefore, I will discuss in the following order: antidepressants, antipsychotics, anxiolytics, mood stabilisers and stimulants. The agents within each category are listed in descending order of level of evidence (i.e. number of reviews that analysed the medication).

Forest plots of all 26 medications were generated, but were only included if more than ten adverse event outcomes could be presented. These medications included amitriptyline, aripiprazole, risperidone, olanzapine, quetiapine, haloperidol, chlorpromazine, valproate, lisdexamfetamine and methylphenidate. The entirety of the results for these ten medications, as well as the remaining 21 medications, were outlined in Appendices D and E. I highlighted the top three adverse events with the strongest associations for each of the ten aforementioned individual medications. The most commonly reported adverse events were weight gain and somnolence, which respectively constituted 17% and 13% of the "top three" adverse events. Other commonly reported adverse events were dry mouth, extrapyramidal symptoms, dizziness and a decrease in appetite, which each made up 7% of the results.

As the extracted results were reported as either OR or RR, the baseline risk for each adverse event was checked to ensure the magnitudes of effect could be directly compared with one another. Of the total results extracted, only 104 reported the baseline risk. Among the 104

reported, a majority (approximately 67%) of the baseline risks were less than 10%. Therefore, when no baseline risk was reported I assumed a baseline risk of less than 10% when comparing ORs with RRs. Certain medications, such as amitriptyline, had all of its results reported in the same type of effect size, which minimized the level of calculation. Amitriptyline was analysed first and was the only antidepressant with more than 10 outcomes.

3.4.1 Amitriptyline

Only one review reported data on amitriptyline, however, it calculated effect sizes for 23 unique adverse events.[30] Therefore, despite other antidepressive agents with a greater number of reviews such as paroxetine (7 studies) and fluoxetine (6 studies), amitriptyline was selected for in-depth analysis. The eligible systematic review on amitriptyline performed subgroup analyses and found no difference between industry-sponsored and non-industry sponsored trials, inpatient versus outpatient trials, or two-arm versus three-arm trials. The most common adverse events reported in descending order of prevalence were 'Other' (39%), neurological (26%), gastrointestinal (22%) and constitutional (13%). The three adverse events with the strongest associations to amitriptyline included sexual dysfunction (OR 16.6 95% CI 4.5 to 60.6), dry mouth (OR 13.5 95% CI 9.4 to 19.4) and urinary problems (OR 8.7 95% CI 2.0 to 39.1) (Figure 2). The data on mortality were rarely reported that it was deemed not estimable. Since only one systematic review was included for amitriptyline, there was no variation in results reported for this drug.

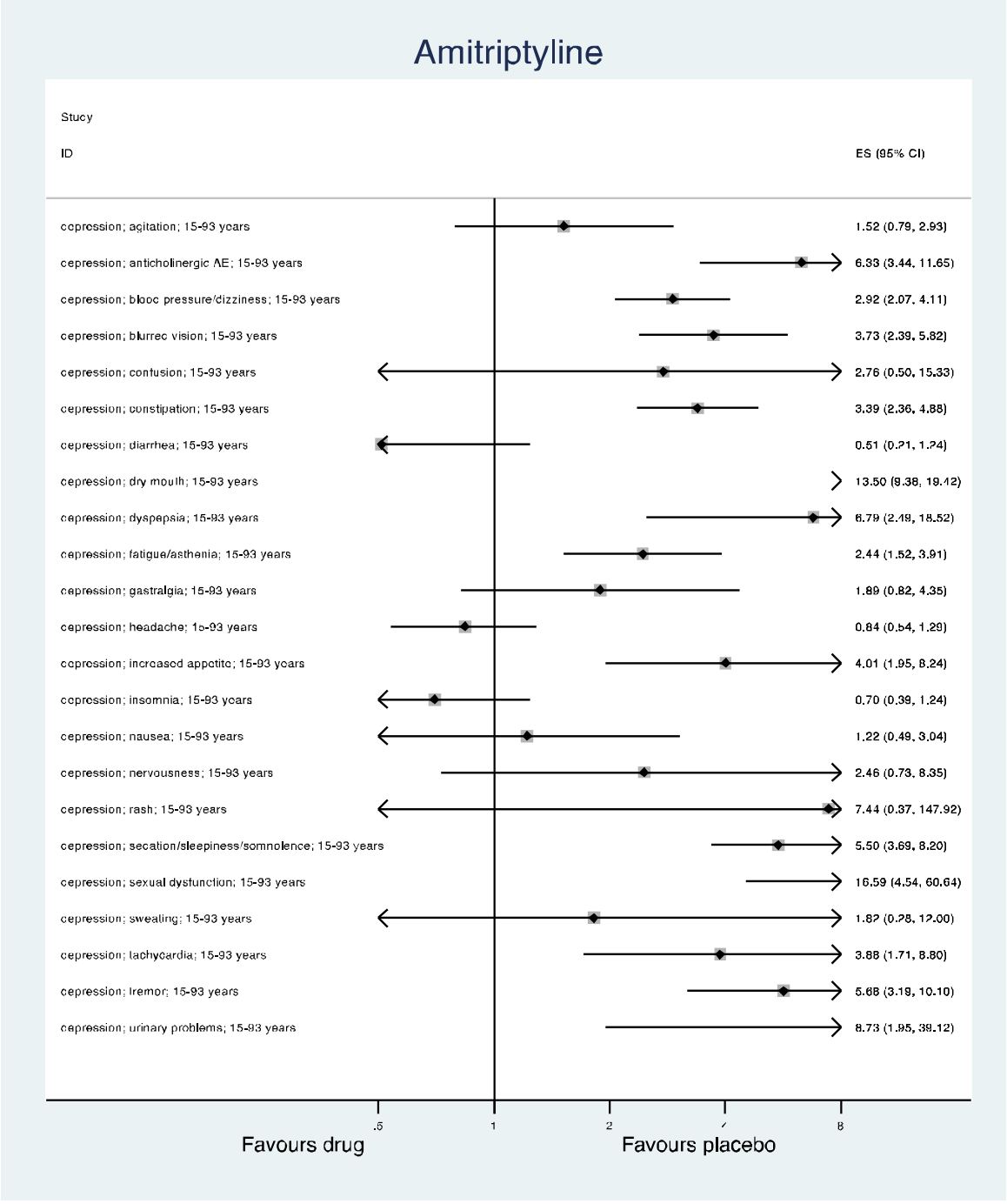

Figure 2 – Summary of effect sizes for amitriptyline

3.4.2 Aripiprazole

Aripiprazole and risperidone were the two antipsychotic drugs that were reported the most frequently. Specifically, 18 studies provided data on these

medications.[4,6,9,35,37,40,42,43,48,50,52,54,56,58,71,76,77] A total of 61 outcomes was reported for aripiprazole. Data were often insufficient for the included systematic reviews to perform subgroup analysis. One review initially planned to assess whether individuals with psychotic mania had different responses to aripiprazole than those with non-psychotic mania but could not due to a lack of data.[71] The most commonly reported adverse events for aripiprazole, in descending order of prevalence, were neurological (60%), constitutional (17%), 'Other' (20%) and gastrointestinal (3%). The three strongest links to aripiprazole were somnolence (OR 25.8 95% CI 1.3 to 112.3), tremor (RR 10.3 95% 1.4 to 76.6) and drooling (RR 9.6 95% CI 1.3 to 72.1) (Figures 3 and 4). The baseline risk was not reported for somnolence and there is a possibility that it was equal to or greater than 10%, which means that the OR reported exaggerated the underlying RR. Therefore, this warranted extra caution when analysing the results as the strength of effect for somnolence may in fact be more comparable to the values extracted for tremor and drooling than initially suspected.

There was conflicting evidence for akathisia, extrapyramidal symptoms, anticholinergic use, tremor, sedation and somnolence. Two reviews reported that sedation occurred more often in the aripiprazole group in children and adolescents with autism spectrum disorder and pervasive developmental disorder. Three other reviews linked sedation to the drug when study participants either had a diagnosis of bipolar disorder or dementia. However, no significant difference was found when the study population comprised of adults with schizophrenia spectrum disorder.

Only one forest plot was generated for the majority of the 31 medications and a distinction was made whether the outcome was measured as either an RR or OR. A marked asterisk indicated that the effect size was an RR and the absence of an asterisk indicated that the effect size was an

OR. Occasionally, there were enough ORs and RRs for a single medication to allow for separate forest plots to be created for each type of effect size, which increased the clarity and comparability of the data within each plot. I made two forest plots for aripiprazole, olanzapine, quetiapine and valproate. Only one forest plot was made for risperidone, which will be discussed next.

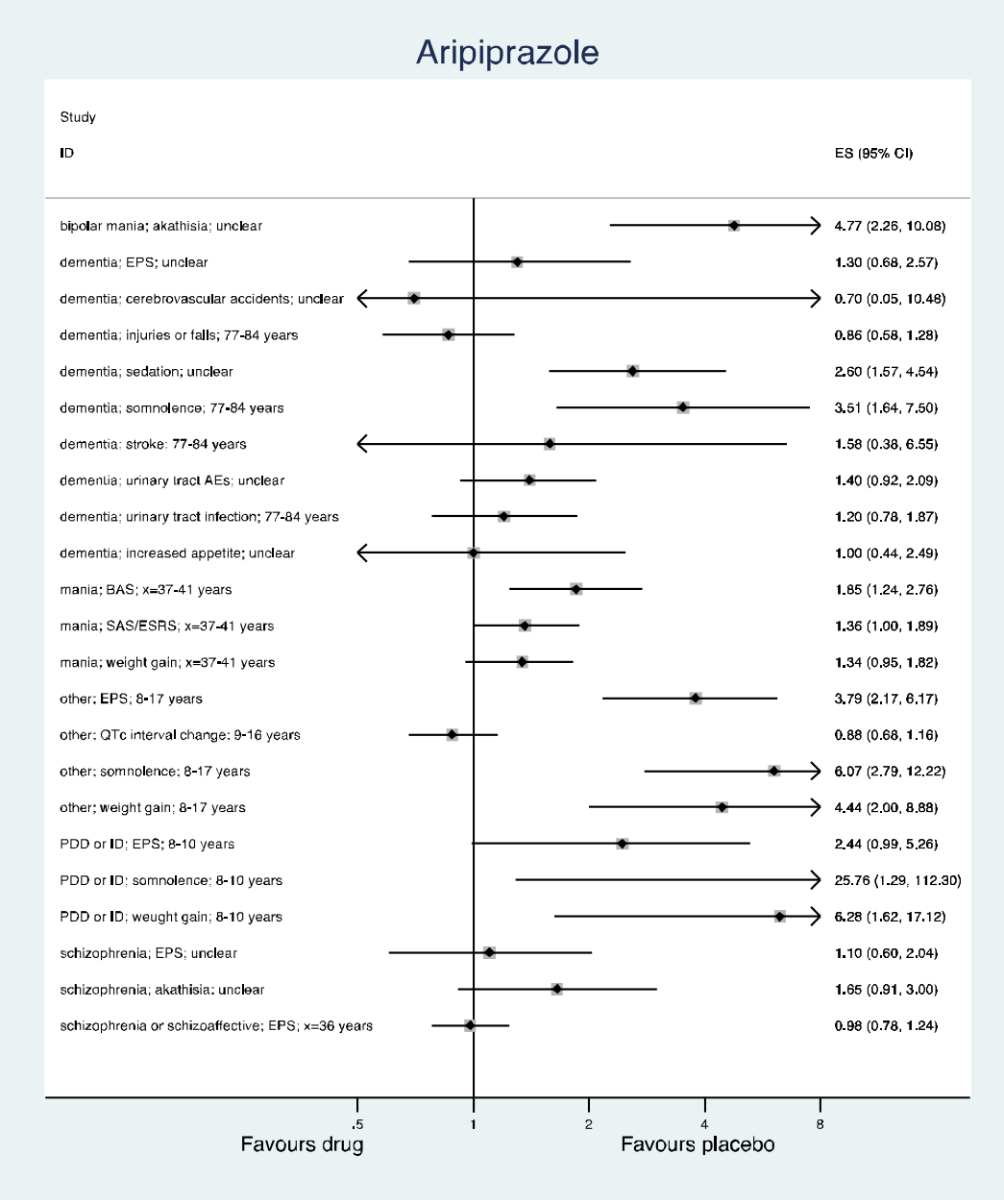

Figure 3 – Summary of effect sizes for aripiprazole (OR only)

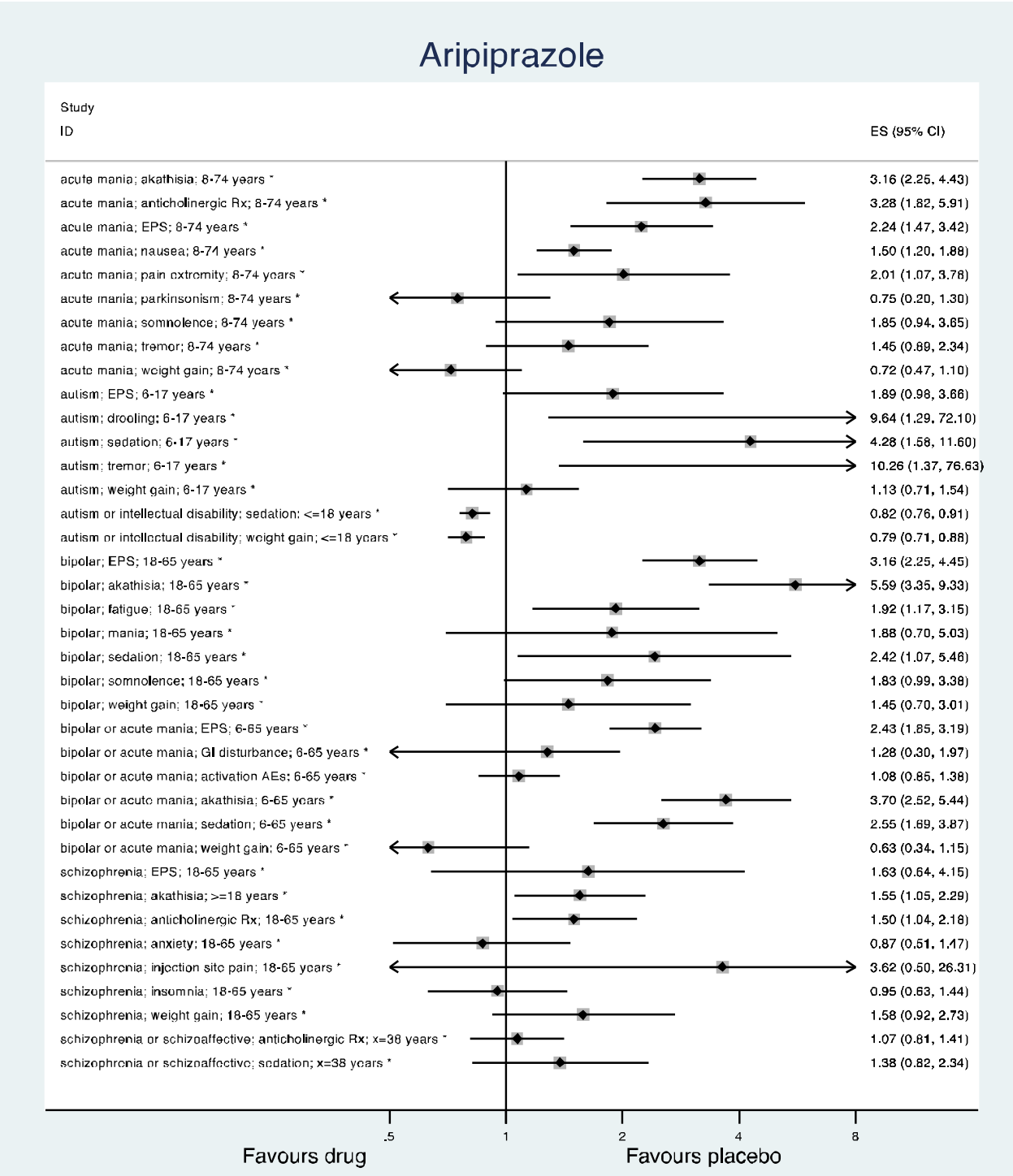

Figure 4 – Summary of effect sizes for aripiprazole (RR only)

3.4.3 Risperidone

As previously mentioned, an equally high number of reviews reported on risperidone and its 50 outcomes.[3,5,6,9,35,37,41,42,49,50,52,54,58,78-80] The AMSTAR appraisal of the risperidone reviews yielded scores ranging from 5/11 to 11/11, which indicated medium to high quality reviews. The most commonly reported adverse events for risperidone, in descending order of prevalence, were neurological (51%), 'Other' (40%), constitutional (9%) and gastrointestinal (0%). In contrast, the three adverse events with the strongest effect sizes for risperidone were somnolence (OR 9.6 95% CI 2.5 to 22.8), weight gain (OR 7.8 95% CI 1.9 to 25.2) and somnolence again (OR 7.3 95% CI 4.6 to 11.2) (Figure 5).

Many of the included systematic reviews found different directions of evidence among the results for risperidone. Both significant and non-significant results were reported for abnormal gait, somnolence, anticholinergic use, extrapyramidal symptoms and weight gain. For example, four reviews that studied children and adolescents with a diagnosis of either schizophrenia, bipolar, pervasive developmental disorder, autism spectrum disorder or intellectual disability associated the drug with weight gain. However, the only systematic review that investigated the same outcome in an adult population (with mania) reported no link to risperidone.

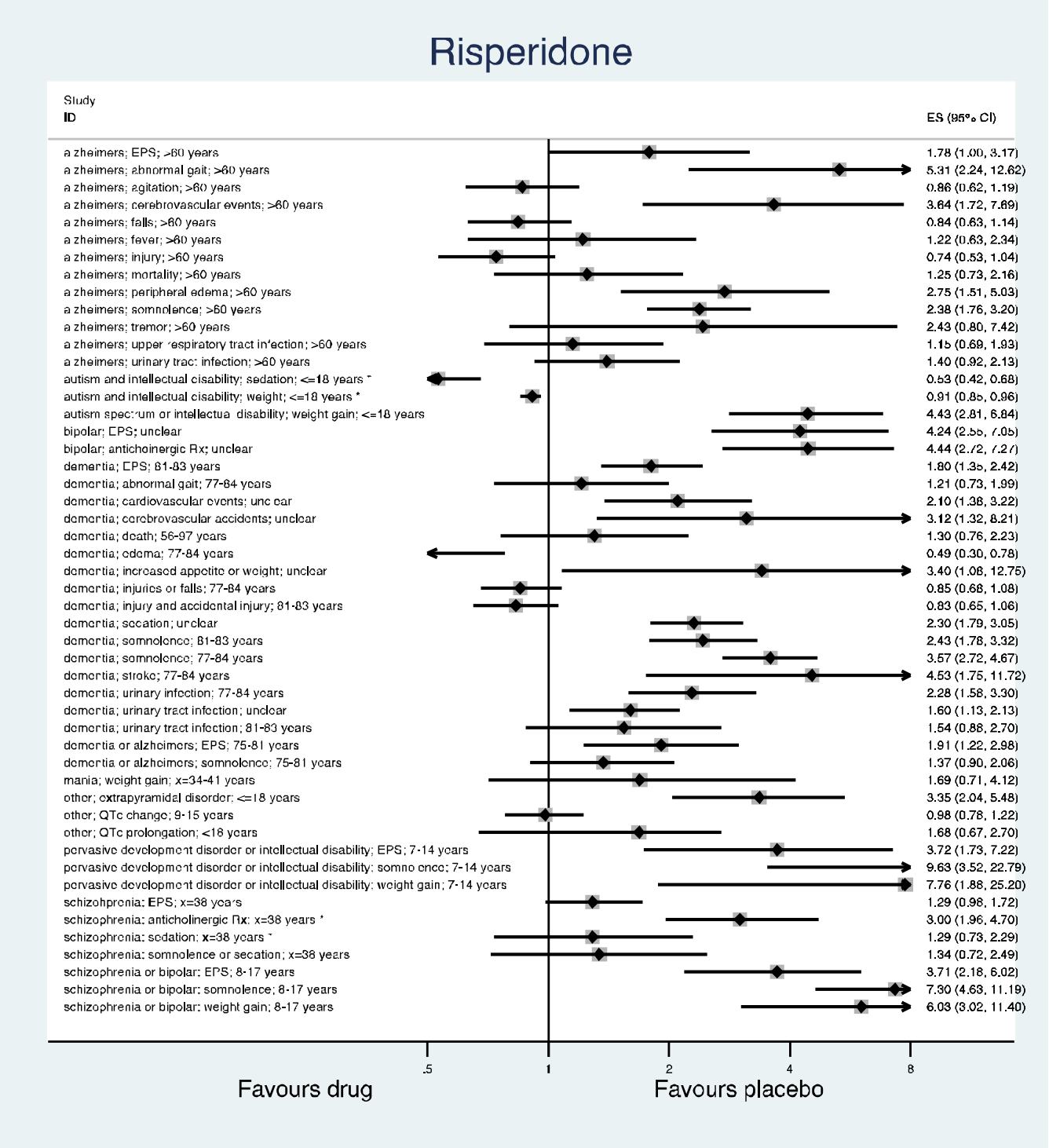

Figure 5 – Summary of effect sizes for risperidone

3.4.4 Olanzapine

There were 17 reviews included for olanzapine and a total of 69 outcomes reported.[5,6,36,37,39,41,42,43,45,50,73,81,82,83] The most commonly reported adverse events in descending order of prevalence were neurological (54%), 'Other' (23%), constitutional (16%) and gastrointestinal (7%). The three strongest associations with olanzapine were weight gain (OR 32.0 95% CI 1.7 to 98.4), weight gain again (OR 15.1 95% CI 6.6 to 31.1) and drowsiness (RR 11.5 95% 2.9 to 44.5) (Figures 6 and 7). There were certain adverse events, such as death, that were poorly documented in numerous systematic reviews on olanzapine. One systematic review stated that there were likely to be fewer deaths amongst study participants in good quality trials than amongst individuals with the same condition who did not participate in a controlled study.[41]

Systematic reviews reported conflicting evidence for olanzapine for the risk of extrapyramidal symptoms and anticholinergic use. The drug was deemed not to be associated with extrapyramidal symptoms in adults with acute mania or schizophrenia in three separate systematic reviews. However, a systematic review that investigated olanzapine in children and adolescents (with a diagnosis of schizophrenia or bipolar disorder) reported that the drug increased an individual's chances of experiencing extrapyramidal symptoms.

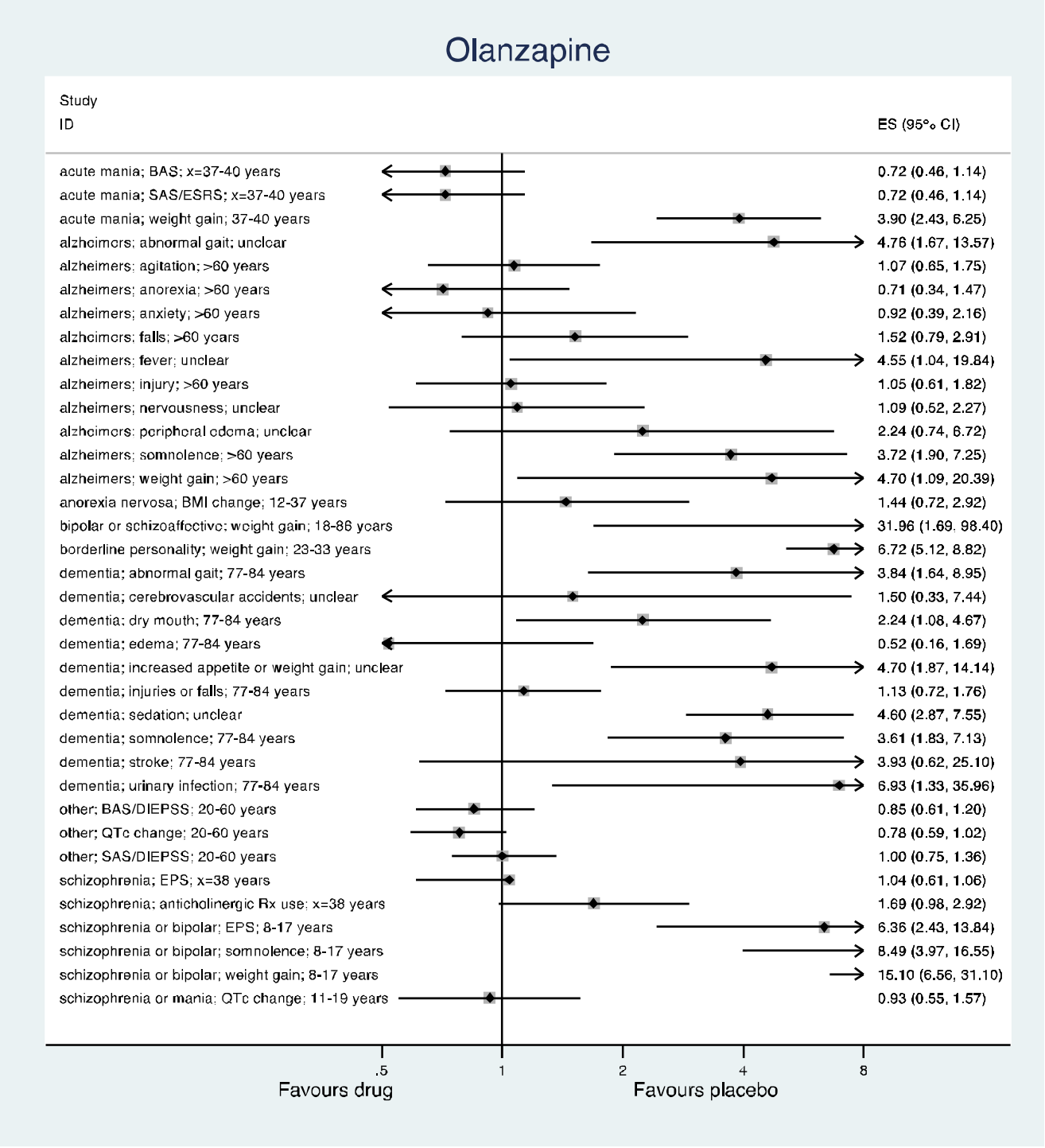

Figure 6 – Summary of effect sizes for olanzapine (OR only)

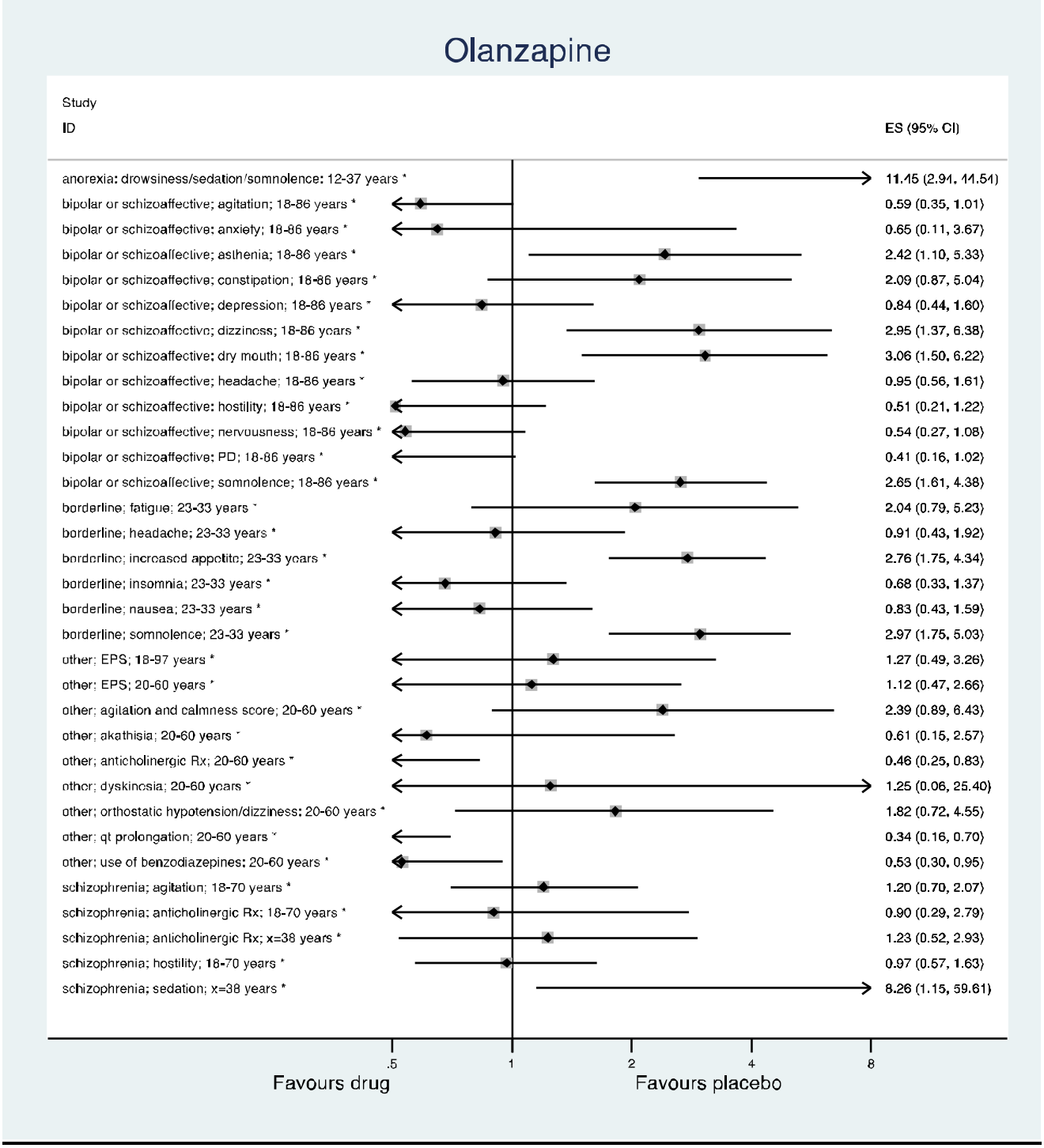

Figure 7 – Summary of effect sizes for olanzapine (RR only)

3.4.5 Quetiapine

There were 13 reviews included for quetiapine and 56 outcomes reported.[3,9,37,42,43,47,48,50,51,55,58,59,80,84] The most common adverse events reported in descending order of prevalence were neurological (54%), 'Other' (23%), constitutional (16%) and gastrointestinal (7%). The three adverse events with the strongest links to quetiapine included weight gain (OR 6.2 95% CI 2.6 to 13.6), somnolence (OR 5.9 95% CI 2.4 to 14.5) and sedation (OR 5.8 95% CI 2.3 to 14.3) (Figures 8 and 9).

Eligible systematic reviews found both significant and non-significant associations between quetiapine and extrapyramidal symptoms, urinary tract symptoms and constipation. For instance, constipation was reported to increase an individual's chances of experiencing this outcome when they had acute bipolar depression. No significant difference was found when the study population comprised of adults with a diagnosis of schizophrenia spectrum disorder.

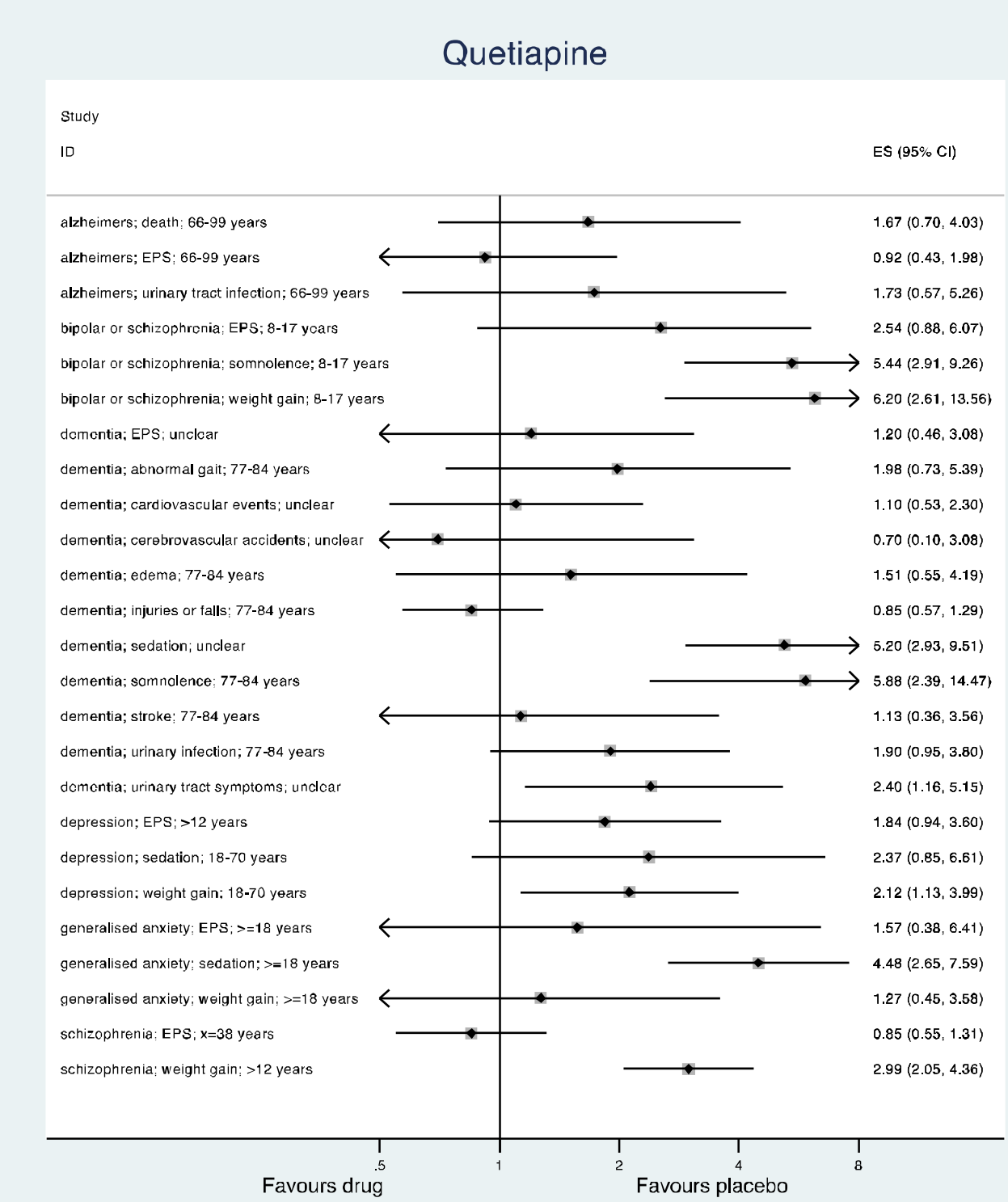

Figure 8 – Summary of effect sizes for quetiapine (OR only)

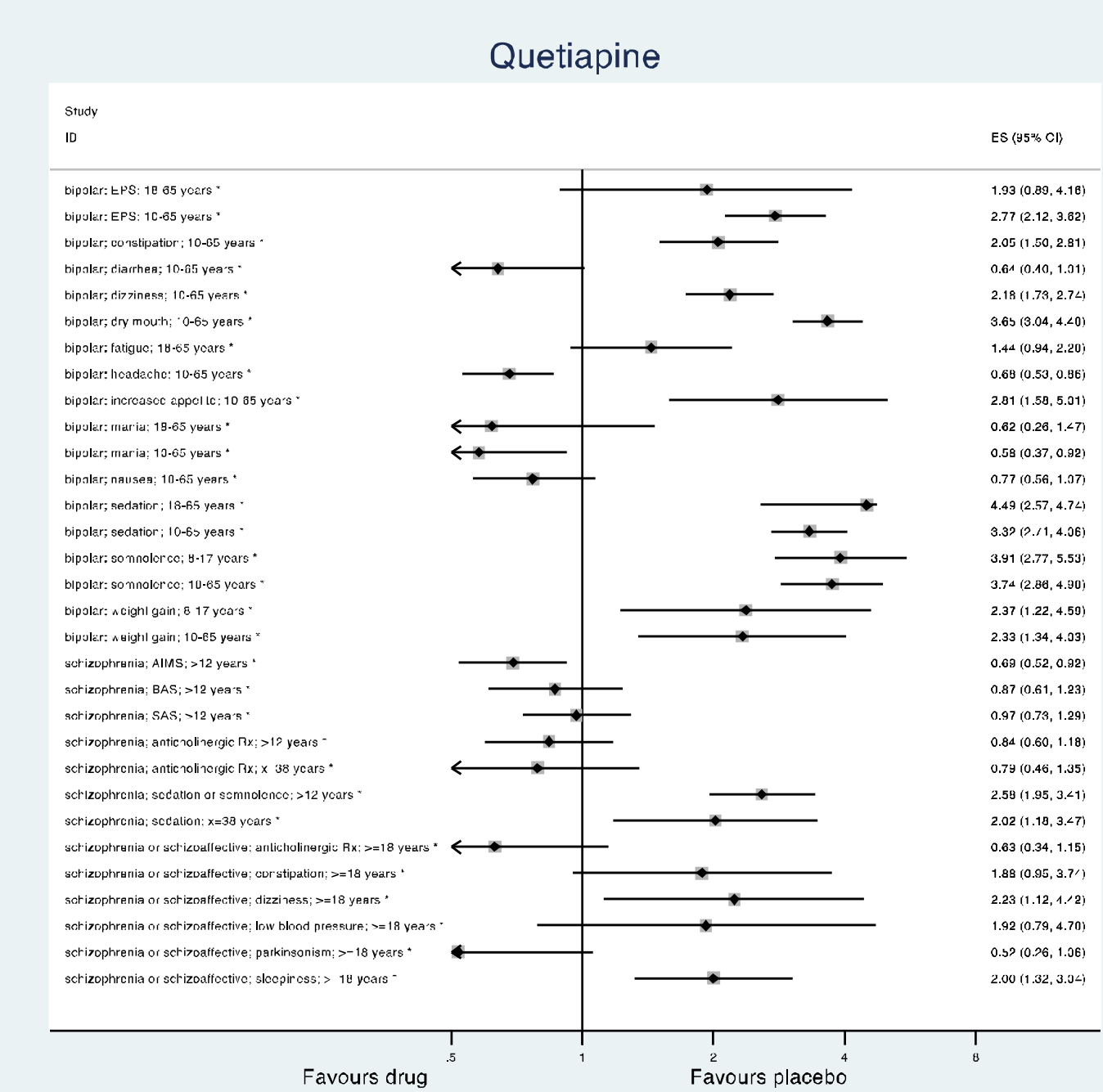

Figure 9 – Summary of effect sizes for quetiapine (RR only)

3.4.6 Haloperidol

There were 7 reviews included for haloperidol and 39 outcomes reported.[35,38,42,44,49,53,85] The most commonly reported adverse events, in descending order of prevalence, were neurological (64%), 'Other' (25%), constitutional (9%) and gastrointestinal (4%). It was noted that although the included reviews were rated as either medium or high quality reviews that their included trials were often poorly rated. One review reported that the quality of its trials as moderate to very low according to GRADE.[38] Typically, trials with few participants were rated poor quality. The three adverse events for haloperidol with the strongest effect sizes were dystonia (RR 11.5 95% CI 3.2 to 40.9), extrapyramidal symptoms (OR 7.8 95% CI 4.5 to 13.4) and extrapyramidal symptoms again (RR 6.8 95% CI 2.2 to 21.1) (Figure 10). No included systematic reviews for haloperidol reported conflicting evidence for the same adverse event.

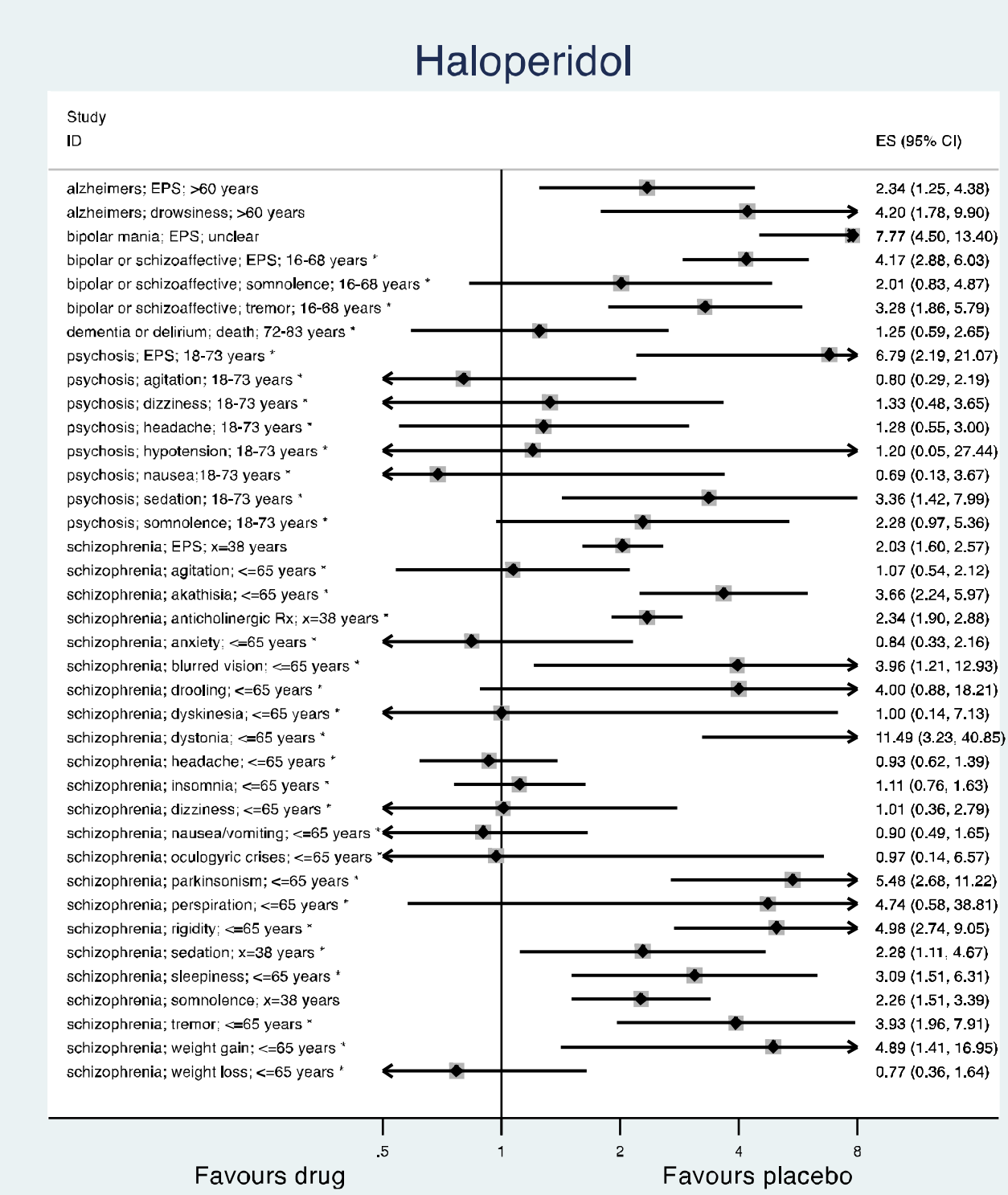

Figure 10 – Summary of effect sizes for haloperidol

3.4.7 Chlorpromazine

One review on chlorpromazine, which studied individuals with schizophrenia or non-affective disorders, was included and a total of 24 adverse events were reported.[46] The most commonly reported types of adverse events, in descending order of prevalence, were 'Other' (52%), neurological (22%), gastrointestinal (17%) and constitutional (9%). The three strongest associations with chlorpromazine were photosensitivity (RR 6.0 95% CI 3.2 to 11.3), weight gain (RR 4.9 95% CI 2.3 to 10.4) and dry mouth (OR 4.6 95% CI 2.4 to 8.9) (Figure 11). There was no variation amongst the results for chlorpromazine given that only one systematic review that studied the drug was eligible for inclusion.

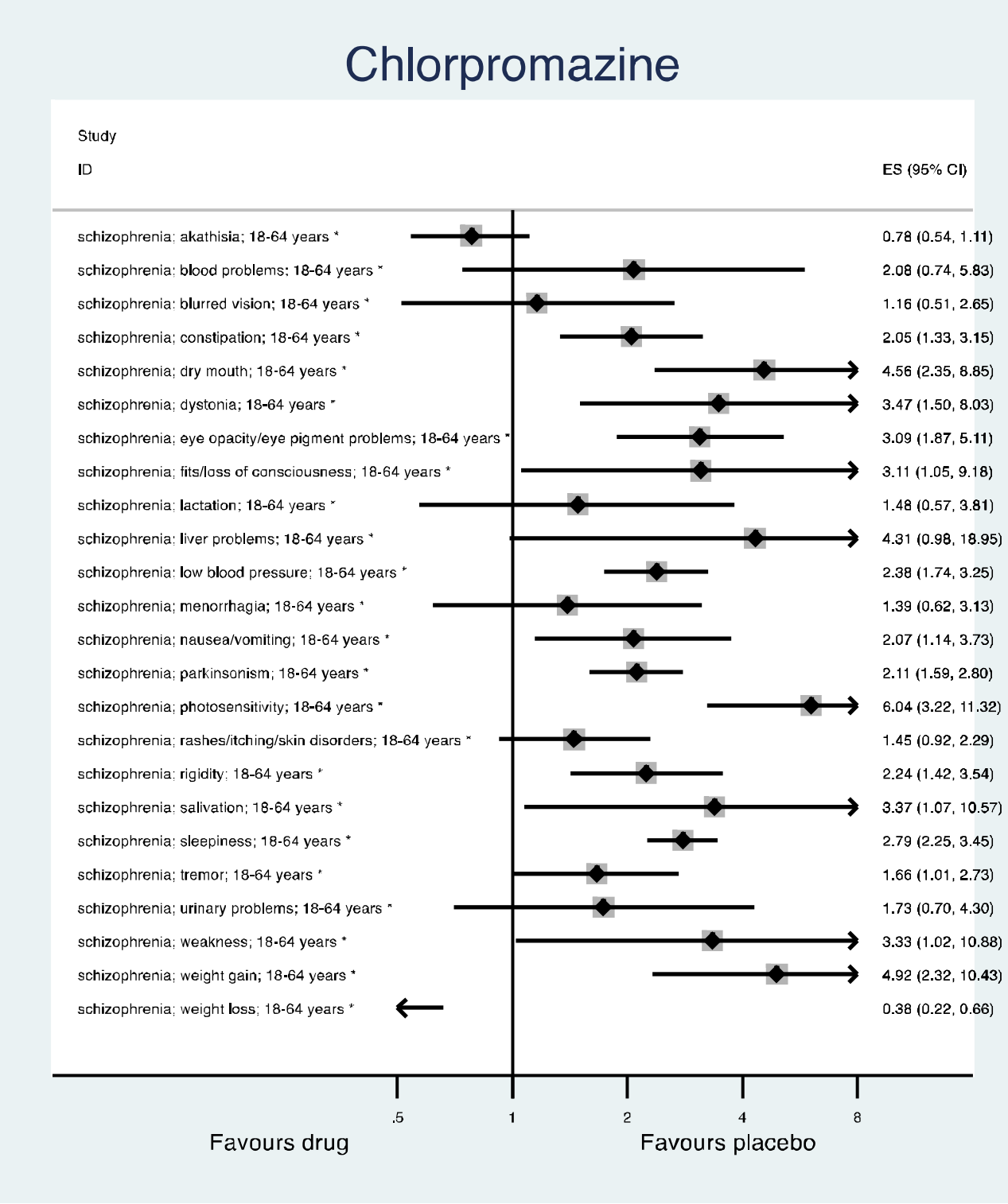

Figure 11 – Summary of effect sizes for chlorpromazine

3.4.8 Valproate

Seven reviews on valproate were included and 31 adverse events were reported in total.[52,64,65,66,74,86,87] The most commonly reported types of adverse events were 'Other' (35%), followed by neurological (23%), gastrointestinal (26%) and constitutional (16%) adverse events. The documented adverse events of valproate include but are not limited to tremor, sedation, ataxia, alopecia, lethargy, dizziness, haematological dysfunction, hepatic failure, polycystic ovaries and teratogenicity.[58] The three adverse events with the strongest associations with valproate included thrombocytopenia (OR 7.9 95% CI 1.9 to 32.6), gastrointestinal problems (OR 7.1 95% CI 1.7 to 29.0) and dizziness (RR 3.2 95% CI 1.1 to 8.9) (Figures 12 and 13).

Different directions of evidence were reported for valproate for sedation and dizziness. For example, one systematic review found no significant link between the drug and dizziness in adults with bipolar disorder. The opposite was found in a study population of adults and older adults with the same diagnosis.

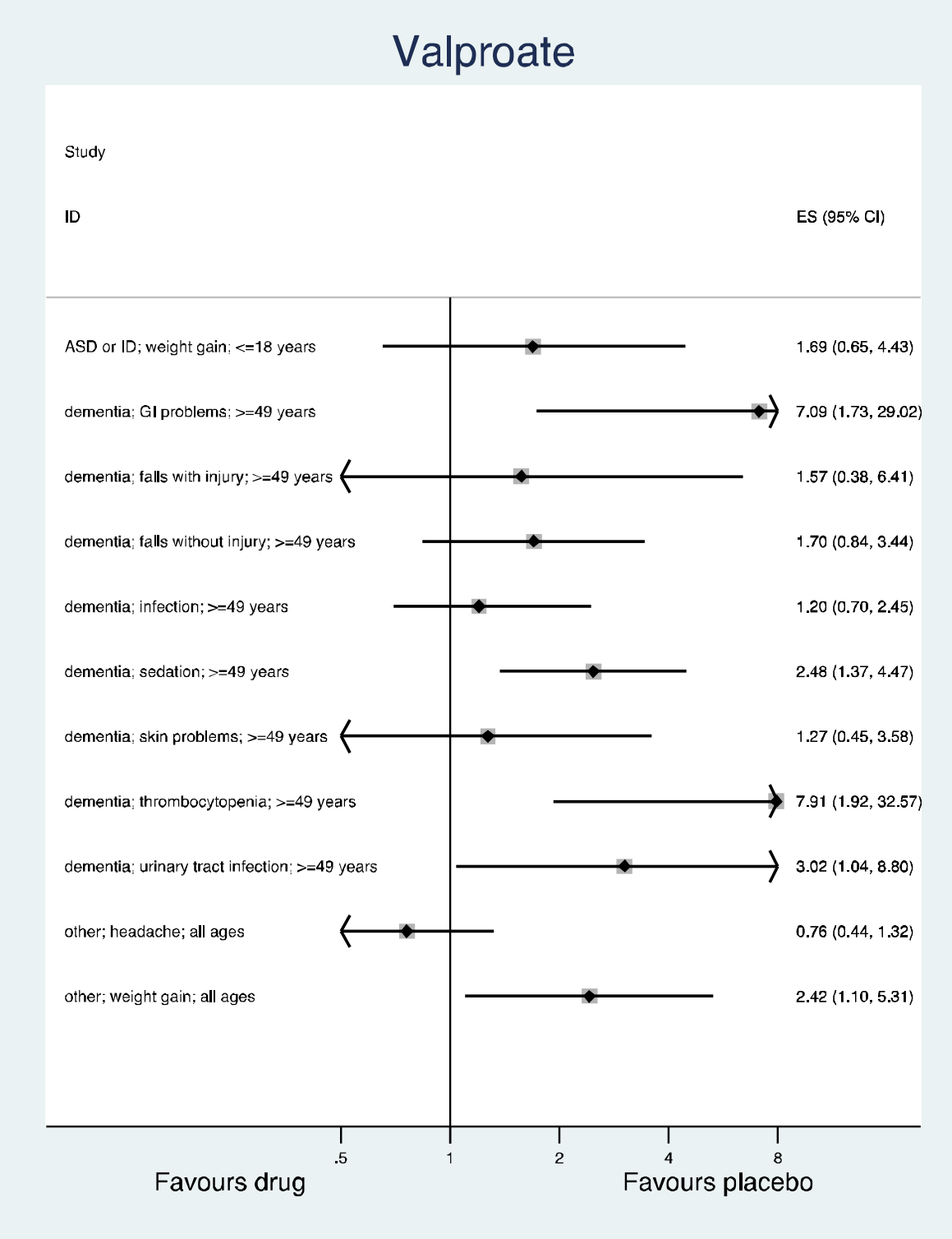

Figure 12 – Summary of effect sizes for valproate (OR only)

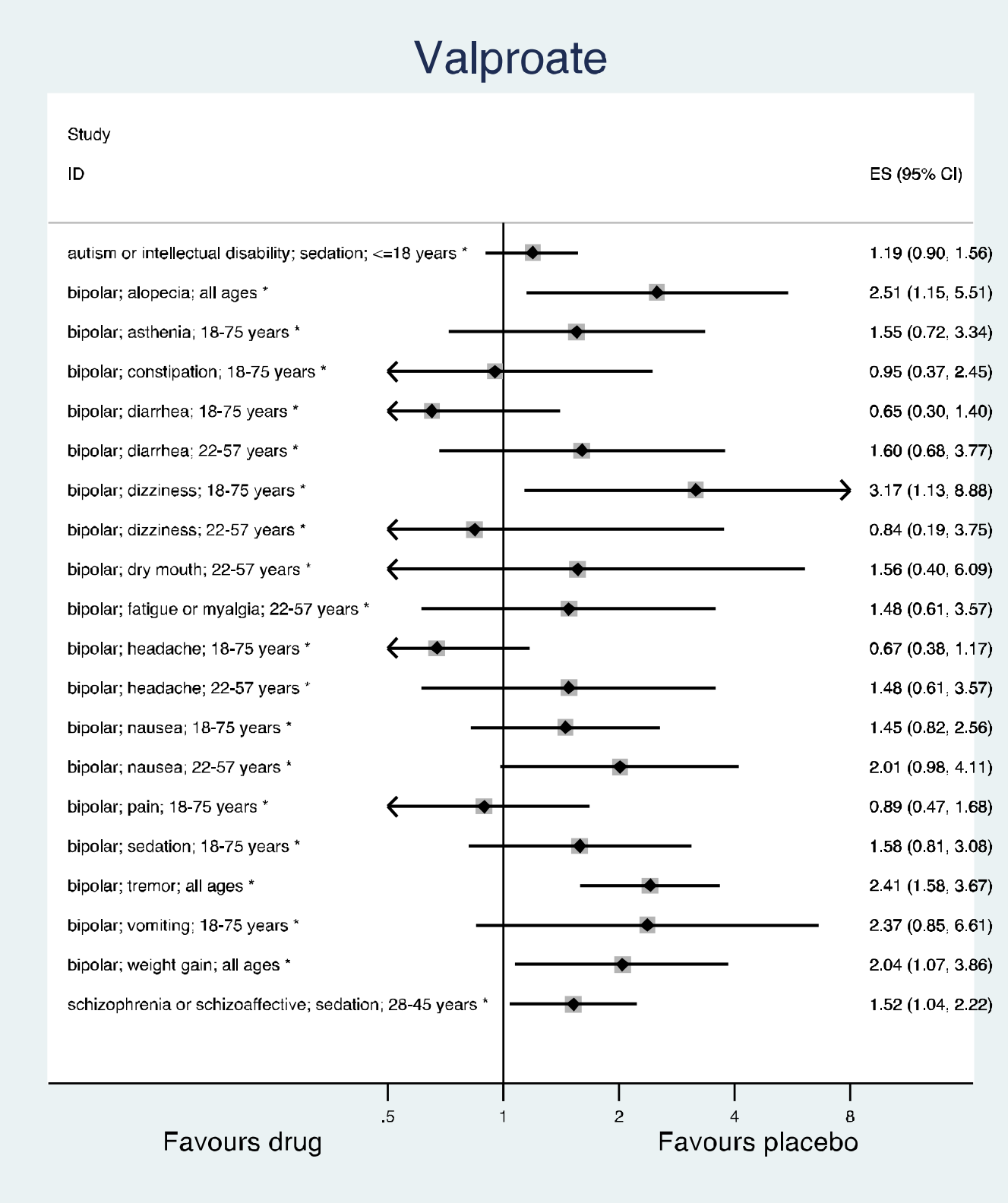

Figure 13 – Summary of effect sizes for valproate (RR only)

3.4.9 Lisdexamfetamine

Two reviews on lisdexamfetamine were included and a total of 14 outcomes was reported.[67-68] The most commonly reported types of adverse events, in descending order of prevalence, were gastrointestinal (43%), 'Other' (29%), constitutional (21%) and neurological (7%). The product label for lisdexamfetamine warns individuals that the drug can increase their chances of experiencing psychotic or manic symptoms and peripheral vasculopathy (i.e. Raynaud's phenomenon) among other adverse events.[67] Additionally, this drug has a well documented level of abuse and dependence similar to other central nervous system stimulants and for this reason the Drug Enforcement Administration has labeled it as a Schedule II medication. The three strongest links to lisdexamfetamine were included feeling jittery (RR 11.3 95% CI 2.4 to 40.6), decreased appetite (RR9.8 95% CI 5.1 to 19.0) and insomnia (RR 5.9 95% CI 2.8 to 12.3) (Figure 14).

Headaches and nausea were reported as being significantly linked to lisdexamfetamine in certain reviews while found to be non-significant in others. The drug reportedly increased an adult's chances of experiencing nausea when a diagnosis of binge eating disorder was present. However, no link was found when the children and adolescents had attention deficit hyperactivity disorder.

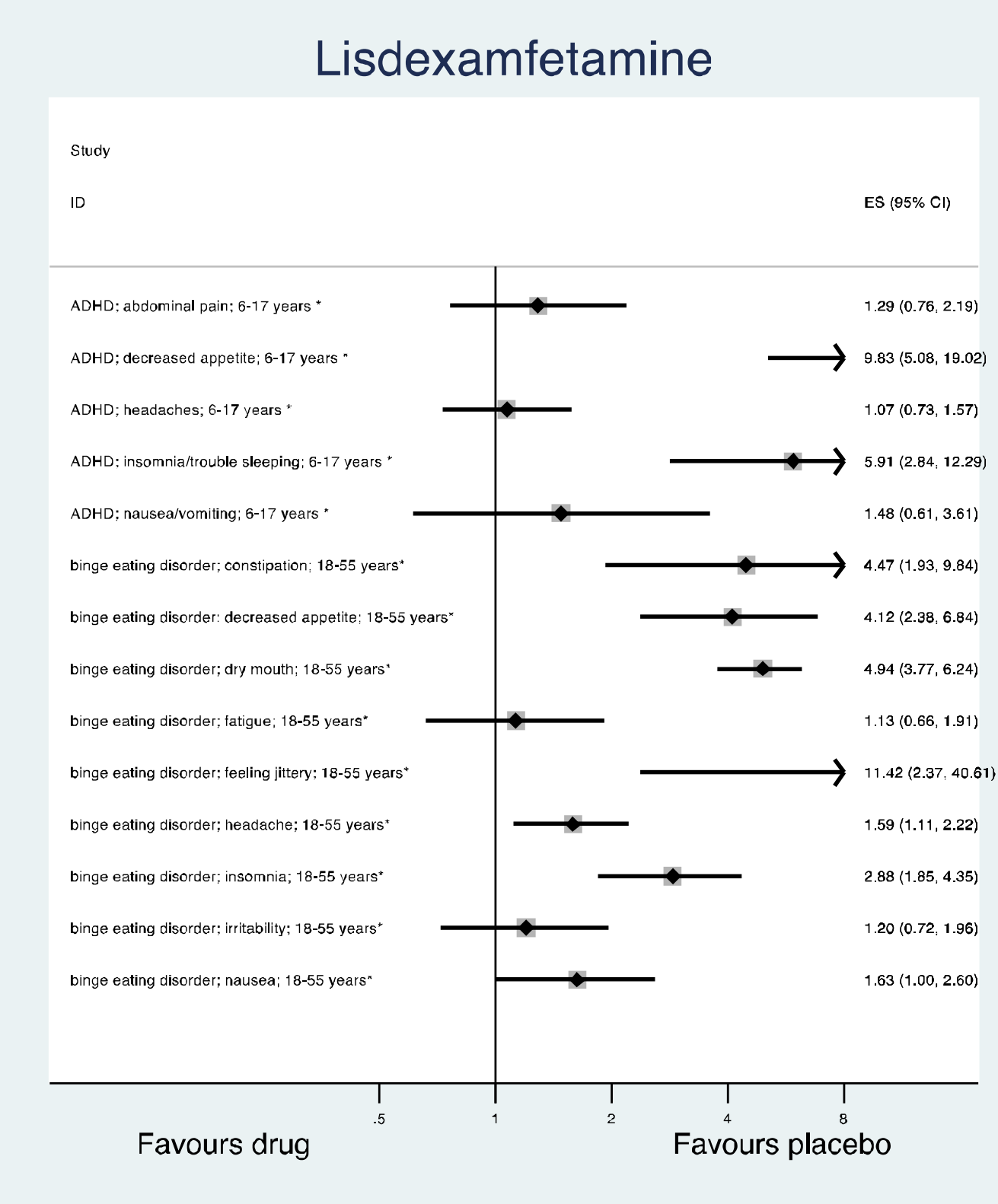

Figure 14 – Summary of effect sizes for lisdexamfetamine

3.4.10 Methylphenidate

Methylphenidate is a commonly used psychostimulant. Previously documented adverse events of methylphenidate include headaches, sleep problems, tiredness and decreased appetite. Psychotic symptoms, mood disorders and other serious adverse events have been estimated to occur in approximately 3% of children who take methylphenidate.[69] Two reviews on methylphenidate were included in this umbrella review and 44 outcomes were reported in total.[69-70] The most commonly reported types of adverse events, in descending order of prevalence, were 'Other' (49%), neurological (25%), gastrointestinal (15%) and constitutional (11%). The three adverse events of methylphenidate with the strongest effect estimates were weight loss (RR 3.9 95% CI 1.4 to 10.6), decreased appetite (RR 3.7 95% CI 2.6 to 5.2) and dizziness (RR 3.5 95% CI 1.2 to 9.3) (Figure 15).

Systematic reviews reported conflicting findings between methylphenidate and abdominal pain, dizziness, insomnia and headache. For instance, the stimulant was significantly linked to insomnia in children and adolescents with attention deficit disorder but not in individuals of the same age range with a diagnosis of attention deficit hyperactivity disorder.

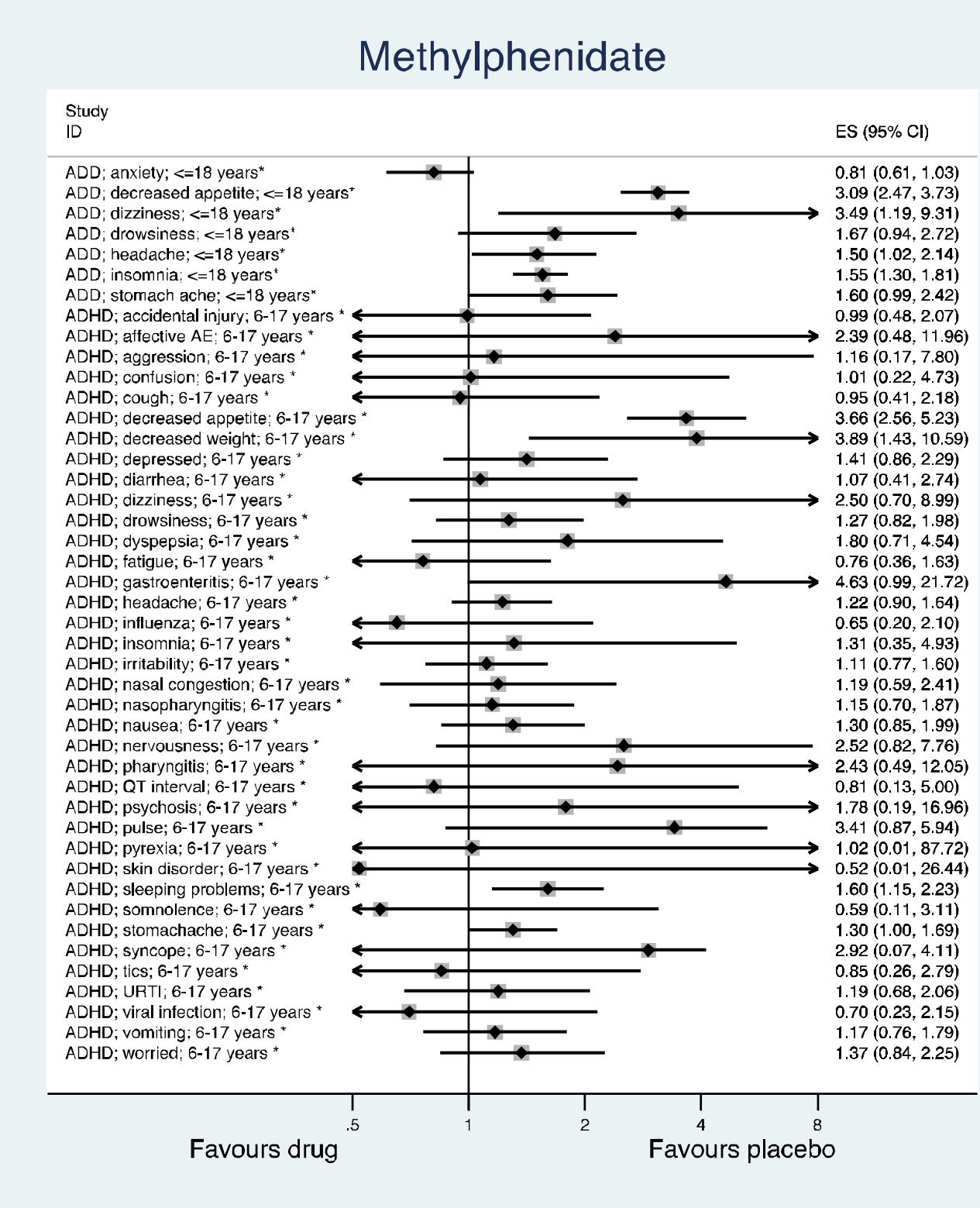

Figure 15 – Summary of effect sizes for methylphenidate

3.5 Decreased Risks

44% of the total results reached statistical significance. The majority of these results indicated an increased risk for the treatment. However, among them there were 11 results that indicated a decreased risk where the adverse event was experienced more often by individuals taking placebo. All of the decreased risks were outlined below in Table 28 along with their respective study characteristics. The only antidepressant to present a decreased risk was bupropion. None were reported for the class of anxiolytics, mood stabilisers or stimulants. The 10 remaining decreased risks pertained to antipsychotics. Specifically, they were reported for aripiprazole, risperidone, olanzapine, quetiapine and chlorpromazine. They were highlighted below in order to offer a complete and non-biased overview of my results regardless of the direction of magnitude. In order to properly rely on the data extracted in this umbrella review, I assessed the quality of the included systematic reviews with the AMSTAR appraisal tool. In the next section, I present the results of the quality appraisal.

Medication	Diagnosis	Age	Adverse Event	OR or RR*	95% CI	N	k
Olanzapine [83]	Other	20-60 years	QT prolongation	*0.3	(0.2, 0.7)	869	6
Chlorpromazine [46]	Schizophrenia or non-affective disorders	18-64 years	Weight loss	0.4	(0.2, 0.7)	165	5
Risperidone [43]	Dementia	77-84 years	Edema	0.5	(0.3, 0.8)	*	4
Olanzapine [83]	Other	20-60 years	Use of benzodiazepines	*0.5	(0.3, 1.0)	1055	7
Risperidone [52]	Autism or ID	<=18 years	Sedation	*0.5	(0.4, 0.7)	*	5
Bupropion [6]	Major depression	>=18 years	Somnolence	0.6	(0.4, 0.9)	4098	*
Quetiapine [55]	Bipolar disorder	10-65 years	Mania	0.6	(0.4, 0.9)	*	6
Quetiapine [55]	Bipolar disorder	10-65 years	Headaches	0.7	(0.5, 0.9)	*	6
Quetiapine [59]	Schizophrenia	>12 years	AIMS	*0.7	(0.5, 0.9)	799	4
Aripiprazole [52]	Autism or ID	<=18 years	Weight gain	0.8	(0.7, 0.9)	*	2
Aripiprazole [52]	Autism or ID	<=18 years	Sedation	0.8	(0.7, 0.9)	*	2
Risperidone [52]	Autism or ID	<=18 years	Weight gain	*0.9	(0.8, 1.0)	*	5

Table 26 – Decreased risks associated with individual medications

3.6 Quality Assessments of Included Reviews (The AMSTAR Tool)

The 'Assessing the Methodological Quality of Systematic Reviews' or 'AMSTAR' tool was used to evaluate the quality of every systematic review included in this umbrella review. In the scoring system, the higher the score, the better the quality of the review, thus scores of 0 to 3 were considered 'low', 4 to 7 'medium', and 8 to 11 'high' quality (http://amstar.ca/index.php). Of the 69 reviews, 10 were rated as 'medium' quality and 59 were rated as 'high' quality (Figure 16). Additional details of the AMSTAR quality assessment are presented in Appendix C.

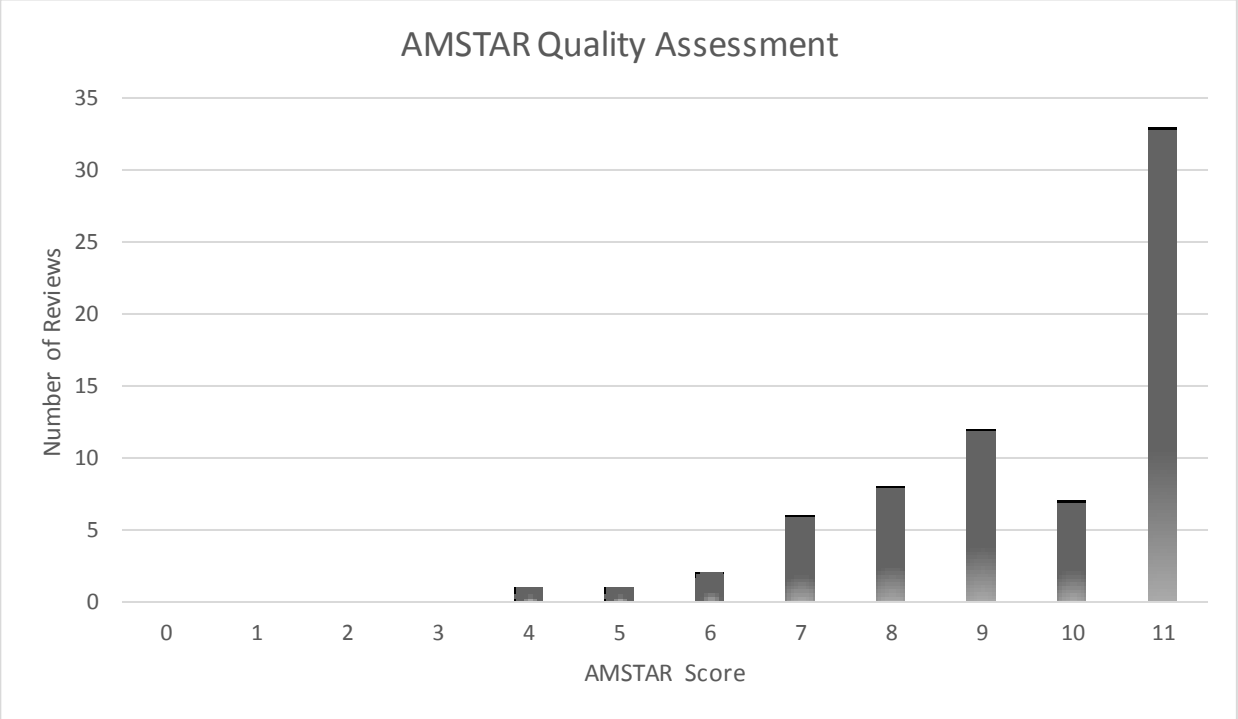

Figure 16 - AMSTAR Scores for Included Reviews – Each bar represents one review. Individual review AMSTAR scores are detailed in Appendix C.

Chapter 4: Discussion

4.1 Overview

The aim of this thesis was to present an umbrella review of the adverse events of the most commonly prescribed psychiatric medications. The previous chapter summarised the main findings of this umbrella review while this chapter will assess its strengths and limitations. Also, the AMSTAR quality appraisal of eligible reviews was discussed and the implications of the review's findings and directions for future research were considered.

4.2 Principal Findings

There was evidence that of the total 24 medications that were strongly associated with specific adverse events, only four could be classified as having very strong magnitudes of effect. Specifically, amitriptyline was linked to sexual dysfunction and dry mouth, aripiprazole was linked to somnolence, clozapine was linked to weight gain and olanzapine was also linked to weight gain. It must be noted that the 95% confidence intervals for these outcomes were wide, which suggests some uncertainty about the exact strength of the associations.

During data analysis, medications whose adverse events met the criteria for "strong" but not "very strong" effect estimates were identified. First, antidepressants were examined. Specifically, sedation, dyspepsia, increased appetite, tachycardia, dizziness, constipation, urinary problems, anticholinergic adverse events and amblyopia met the threshold and were linked to amitriptyline in individuals with major depression. Somnolence was strongly associated with citalopram, desvenlafaxine, duloxetine and escitalopram in individuals with major depression. Somnolence and suicidal tendencies were observed with paroxetine. Venlafaxine seemed to increase an individual's chances of experiencing somnolence and suicide-related events in individuals with

major depression. No adverse events of bupropion, fluoxetine, sertraline and trazodone were sufficiently prevalent to have statistical strength and could not be classified as strong.

Next, the adverse events of antipsychotics with strong effect sizes were analysed. For instance, aripiprazole was linked to akathisia, extrapyramidal symptoms, sedation, drooling, tremor, weight gain, and somnolence. Acute movement disorders (dystonia), loss of consciousness, weakness, photosensitivity, eye pigment problems, dry mouth, weight increase and salivation were linked to chlorpromazine. Aside from weight gain, clozapine had significant zero adverse events. Akathisia, rigidity and tremor occurred more frequently in individuals who took fluphenazine and had a diagnosis of schizophrenia. Haloperidol was strongly associated with dystonia, akathisia, parkinsonism, needing antiparkinson medication, blurred vision, tremor, rigidity, sleepiness, weight gain, drowsiness, extrapyramidal symptoms and sedation. The evidence indicated that olanzapine was linked to abnormal gait, fever, weight gain, somnolence, extrapyramidal symptoms, drowsiness, sedation, increased appetite, dry mouth, abnormal gait, and urinary infection. Quetiapine can increase individuals' chances of experiencing weight gain, somnolence, sedation, somnolence and dry mouth. The data indicated that risperidone was linked to cerebrovascular events, abnormal gait, peripheral edema, weight gain, somnolence, extrapyramidal symptoms, increased appetite and stroke.

Subsequently, I considered the adverse events of sufficient statistical strength for mood stabilisers, anxiolytics and stimulants. None were found for lithium. Valproate was associated with gastrointestinal problems and urinary tract infection, thrombocytopenia and dizziness. In terms of anxiolytics, no adverse events were associated with hydroxyzine, however, dizziness was linked to buspirone. Lastly, I analysed the results for psychostimulants. Amphetamine salts

and lisdexamfetamine had a strong association with decreased appetite and insomnia in children and adolescents with attention deficit hyperactivity disorder. Meanwhile, decreased appetite and weight loss were linked to methylphenidate in children and adolescents with attention deficit hyperactivity disorder.

Many medications were linked to adverse events through a weak or moderate strength of association. Certain medications, such as bupropion, fluoxetine, sertraline and lithium, only reported weak or moderate strengths of association.

Additionally, there were no eligible papers for a select number of included medications. These medications were clomipramine, alprazolam, diazepam, lorazepam and carbamazepine. It cannot be assumed that no evidence existed for these medications in relation to adverse events, merely it was highlighted that no relevant reviews were identified. Also, the evidence indicated that trazodone and hydroxyzine were not linked to any adverse events.

The high heterogeneity in the results prevented pooling the risk estimates for adverse events. The included systematic reviews studied populations of different age ranges and diagnoses. Additionally, these papers typically looked at varying outcomes. The clear differences in populations, diagnoses, interventions, dosages, and treatment durations across the reviews would render summary effects meaningless.[88] However, the results were stratified according to diagnosis and then by adverse event to maximize the clarity and organisation of the extracted data in the forest plots.

Certain adverse events demonstrated statistical strength in one review and not in another. This variation in results including examples will be examined in a section below entitled Variation in

Results: Exploring Different Directions of Evidence. The variation is important to investigate as it may affect the clinical implications of the results. It is required when considering the results to also take into account the study characteristics extracted from the eligible reviews, including the age and diagnosis of research participants, as well as the medication and quality rating of the review.

This umbrella review found more non-significant associations with adverse events than significant associations among the included systematic reviews. In Table 25, I highlighted the percentage of adverse events that reached statistical significance and those that did not per class of medications and overall I found that 56% of the overall results were non-significant, which suggests that any simplistic notion that all these medications are associated with adverse effects across all domains is not supported by evidence. It is therefore misleading to exclusively present the significant associations as the proportion of non-associations is high.

4.3 Challenges in Analysing Adverse Events

There were challenges that arose when trying to retrieve data on adverse events. First, many of the identified papers were solely analysing efficacy outcomes without investigating tolerability outcomes. Additionally, when tolerability outcomes were included, they were often summarised by the total number of dropouts in the review without analysing the prevalence rates or effect estimates for specific adverse events. This umbrella review did not focus on the number of participants who experienced an adverse event so severe that they dropped out of the study but the overall prevalence of an adverse event occurring. However, the Cochrane Collaboration has published numerous systematic reviews that are very thorough in terms of reporting adverse events.

Another difficulty was that the included systematic reviews used different labels for similar adverse events. For example, I extracted data for "suicide," "suicidality," "suicide-related events," "suicide attempts," and "treatment emergent suicidal ideation/suicide attempt/preparatory actions toward imminent suicidal behavior." It was difficult to determine when the differences between definitions of adverse events warranted the creation of separate categories of adverse events instead of grouping them all together in order to make the presentation of results as clear as possible. Additionally, certain reviews grouped two or three adverse events into one category and others did not. Specifically, the following adverse events were frequently categorized into one outcome: nausea and vomiting; sedation, sleepiness, drowsiness, sleeping problems and somnolence; extrapyramidal symptoms and needing anticholinergic medication. This reporting style added additional difficulty to the process of classifying adverse events into neurological, constitutional, gastrointestinal and other categories. For instance, a label such as "insomnia/somnolence" could be classified into two categories as insomnia is regarded as a constitutional outcome and somnolence or a depressed level of consciousness is considered a neurological outcome.

On occasion, reviews included participants without co-morbidities but with a variety of different diagnoses. For instance, one review included participants with a diagnosis of either bipolar disorder, schizophrenia spectrum disorder, autism spectrum disorders or oppositional defiant disorder. It was difficult to compare and contrast the results of this paper with other reviews when the populations did not share the same diagnosis or set of diagnoses. Additionally, it was challenging to extrapolate the clinical implications of the reported effect estimates to other settings given that the population inclusion criteria in certain reviews were so broad.

Certain systematic reviews indicated that their included studies only reported adverse events if the incidence was either statistically significant or had a frequency of 10% or greater. This type of methodology might lead to an underreporting rare adverse events, such as agranulocytosis, which has been linked to clozapine, or ocular problems, which have associated with thioridazine.[81] Thus decreased likelihood of extracting and analysing rare adverse events is a limitation of this umbrella review.

An additional challenge of this umbrella review was the quantification of certain adverse events. Tardive dyskinesia, among other adverse events, develop as a result of long-term treatment. Systematic reviews with long-term data were needed to properly assess these types of outcomes however long-term data is often absent.[38] Additionally, there are ethical factors to consider. Concerns have been raised regarding the design of long-term placebo-controlled trials that involve participants with severe mental illness who may need effective treatment immediately instead of being given placebo.

4.4 Variation in Results: Exploring Different Directions of Evidence

The results of this umbrella review suggest that age and diagnosis can affect the risk of an adverse event. It has been previously reported that the incidence and severity of an adverse event can vary depending on a number of patient characteristics including age, diagnosis, sex, ethnicity, medical comorbidity, genetic and geographic factors.[89] However, I found no umbrella review that previously documented and compared the variation in adverse event rates between the most commonly prescribed psychiatric medications and for a wide spectrum of psychiatric conditions.

I analysed the variation in results to highlight which drugs and populations reported different directions of evidence. I started by looking at any contrasting results among the class of antidepressants. Fluoxetine and paroxetine were the only antidepressants of interest. Fluoxetine associated with insomnia in a meta-analysis comprised of adults with depression. However, this link was not reported in adults with obsessive compulsive disorder. I also found variation in the evidence extracted for paroxetine. Specifically, paroxetine and suicidality were linked in adults with major depression but not in children and adolescents with the same diagnosis, nor in children and adolescents with obsessive compulsive disorder.

62% of the total variation reported in this umbrella review was for antipsychotic medications. This can be potentially attributed to the sheer volume of data reported for this class of medications relative to the others. Specifically, four of the seven antipsychotics had variation in their extracted results. The medications with the most variation in their results were summarised in Table 27 below (with the results reported in full in Appendix F). I first analysed the variation for aripiprazole.

Variation was found for akathisia, extrapyramidal symptoms, tremor and somnolence in the systematic reviews studying aripiprazole. Akathisia was linked to aripiprazole in individuals with bipolar disorder and schizoaffective disorder, as well as in adults with schizophrenia. However, a separate systematic review that involved participants with schizophrenia directly challenged this conclusion by reporting no significant association. This review failed to report certain basic study characteristics, such as the population's age range, which made further investigation difficult.

Extrapyramidal symptoms, somnolence and tremor was associated with aripiprazole in certain populations but not in others. For instance, Ching found a strong association between aripiprazole and tremor in 6- to 17-year-olds with either autism spectrum disorder or pervasive developmental disorder.[40] Conversely, Brown found no association in individuals with either bipolar or schizoaffective disorder. However, the age range used in the latter review was very wide and included children, adolescents, adults and older adults.

In terms of the results for risperidone, differences were found for abnormal gait, weight gain, somnolence, anticholinergic use and extrapyramidal symptoms. For instance, abnormal gait was linked to risperidone in older adults with Alzheimer's disease.[49] However, Tan found no association abnormal gait in 77- to 94-year-old individuals with a dementia diagnosis.[43]

There was variation in the results for olanzapine, specifically for anticholinergic use and extrapyramidal symptoms. For example, the drug associated with extrapyramidal symptoms in children and adolescents with schizophrenia and bipolar disorder. However, other systematic reviews reported no link between olanzapine and participants with schizophrenia spectrum disorder or major depression (with separate reviews reporting ORs or RR between 0.7 and 1.1).[42,54,83]

During the analysis, I recognized that there may have been additional factors that contributed to the variability in adverse outcome reporting aside from patient characteristics. Drug-related variables such as the type of drug, administration route, treatment duration, dosage and bioavailability have also been documented as factors that can influence the incidence and severity of adverse events.[89] I analysed the difference in drug-related variables, such as dosage and study duration, for quetiapine.

There was variation in quetiapine's results for extrapyramidal symptoms, urinary tract symptoms, and constipation. For instance, there was disagreement with respect to quetiapine's association with extrapyramidal symptoms in individuals with a diagnosis of bipolar depression. One study found a moderate link in individuals with acute bipolar depression between the ages of 10 and 65. In the second systematic review involving outpatients between the ages of 18 and 65 years with a diagnosis of bipolar depression, quetiapine did not associate with extrapyramidal symptoms. There was much more variability in the first systematic review's duration (1 to 12 weeks) and dosage (60 to 600 mg/day), and the setting was unclear. The dosage used in the second review was 300 mg/day for a total duration of eight weeks. No association was found between quetiapine and extrapyramidal symptoms in individuals with Alzheimer's disease, dementia, schizophrenia or major depression.[3,42,50,59] Many methodological differences, such as differences in patient-related and drug-related variables, existed among the included systematic reviews for quetiapine. Taking into account these differences provided a greater depth of analysis.

Valproate was the only mood stabiliser to report variation in its results. Specifically, different directions of evidence were found for dizziness and sedation. For instance, valproate associated with sedation when individuals had a diagnosis of dementia, schizophrenia and schizoaffective disorder but not bipolar disorder, autism spectrum disorder or intellectual disability.

Lastly, I observed different directions of evidence reported in the stimulant class of medications, namely lisdexamfetamine and methylphenidate. Variation in the outcomes for headaches and nausea were found for lisdexamfetamine. Citrome reported significant associations between lisdexamfetamine and these outcomes in adults with binge eating disorder, but none were found

in children and adolescents with attention deficit hyperactivity disorder.[67] However, the study durations were quite different; Citrome's study duration ranged between 11 and 104 weeks whereas the Punja review ranged from 14 to 63 days. The outcomes with different directions of evidence for methylphenidate were abdominal pain, dizziness, insomnia and headaches. For instance, the drug associated with dizziness, insomnia and headaches in children and adolescents with attention deficit disorder but not in children and adolescents diagnosed with attention deficit hyperactivity disorder.[70] In the systematic review by Citrome, the setting, dosage and duration were unclear. In the Punja review, the study population included inpatients and outpatients, the dosage administered ranged from 5 to 70 mg per day and the study duration ranged from one week to six months. Without the relevant data from the first systematic review, it was challenging to investigate further or to hypothesise which factors the variation in results for methylphenidate could have been attributed.

It is uncertain if common mechanisms exist between the included medications and the variation in reported adverse events. One factor to consider is the possibility of drug-disease interactions for these psychiatric medications. Drug-condition or drug-disease interactions can occur between a drug and a patient's medical condition and can make the drug potentially more harmful to the individual.[90] Drug-disease interactions were not mentioned in the majority of the eligible systematic reviews in this umbrella review. The drug mechanisms of many psychiatric medications including the impact that alterations in drug metabolism, absorption, excretion and distribution can have on the efficacy and tolerability outcomes in patients is not yet entirely understood.[92] However, the investigation of drug mechanisms and their outcomes was beyond the scope of this review.

	Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4	Diagnosis 5	Diagnosis 6	Diagnosis 7	Diagnosis 8	Diagnosis 9	Diagnosis 10
ARIPIPRAZOLE										
Extrapyramidal symptoms	Bipolar or schizoaffective disorder [71]	ASD or PDD [40]	Acute mania [54]	PDD or ID [41]	Bipolar depression [48]	Schizophrenia [35]	Schizophrenia spectrum [42]	Dementia [50]	Bipolar I, II, Acutely Manic or Mixed States [56]	Schizophrenia [77]
Age:	All ages	C&A	Adults	Children	Adults	Unclear	Adults	Unclear	All ages	Adults
OR or RR*:	* 2.2 (1.5, 3.4)	* 1.9 (0.9-3.7)	1.4 (1.0 1.9)	2.4 (0.9, 5.2)	* 3.2 (2.3, 4.5)	1.1 (0.6, 2.0)	1.0 (0.8, 1.2)	1.3 (0.7, 2.6)	* 2.4 (1.9, 3.2)	* 1.6 (0.6, 4.2)
RISPERIDONE										
Extrapyramidal symptoms	Alzheimer's disease [49]	Schizophrenia or bipolar [37]	PDD or ID [41]	Dementia or Alzheimer's [79]	Schizophrenia [35]	Bipolar disorder [35]	Schizophrenia [42]	Dementia [50]	Other [58]	Dementia [80]
Age:	Older adults	C&A	C&A	Older adults	Unclear	Unclear	Adults	Unclear	C&A	Older adults
OR or RR*:	1.8 (1.0, 3.2)	3.7 (2.2, 6.0)	3.7 (1.7, 7.2)	1.9 (1.2, 3.0)	1.1 (0.5, 2.6)	4.2 (2.6, 7.1)	1.3 (0.9,1.7)	3.0 (2.0, 4.7)	3.4 (2.0, 5.5)	1.8 (1.4, 2.4)
QUETIAPINE										
Extrapyramidal symptoms	Schizophrenia or bipolar [37]	Bipolar depression [48]	Generalised anxiety [51]	Schizophrenia [59]	Major depression [59]	Schizophrenia [42]	Dementia [50]	Alzheimer's disease [80]	Acute bipolar depression [55]	*
Age:	C&A	Adults	Adults	All ages	All ages	Adults	Unclear	Older adults	All ages	*
OR or RR*:	2.5 (0.9, 6.1)	* 1.4 (0.9, 2.2)	1.8 (1.1, 2.9)	* 1.0 (0.7, 1.3)	1.8 (0.9, 3.6)	0.9 (0.6, 1.3)	1.2 (0.5, 3.1)	0.9 (0.4, 2.0)	* 2.8 (2.1, 3.6)	*

Table 27 – Variation in results by individual medication
= association is not significant, C&A = Children and adolescents, * = RR

4.6 Strengths and Limitations

This is the first umbrella review to synthesise data for a broad range of adverse events for an extensive list of psychiatric medications and across psychiatric diagnoses. A large volume of data was collected from research publications in many different countries. Although it was not feasible to combine all the extracted data into forest plots, the characteristics for every review that met inclusion criteria are displayed in the appendix section. Hence, a greater depth of analysis was achieved with this umbrella review. The study characteristics and quality of each review were analysed allowing for a comprehensive overview.

There are strengths and limitations of the umbrella review design. An advantage of this methodology is that it allows for the analysis of multiple outcomes and/or multiple treatments at the same time. For the purpose of comparing a broad spectrum of medications with one another for the prevalence of adverse events, the umbrella design is preferable. The umbrella review inherently provides a "wide view of the evidence landscape" (Leucht, 2015). This large scope of analysis is often necessary to inform clinical guidelines and practice, which is the main purpose of this umbrella review. I aim to offer a clear view of the harms associated with each medication of interest. In addition, the Cochrane collaboration has shown interest in using the umbrella review methodology to group its pre-existing systematic reviews under larger umbrella reviews. Arguably, this methodology will become more commonplace once researchers and clinicians recognize its importance in the synthesis and analysis of clinical data as the literature continues to grow in the medical field. I prospectively registered the protocol for the review on PROSPERO, an international register of systematic reviews, on March 31st, 2016. As a result, there was increased transparency and accountability with regard to the research objectives and methodology. In addition, there was no funding for this umbrella review, which minimizes the risk of sponsorship bias, although it may still be present in the individual systematic reviews that comprised this umbrella review.

The umbrella review research design has a number of limitations. The researcher must assess whether the data can be analysed together and whether the data can be extrapolated to individual patients. I accounted for these limitations by searching for reviews with similar research designs and populations so that the data were either comparable or if there were great differences, that they would be explicitly written in this report. The included reviews were largely comprised of RCTs that used a placebo comparator and whose population had no comorbidities and was taking

no other medication at the time of the trials. Furthermore, in the quantitative analysis reviews were separated by diagnosis so that the results could be appropriately interpreted and extrapolated to patients with corresponding conditions. In addition, either the age range or the median age for the included reviews was indicated in the forest plots so the reader can distinguish between children and adolescents, adults and older adults. I aimed to retrieve data that could be converted into ORs or RRs, however, reviews often did not report the necessary prevalence data. Therefore, I extracted SMDs and converted them to ORs, however, papers that presented data that could not be converted to ORs or RRs were not a main component of this thesis.

As with every systematic review, the quality of an umbrella review is highly dependent on the studies that it comprises. To address this concern, the AMSTAR quality assessment tool (Table 2) was used. All of the included reviews had a quality rating that was either medium or high. A limitation of the AMSTAR tool is that it largely analyses the quality of the review and not of the primary studies involved. Therefore, even low quality trials could constitute a review that is given a high AMSTAR rating. However, given the scale of this umbrella review it was not feasible to do a risk of bias assessment for each primary study in the included systematic reviews. When two reviews focused on the same population, adverse events and medication, the most recent review was selected to be included in the final set. Theoretically, this could have been a limitation as the AMSTAR quality assessment rating was not factored in during this process.

This umbrella review almost meets each of the criteria in the AMSTAR quality assessment for systematic reviews. I provided an ‘a priori’ design, conducted a comprehensive search, included

grey literature, provided the characteristics of the included reviews, documented and assessed the quality of the reviews, accounted for the heterogeneity of the data and thus avoided any pooling of data and calculation of summary effect sizes, displayed the extracted data in an appropriate manner, checked for publication bias and accounted for potential conflicts of interest in all eligible reviews. Although there were two independent researchers screening the data, only one was available to extract the data from the 70 reviews. However, the second researcher rigorously checked the work of the first extractor to minimize any chance of error and disagreements were arbitrated by a third researcher, Andrea Cipriani.

The umbrella review methodology provides a wide scope of the literature, however, it may have caused me to exclude clinically relevant data. There exist trials that have analysed adverse events and the included medications of interest but were ultimately undetected as they were not part of a larger systematic review. None of the reviews in the final set provided data on clomipramine, alprazolam, diazepam or lorazepam. The lack of data may be a result of the filters that sifted out studies that were not systematic reviews.

Although my inclusion criteria were based on the most commonly prescribed medications in 2013 in addition to the World Health Organization's Essential Medicine List, certain common medications were excluded. For example, atomoxetine, a medication that is often prescribed for individuals with attention deficit hyperactivity disorder was excluded. In addition, the focus of my inclusion criteria was antidepressants, antipsychotics, anxiolytics, mood stabilisers and stimulants. Other types of medications, such as Z-drugs and melatonin, were excluded.

Outcome reporting bias was accounted for in this umbrella review. Non-significant results were presented in Main Results by Individual Medication in the forest plots and in full in Appendices

D and E. Additionally, they were taken into account in the Variation in Results Section and Appendix F where I compared the different directions of evidence for the same adverse events and medications. My aim in disclosing, analysing and discussing non-significant results was address outcome reporting bias.

The possibility of publication bias in this umbrella review was considered. The grey literature was searched. There were conference abstracts that were included after the screening and data extraction process into the final set of reviews. No unpublished reviews were intentionally excluded however there may exist reviews that were not accessible online with the rigorous search strategy implemented. Additionally, publication bias was accounted for and reported in a number of my included systematic reviews. For instance, Almandil generated a funnel plot that was slightly asymmetrical, which indicated a low level of publication bias.[6] Reasons for bias in this review were explored and the bias was ultimately explained by a small sample size for a select number of studies.

Outcome reporting and sponsorship bias were considered as limitations of this umbrella review. For example, the only systematic review on chlorpromazine reported that 47 of its included trials were judged as having a high risk of bias for selective reporting.[46] It was also reported that many of its trials were funded by the pharmaceutical industry. Another eligible systematic review indicated that the majority of its included trials that studied quetiapine were funded by AstraZeneca, a manufacturer of the drug.[55] However, all of the risks that were present in the systematic reviews were documented and accounted for in the AMSTAR appraisal, which can be found in Appendix C.

The quality of the trials in the included systematic reviews was at times moderate to very low according to GRADE.[46] Often, trials with few participants accounted for these poor quality ratings. I used the AMSTAR tool to measure the quality of the eligible systematic reviews but a highly rated systematic review by AMSTAR can still include poorly rated trials.

As a consequence of using only systematic reviews majorly comprised of randomised controlled trial design as an inclusion criterion, this umbrella review overlooked a number of serious adverse events. For instance, no extracted results were found for teratogenic effects despite the established links between valproate and neural tube defects, congenital heart lesions, oral clefts and craniofacial dysmorphic features among other forms of teratogenicity.[64]

Reviews that were more than 20% comprised of populations with medical co-morbidities were excluded, which could be a limitation. It is very common for patients with a psychiatric medical condition to have at least one co-morbidity. However, adding these types of reviews to the set of eligible reviews was beyond the scope of this thesis.

4.7 Overall Implications of Findings

Any incremental knowledge on the harms of a medication that a clinician is prescribing and that a patient is taking is necessary to both parties. Adverse events have historically been underreported and have prompted national reporting schemes, such as the United Kingdom's Yellow Card Scheme, so that more data can be collected about mild, moderate, severe, life-threatening adverse events as well as any deaths related to adverse events.[93] Greater efforts should be put into establishing these types of national reporting systems to increase knowledge in this area, which could potentially lead to medications with better tolerability profiles.

This review may confirm what physicians already perceived or realized to be true through their own clinical experience. However, it does offer the appropriate quantification of data to support various claims of association. Additionally, the quality of the vast majority of the included reviews is high, so clinicians can trust the reported data. However, the data in this review is insufficient for clinicians to decide on a treatment plan for their patients. Clinicians need to assess the established efficacy outcomes for their medications of interest and weigh it with the results provided in this review. People may think that a review solely focused on the adverse events of psychiatric medications is to propagate the frequently publicised objections to the use of these drugs and the notion that they should not be used as a treatment option. To the contrary, clinicians should utilize this data on harms to be more precise when choosing medical agents to treat their patients.

Adverse events often lead to poor compliance outcomes with medication, therefore additional research on this topic is clinically relevant.[71] More data could have been analysed if authors had clearly explained their populations, interventions, comparators, outcomes, as well as the types of studies in their reviews. For future systematic reviews, these details should be clearly and concisely stated. Additionally, there were no eligible reviews on clomipramine, alprazolam, diazepam, lorazepam, and carbamazepine. However, good quality trials of these medications may exist and the lack of data may simply be an indication of few, if any, systematic reviews and meta-analyses. Therefore, there should be greater efforts to synthesize existing randomised controlled trials into good quality systematic reviews because otherwise the synthesis of systematic reviews under larger umbrella reviews will not be feasible.

4.8 Conclusion

Most of the medications in the inclusion criteria were linked to adverse events. The strength of the effect sizes varied greatly, however. The statistically strongest associations were the following: amitriptyline was linked to sexual dysfunction and dry mouth, aripiprazole was linked to somnolence, clozapine was linked to weight gain and olanzapine also was linked to weight gain. I identified additional adverse events that demonstrated significant differences, although weaker than those mentioned above, for most of the included medications and reported the variability in outcomes among individuals with different ages and diagnoses. The specific harms of medications should be taken into account during clinical decision making, especially if the patient's medical history indicates that an alternative treatment option would be better suited. The efficacy profiles of the included medications should be weighed in tandem with the provided results to optimize patient outcomes.

The burden of adverse events on patients has been documented and the impact can be long term. Therefore, further investigation into the adverse events of psychiatric medication is needed to facilitate clinical decision-making, optimize patients' compliance with their medication and improve overall health outcomes.

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Appendix A – Formulae Used in Methods

1) Converting a Cohen's d or alternative SMDs to an Odds Ratio:

$$\text{Cohen's d} = \text{Log OR}(\sqrt{3}/\pi)$$
$$\text{Or, OR} = e^{\pi d/\sqrt{3}}$$

2) Converting prevalence rates to an Odds Ratio:

$$OR = (a / b) / (c / d)$$
$$= (a * d) / (b * c)$$

Where a = number of individuals in the exposed group who experienced the adverse event
b = number of individuals in the exposed group who did not experience the adverse event
c = number of individuals in the control group who experienced the adverse event
d = number of individuals in the control group who did not experience the adverse event

3) Converting an Odds Ratio to a Relative Risk:

$$RR = OR/[1-P_0+(P_0 \times OR)]$$

Where P_0 = baseline risk or prevalence

Appendix B - PRISMA Checklist

Section/topic	Page #	Checklist item
TITLE		
Title	3	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	iv	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	1-3	Describe the rationale for the review in the context of what is already known.
Objectives	3	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	5-7	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	4-5	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	4-5	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	6, 15	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	7-8	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	7-9	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	8	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.

Summary measures	9-10	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	9-10	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.)
Risk of bias across studies	4, 8	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	-	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	12-15	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	85, H-ZZ	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	66, D-F	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	H-ZZ	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	16-65	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	66, D-F	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	-	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	67-77,82-83	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	77-82	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	83-84	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	78	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

Appendix C - Quality Rating of Included Reviews (Using the AMSTAR Checklist)

Review	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score	Quality
Adams_2014 [46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Adams_2013 [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Alberti_2015 [7]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	8	High
Aleman_2001 [78]	Yes	Unclear	Yes	Unclear	No	Yes	Yes	Yes	No	No	No	5	Medium
Almandil_2013 [6]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Arbaizar_2009 [76]	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Ballard_2006 [49]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Barbui_2008 [34]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10	High
Beach_2014 [94]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	9	High
Belgamwar_2009 [73]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Bridge_2007 [72]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Brown_2013 [71]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Burgess_2001 [61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Chessick_2006 [60]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Ching_2012 [40]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Cipriani_2013 [64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Cipriani_2006 [53]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Citrome_2015 [67]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	7	Medium
Cohen_2012 [37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	9	High
Cohen_2013 [41]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	8	High
Coleman_2012 [33]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	7	Medium
Davidson_2000 [79]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Unclear	8	High
DeFruyt_2012 [48]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	10	High
DeHert_2011 [9]	Yes	Yes	Yes	Yes	No	Yes	Yes	Unclear	Yes	Unclear	No	7	Medium

Depping_2010[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Duggan_2009[81]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Fink_2003[75]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	No	8	Medium
Flank_2014[82]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	7	Medium
Gao_2008[35]	Yes	Unclear	No	No	Yes	Unclear	Yes	Yes	Yes	Yes	No	6	Medium
Gartlehner_2015[95]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Geddes_2004[62]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	9	High
Guaiana_2010[96]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Hetrick_2010[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Holtmann_2006[16]	Unclear	Unclear	Yes	Yes	No	Yes	No	No	Yes	No	No	4	Medium
Huband_2010[74]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Hulshof_2015[85]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10	High
Hutton_2015[59]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Jensen_2015[5]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Kishi_2012[39]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Kishi_2015[83]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Komossa_2010[47]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Leucht_2012[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Leucht_2009[42]	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	9	High
Lonergan_2009[66]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Macritchie_2003[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Maher_2011[50]	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	9	High
Matar_2013[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
McKnight_2012[63]	Yes	Yes	Yes	Yes	Unclear	No	Yes	Yes	Yes	No	No	7	Medium
McQuire_2015[52]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10	High
Meduri_2016[56]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10	High

Oya_2015[77]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Powney_2012[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Pringsheim_2011[58]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	6	Medium
Punja_2016[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Rendell_2003[36]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Schachter_2001[80]	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	8	High
Scherk_2007[54]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Schneider_2006[80]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Schneider_2005[3]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Schwarz_2008[86]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Smith_2010[87]	Yes	Unclear	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	8	High
Soomro_2008[97]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Srisurapanont_2004[84]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Stoffers_2010[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Storebo_2015[69]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11	High
Suttajit_2014[55]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10	High
Tan_2015[43]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	10	High
Thomas_2015[4]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	9	High
Whittington_2004[32]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Unclear	Unclear	7	Medium

Appendix D – Study Characteristics of Included Reviews

Items not recorded in the review are marked with an asterisk.

Abbreviations: N = sample size, k = number of studies. For reviews that did not provide an age range but reported either a mean or median age, it was recorded instead.

ANTIDEPRESSANTS																
AMITRIPTYLINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Leucht, 2012	Major Depression	Sedation/ Sleepiness/ Somnolence/ Drowsiness	15-93 years	OR	*	*	5.5	3.69 - 8.2	1690	13	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Tremor	15-93 years	OR	*	*	5.68	3.19 - 10.1	1230	10	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Rash (Dermal Rash)	15-93 years	OR	*	*	7.44	0.37 - 147.92	140	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Sweating	15-93 years	OR	*	*	1.82	0.28 - 12	339	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Sexual Dysfunction	15-93 years	OR	*	*	16.59	4.54 - 60.64	442	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Dyspepsia	15-93 years	OR	*	*	6.79	2.49 - 18.52	859	5	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Gastralgia	15-93 years	OR	*	*	1.89	0.82 - 4.35	172	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Increased appetite	15-93 years	OR	*	*	4.01	1.95 - 8.24	460	3	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Nausea	15-93 years	OR	*	*	1.22	0.49 - 3.04	749	6	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Fatigue/Asthenia/ Slowed down	15-93 years	OR	*	*	2.44	1.52 - 3.91	1051	6	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Tachycardia	15-93 years	OR	*	*	3.88	1.71 - 8.8	384	5	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Low blood pressure/ Dizziness/ Syncope	15-93 years	OR	*	*	2.92	2.07 - 4.11	1246	8	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Constipation	15-93 years	OR	*	*	3.39	2.36 - 4.88	1255	9	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Urinary Problems	15-93 years	OR	*	*	8.73	1.95 - 39.12	418	3	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Blurred Vision and Ambloyopia	15-93 years	OR	*	*	3.73	2.39 - 5.82	1055	10	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients

Leucht, 2012	Major Depression	Dry Mouth	15-93 years	OR	*	*	13.5	9.38 - 19.42	1414	11	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Agitation	15-93 years	OR	*	*	1.52	0.79 - 2.93	339	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Confusion	15-93 years	OR	*	*	2.76	0.5 - 15.33	228	4	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Headache	15-93 years	OR	*	*	0.84	0.54 - 1.29	1173	9	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Insomnia	15-93 years	OR	*	*	0.7	0.39 - 1.24	923	5	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Diarrhoea	15-93 years	OR	*	*	0.51	0.21 - 1.24	339	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Nervousness	15-93 years	OR	*	*	2.46	0.73 - 8.35	449	4	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
Leucht, 2012	Major Depression	Anticholinergic AE	15-93 years	OR	*	*	6.33	3.44 - 11.65	279	2	*	*	*	25-350 mg/d	3-12 weeks	Inpatients and outpatients
BUPROPION																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	0.58	0.39 - 0.86	4098	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	2.28	1.84 - 2.83	5249	*	*	*	*	Unclear	=>6 weeks	Unclear
Gartlehner, 2015	Seasonal Affective Disorder	Headache	42 years (mean)	*	RR	*	1.26	1.02 - 1.56	1048	3	*	*	*	150-300 mg/d	Unclear	Unclear
Gartlehner, 2015	Seasonal Affective Disorder	Insomnia	42 years (mean)	*	RR	*	1.46	1.1 - 1.93	1048	3	*	*	*	150-300 mg/d	Unclear	Unclear
Gartlehner, 2015	Seasonal Affective Disorder	Nausea	42 years (mean)	*	RR	*	1.63	1.12 - 2.38	1048	3	*	*	*	150-300 mg/d	Unclear	Unclear
Gartlehner, 2015	Seasonal Affective Disorder	Diarrhoea	42 years (mean)	*	RR	*	1.04	0.66 - 1.64	1048	3	*	*	*	150-300 mg/d	Unclear	Unclear
CITALOPRAM																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	3	1.85 - 4.87	3034	*	*	*	*	Unclear	=>6 weeks	Unclear

Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	2.15	1.21 - 3.83	3607	*	*	*	*	Unclear	=>6 weeks	Unclear
Beach, 2014	Major Depression and Healthy Subjects	QTc Interval	31-58 years	*	*	Difference in QTC, ms	10.58	3.93 - 17.23	696	5		*	*	20-60 mg/d	9-84 days	Unclear
Hetrick, 2012	Major Depression	Suicidality	6-18 years	*	RR	*	1.53	0.55 - 4.27	418	2	*	*	*	10-40 mg/d	2-15 weeks	Outpatients and mixed
Holtmann, 2006	Major Depression	Suicidality	7-18 years	*	RR	*	1.22	0.61 - 2.47	418	2	*	*	*	Unclear	8-12 weeks	Unclear
Whittington, 2004	Major Depression	Suicide-related Events	6-17 years	*	RR	*	1.99	0.83 - 4.77	*	2	*	*	*	Unclear	10 weeks	Unclear
DESVENLAFAXINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.9	2.47 - 3.4	9593	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	2.34	2.03 - 2.69	9873	*	*	*	*	Unclear	=>6 weeks	Unclear
Coleman, 2012	Major Depression	Nausea	=>18 years	OR	*	*	2.99	1.39	6.44	27	27%	9-12%	*	50-200 mg/d	Unclear	Unclear
DULOXETINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.91	2.2 - 3.83	5612	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	1.99	1.62 - 2.45	5924	*	*	*	*	Unclear	=>6 weeks	Unclear
ESCITALOPRAM																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.61	1.81 - 3.75	5276	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	1.89	1.54 - 2.32	6981	*	*	*	*	Unclear	=>6 weeks	Unclear
Hetrick, 2012	Major Depression	Suicidality	6-18 years	*	RR	*	0.91	0.47 - 1.76	575	2	*	*	*	10-45 mg/d	2-15 weeks	Outpatients and mixed

FLUOXETINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	1.98	1.41 - 2.78	2080	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	1.91	1.48 - 2.45	2964	*	*	*	*	Unclear	=>6 weeks	Unclear
Bridge, 2007	Major Depression	Treatment-emergent Suicidal Ideation/ Suicide Attempt/ Preparatory Actions Toward Imminent Suicidal Behavior	5-18 years	OR	*	*	1.44	0.68 - 3.08	576	*	6%	4%	*	Flexible Dosing	6-16 weeks	Unclear
Bridge, 2007	Obsessive Compulsive Disorder	Treatment-emergent Suicidal Ideation/ Suicide Attempt/ Preparatory Actions Toward Imminent Suicidal Behavior	5-18 years	OR	*	*	3.05	0.12 - 76.14	132	*	1%	0%	*	Flexible Dosing	6-16 weeks	Unclear
Hetrick, 2012	Major Depression	Suicidality	6-18 years	*	RR	*	1.77	0.85 - 3.69	536	3	*	*	*	10-40 mg/d	2-15 weeks	Outpatients and mixed
Holtmann, 2006	Major Depression	Suicidality (Self-harm Thoughts, Self-harm, Suicidal Ideation, Suicide Attempt)	8-18 years	*	RR	*	1.05	0.47 - 2.34	458	2	6%	5.70%	*	Unclear	8-9 weeks	Unclear
Soomro, 2008	Obsessive Compulsive Disorder	Nausea	=>18 years	*	RR	*	1.19	0.44 - 3.25	569	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Headache	=>18 years	*	RR	*	1.11	0.79 - 1.58	569	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Insomnia	=>18 years	*	RR	*	1.18	0.83 - 1.68	569	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Whittington, 2004	Major Depression	Suicide-related Events	7-18 years	*	RR	*	0.94	0.37 - 2.4	458	*	3.61%	3.83%	*	Unclear	7-8 weeks	Mixed

Whittington, 2004	Major Depression	Suicide Attempts	7-18 years	*	RR	*	1.26	0.36 - 4.4	458	*	2.41%	1.91%	*	Unclear	7-8 weeks	Mixed
PAROXETINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.84	2.38 - 3.39	6181	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	1.73	1.34 - 2.25	4278	*	*	*	*	Unclear	=>6 weeks	Unclear
Barbui, 2008	Major Depression	Suicidal Tendencies	>=18 years	OR	*	*	2.55	1.17 - 5.54	3739	15	1.02%	0.36%	*	10-50 mg/d	4-12 weeks	Unclear
Beach, 2014	Major Depression	QTc interval	40-43 years	*	*	Mean difference in QTc, ms	-1.04	-5.76 - 3.68	1486	2	*	*	*	20-30 mg/d	28-56 days	Unclear
Bridge, 2007	Obsessive Compulsive	Treatment-emergent Suicidal Ideation/Suicide Attempt/Preparatory Actions Toward Imminent Suicidal Behavior	5-18 years	OR	*	*	3.41	0.93 - 12.49	662	3	3%	1%	*	Flexible Dosing	6-16 weeks	Unclear
Hetrick, 2012	Major Depression	Suicidality	6-18 years	*	RR	*	1.57	0.46 - 5.31	702	4	*	*	*	10-45 mg/d	2-15 weeks	Outpatients and mixed
Holtmann, 2006	Major Depression	Suicidality (Self-harm Thoughts, Self-harm, Suicidal Ideation, Suicide Attempt)	12-18 years	*	RR	*	1.51	0.58 - 4.09	663	6	3.70%	2.50%	*	Unclear	8-12 weeks	Unclear
Soomro, 2008	Obsessive Compulsive	Somnolence	=>18 years	*	RR	*	1.85	1.12 - 3.06	537	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive	Headache	=>18 years	*	RR	*	0.95	0.53 - 1.69	648	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive	Insomnia	=>18 years	*	RR	*	1.71	1.15 - 2.53	648	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
SERTRALINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**

Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.09	1.67 - 2.62	4037	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	1.79	1.48 - 2.16	4418	*	*	*	*	Unclear	=>6 weeks	Unclear
Bridge, 2007	Major Depression	Treatment-emergent Suicidal Ideation/Suicide Attempt/Preparatory Actions Toward Imminent Suicidal Behavior	5-18 years	OR	*	*	0.33	0.01 - 8.20	243	*	0%	1%	*	Flexible Dosing	Unclear	Unclear
Holtmann, 2006	Major Depression	Suicidality (Self-harm Thoughts, Self-harm, Suicidal Ideation, Suicide Attempt)	6-17 years	*	RR	*	2.43	0.43 - 18.04	373	2	2.70%	1.10%	*	Unclear	10 weeks	Unclear
Soomro, 2008	Obsessive Compulsive Disorder	Nausea	=>18 years	*	RR	*	2.6	0.89 - 7.63	598	4	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Headache	=>18 years	*	RR	*	1.22	0.74 - 2.03	431	3	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Insomnia	=>18 years	*	RR	*	2.23	1.09 - 4.56	579	3	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Dyspepsia	=>18 years	*	RR	*	4.4	0.32 - 59.74	412	2	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Sedation	=>18 years	*	RR	*	1.31	0.65 - 2.62	511	3	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Diarrhoea	=>18 years	*	RR	*	2.16	1.11 - 4.23	579	3	*	*	*	50-200 mg/d	6-13 weeks	Mixed
Soomro, 2008	Obsessive Compulsive Disorder	Sexual Side Effects	=>18 years	*	RR	*	5.74	0.68 - 48.31	598	4	*	*	*	50-200 mg/d	6-13 weeks	Mixed
TRAZODONE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Fink, 2003	Erectile Dysfunction	Sedation	38-65 years (mean)	*	RR	*	2.1	0.97 - 4.4	254	2	16%	6%	*	50-200 mg/d	=>7 days	Unclear

Fink, 2003	Erectile Dysfunction	Dry Mouth	38-65 years (mean)	*	RR	*	1.6	0.8 - 3.5	146	2	19%	11%	*	50-200 mg/d	=>7 days	Unclear
Fink, 2003	Erectile Dysfunction	Nausea	38-65 years (mean)	*	RR	*	1.2	0.1 - 42.8	119	2	5%	3%	*	50-200 mg/d	=>7 days	Unclear
VENLAFAXINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Alberti, 2015	Major Depression	Somnolence	=>18 years	OR	*	*	2.84	2.34 - 3.44	9327	*	*	*	*	Unclear	=>6 weeks	Unclear
Alberti, 2015	Major Depression	Insomnia	=>18 years	OR	*	*	2.12	1.76 - 2.55	8712	*	*	*	*	Unclear	=>6 weeks	Unclear
Bridge, 2007	Anxiety Disorder (Non-OCD)	Suicidal behaviour	5-18 years	OR	*	*	3.03	0.12 - 75.28	*	*	1%	0%	*	Flexible Dosing	Unclear	Unclear
Coleman, 2012	Major Depression	Nausea	=>18 years	OR	*	*	2.99	1.55 - 5.79	*	*	38%	5-28%	*	75-225 mg/d	Unclear	Unclear
Holtmann, 2006	Major Depression	Suicidality (Self-harm Thoughts, Self-harm, Suicidal Ideation, Suicide Attempt)	6-17 years		RR	*	68.17	0.53 - 4,424.08	334	2	1.80%	0%	*	Unclear	8 weeks	Unclear
Whittington, 2004	Major Depression	Suicide-related Events	8-18 years		RR	*	13.77	1.83 - 103.61	*	2	*	*	*	Unclear	7-8 weeks	Unclear
ANTIPSYCHOTICS																
ARIPIPRAZOLE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Almandil_2013	Conduct Disorder, Behavioral Disorder, Autism, Pervasive Developmental Disorder, Bipolar Disorder, Mania, Schizophrenia or Attention Deficit Hyperactivity Disorder	Weight Gain (kg)	<=18 years	*	*	Mean difference	0.94	0.65 - 1.24	432	4	*	*	*	0.01-30 mg/d	3-26 weeks	Unclear

Arbaizar_2009a	Major Depression	Akathisia	Unclear	*	*	Rate difference	20.3	16.9 - 23.7	*	8	*	*	*	2-30 mg/d	6-8 weeks	Unclear
Arbaizar_2009a	Major Depression	Nausea	Unclear	*	*	Rate difference	2	0 - 4.5	*	8	*	*	*	2-30 mg/d	6-8 weeks	Unclear
Arbaizar_2009a	Major Depression	Insomnia	Unclear	*	*	Rate difference	6.9	4.4 - 9.4	*	6	*	*	*	2-30 mg/d	6-8 weeks	Unclear
Arbaizar_2009a	Major Depression	Restlessness	Unclear	*	*	Rate difference	8.5	6 - 11	*	4	*	*	*	2-30 mg/d	6-8 weeks	Unclear
Arbaizar_2009a	Major Depression	Upper Respiratory Tract Infection	Unclear	*	*	Rate difference	-0.4	-2.7 - 1.9	*	3	*	*	*	2-30 mg/d	6-8 weeks	Unclear
Arbaizar_2009b	Mania	Akathisia	Unclear	*	*	Rate difference	10.5	7.4 - 13.5	*	8	*	*	*	15-30 mg/d	3-6 weeks	Unclear
Arbaizar_2009b	Mania	Nausea	Unclear	*	*	Rate difference	6.5	2.9 - 10	*	8	*	*	*	15-30 mg/d	3-6 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Abnormal Involuntary Movement Scale	Unclear	*	*	Mean difference	0.02	-0.1 - 0.15	1068	4	*	*	*	10-50mg/d and variable dose	3-12 weeks	Inpatients and mixed
Brown_2013	Bipolar or Schizoaffective Disorder	Parkinsonism	8-74 years	*	RR	*	0.75	0.2 - 1.3	1233	4	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Akathisia	8-74 years	*	RR	*	3.16	2.25 - 4.43	2305	7	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Nausea	8-74 years	*	RR	*	1.5	1.2 - 1.88	2305	7	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Pain Extremity	8-74 years	*	RR	*	2.01	1.07 - 3.78	673	2	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Somnolence	8-74 years	*	RR	*	1.85	0.94 - 3.65	970	3	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	EPS	8-74 years	*	RR	*	2.24	1.47 - 3.42	1001	3	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear

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Brown_2013	Bipolar or Schizoaffective Disorder	EPS (Requiring Anticholinergic Medication)	8-74 years	*	RR	*	3.28	1.82 - 5.91	730	2	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Weight gain (=>7% Increase From Baseline)	8-74 years	*	RR	*	0.72	0.47 - 1.1	1596	5	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Brown_2013	Bipolar or Schizoaffective Disorder	Tremor	8-74 years	*	RR	*	1.45	0.89 - 2.34	1105	3	*	*	*	10-50mg/d and variable dose	3-12 weeks	Unclear
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Clinically Relevant Weight Gain	6-17 years	*	RR	*	1.13	0.71 - 1.54	308	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Sedation	6-17 years	*	RR	*	4.28	1.58 - 11.6	313	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Drooling	6-17 years	*	RR	*	9.64	1.29 - 72.1	313	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Tremor	6-17 years	*	RR	*	10.26	1.37 - 76.63	313	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	Any EPS	6-17 years	*	RR	*	1.89	0.98 - 3.66	313	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care
Ching_2012	Autism Spectrum Disorder, Asperger's Disorder or Pervasive Developmental Disorder	BMI Change From Baseline	6-17 years	*	*	Mean difference	0.44	-0.27 - 1.16	313	2	*	*	*	2.5-15mg/d	Any duration	Ambulatory care

Cohen_2012	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Weight Gain (kg)	8-17 years	*	*	Mean difference	0.89	0.26 - 1.51	*	*	*	*	*	2.5-15mg/d	Any duration	Unclear
Cohen_2012	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Weight Gain	8-17 years	OR	*	*	4.44	2 - 8.88	1615	*	*	*	*	2.5-15mg/d	3-12 weeks	Unclear
Cohen_2012	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	Somnolence	8-17 years	OR	*	*	6.07	2.79 - 12.22	1632	*	*	*	*	2.5-15mg/d	3-12 weeks	Unclear
Cohen_2012	Attention Deficit Hyperactivity Disorder, Schizophrenia, Behavioral Disorder, Pervasive Developmental Disorder or Intellectual Disability	EPS	8-17 years	OR	*	*	3.79	2.17 - 6.17	1500	*	*	*	*	2.5-15mg/d	3-12 weeks	Unclear
Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	Significant Weight Gain	8-10 years	OR	*	*	6.28	1.62 - 17.12	507	*	*	*	*	2-15 mg/d	6-10 weeks	Unclear
Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	EPS	8-10 years	OR	*	*	2.44	0.99 - 5.26	556	*	*	*	*	2-15 mg/d	6-10 weeks	Unclear

Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	Somnolence	8-10 years	OR	*	*	25.76	1.29 - 112.3	569	*	*	*	*	2-15 mg/d	6-10 weeks	Unclear
De Fruyt_2012	Bipolar Depression	Somnolence	18-65 years	*	RR	*	1.83	0.99 - 3.38	727	2	8%	4%	*	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	Significant Weight Gain	18-65 years	*	RR	*	1.45	0.7 - 3.01	727	2	5%	3%	*	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	Fatigue	18-65 years	*	RR	*	1.92	1.17 - 3.15	727	2	12%	6%	17 (10, 65) NNH	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	Sedation	18-65 years	*	RR	*	2.42	1.07 - 5.46	727	2	5%	2%	32 (17, 289) NNH	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	Akathisia	18-65 years	*	RR	*	5.59	3.35 - 9.33	727	2	24%	4%	4 (3,6) NNH	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	Mania	18-65 years	*	RR	*	1.88	0.7 - 5.03	727	2	3%	2%	*	5-30 mg/d	8 weeks	Outpatients
De Fruyt_2012	Bipolar Depression	EPS	18-65 years	*	RR	*	3.16	2.25 - 4.45	727	2	32%	10%	4 (3, 6)	5-30 mg/d	8 weeks	Outpatients
De Hert_2011	Schizophrenia, Bipolar Disorder, Autism or Attention Deficit Hyperactivity Disorder	Weight Change (kg)	5-18 years	*	*	Mean difference	0.79	0.54 - 1.04	1125	9	*	*	*	5-30 mg/d	4-8 weeks	Unclear
Gao_2008	Schizophrenia	Akathisia	Unclear	OR	*	*	1.65	0.91 - 3.00	407	2	15.40%	9.60%	-17 (142, -8) NNTB/NNTH	15-20mg/d	5 weeks	Unclear
Gao_2008	Schizophrenia	Overall EPS	Unclear	OR	*	*	1.1	0.60 - 2.04	410	2	11.80%	10.60%	-84 (20, -13) NNTB or NNTH	15-20mg/d	5 weeks	Unclear
Gao_2008	Bipolar Mania	Akathisia	Unclear	OR	*	*	4.77	2.26 - 10.08	523	3	14.60%	3.40%	-9 (-16, -6) NNTB/NNTH	28mg/d	6 weeks	Unclear
Jensen_2015	Bipolar Spectrum Disorder, Schizophrenia, Autism Disorder, Conduct Disorder, Asperger, Tourette Syndrome or Tic Disorder	QTc Interval Change (QTc)	9-16 years	OR	*	*	0.88	0.68 - 1.16	571	8	*	*	*	10-18 mg/d	11-19 weeks	Unclear
Leucht_2009	Schizophrenia, Schizoaffective Disorder or Acute Relapse of Schizophrenia	Use of Antiparkinson Medication	38 years (median)	OR	*	Risk difference	0.01	-0.02 - 0.05	1310	6	*	*	*	59-106 mg/d	4-26 weeks	Unclear

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Leucht_2009	Schizophrenia, Schizoaffective Disorder or Acute Relapse of Schizophrenia	Use of Antiparkinson Medication	38 years (median)	*	RR	*	1.07	0.81 - 1.41	1310	6	*	*	*	59-106 mg/d	4-26 weeks	Unclear
Leucht_2009	Schizophrenia, Schizoaffective Disorder or Acute Relapse of Schizophrenia	EPS	38 years (median)	*	*	*	0.98	0.78 - 1.24	1519	6	*	*		59-106 mg/d	4-26 weeks	Unclear
Leucht_2009	Schizophrenia, Schizoaffective Disorder or Acute Relapse of Schizophrenia	Sedation	38 years (median)	*	RR	*	1.38	0.82 - 2.34	1107	4	*	*		59-106 mg/d	4-26 weeks	Unclear
Leucht_2009	Schizophrenia, Schizoaffective Disorder or Acute Relapse of Schizophrenia	Somnolence	38 years (median)	*	*	Risk difference	0.02	0 - 0.005	1107	4	*	*		59-106 mg/d	4-26 weeks	Unclear
Maher_2011	Dementia	Cerebrovascular Accident	Unclear	OR	*	*	0.7	0.05 - 10.48	593	3	0.80%	0.60%	*	2-10 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Increased Appetite or Weight Increase	Unclear	OR	*	*	1	0.44 - 2.49	695	2	4.50%	4.90%	*	2-10 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Sedation	Unclear	OR	*	*	2.6	1.57 - 4.54	1080	4	5.90%	16.40%	*	2-10 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	EPS	Unclear	OR	*	*	1.3	0.68 - 2.57	1080	4	5.90%	5.50%	*	2-10 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Urinary Tract Symptoms	Unclear	OR	*	*	1.4	0.92 - 2.09	951	3	12.60%	19.10%	*	2-10 mg/d	6-12 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Weight Gain	=<18 years	*	RR	*	0.79	0.71 - 0.88	*	*	*	*	*	8.9-10 mg/d	8 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Sedation	=<18 years	*	RR	*	0.82	0.76 - 0.91	*	2	*	*	*	8.9-10 mg/d	8 weeks	Unclear
Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Sedation	6-65 years	*	RR	*	2.55	1.69 - 3.87	841	3	*	*	*	5-30 mg/d	3 weeks	Inpatients and outpatients
Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	EPS	6-65 years	*	RR	*	2.43	1.85 - 3.19	1807	6	*	*	*	5-30 mg/d	3 weeks	Inpatients and outpatients
Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Akathisia	6-65 years	*	RR	*	3.7	2.52 - 5.44	1807	6	*	*	*	5-30 mg/d	3 weeks	Inpatients and outpatients

Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Activation Symptoms	6-65 years	*	RR	*	1.08	0.85 - 1.38	1489	5	*	*	*	5-30 mg/d	3 weeks	Inpatients and outpatients
Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Weight Gain	6-65 years	*	RR	*	0.63	0.34 - 1.15	1621	6	*	*	*	5-30 mg/d	3 weeks	Inpatients and outpatients
Meduri_2016	Bipolar I, Bipolar II, Acutely Manic or Mixed States	Gastroenteric Disturbance	6-65 years		RR		1.28	0.3 - 1.97	1488	5				5-30 mg/d	3 weeks	Inpatients and outpatients
Oya_2015	Schizophrenia	Insomnia	18-65 years	*	RR	*	0.95	0.63 - 1.44	*	*	*	*	*	25-300 mg/month	12-52 weeks	Unclear
Oya_2015	Schizophrenia	Anxiety	18-65 years	*	RR	*	0.87	0.51 - 1.47	*	*	*	*	*	25-300 mg/month	12-52 weeks	Unclear
Oya_2015	Schizophrenia	EPS	18-65 years	*	RR	*	1.63	0.64 - 4.15	*	*	*	*	*	25-300 mg/month	12-52 weeks	Unclear
Oya_2015	Schizophrenia	Anticholinergic Use	18-65 years	*	RR	*	1.5	1.04 - 2.18	*	*	*	*	17 NNH	25-300 mg/month	12-52 weeks	Unclear
Oya_2015	Schizophrenia	Weight Gain	18-65 years	*	RR	*	1.58	0.92 - 2.73	*	*	*	*	16 NNH	25-300 mg/month	12-52 weeks	Unclear
Oya_2015	Schizophrenia	Injection site pain	18-65 years	*	RR	*	3.62	0.5 - 26.31	*	*	*	*	*	25-300 mg/month	12-52 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Mean Weight Gain (kg)	=<18 years	*	*	Mean difference	0.85	0.57 - 1.13	861	5	*	*	*	0.15-6 mg/d	3-10 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Change in BMI From Baseline	=<18 years	*	*	Mean difference	0.27	0.11 - 0.42	720	3	*	*	*	0.15-6 mg/d	3-10 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Extrapyramidal Disorder	=<18 years	*	*	Mean difference	3.7	2.37 - 5.77	952	5	*	*	*	0.15-6 mg/d	3-10 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Prolongation of QTc Interval	=<18 years	*	*	Mean difference	-5.03	-7.8 - - 2.26	796	4	*	*	*	0.15-6 mg/d	3-10 weeks	Unclear

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Scherk_2007	Acute mania	Weight Gain (kg)	37-41 years (mean)	OR	*	*	1.34	0.95 - 1.82	514	2	*	*	*	15-30 mg/d	3 weeks	Unclear
Scherk_2007	Acute mania	SAS/ESRS	37-41 years (mean)	OR	*	*	1.36	1.0 - 1.89	507	2	*	*	*	15-30 mg/d	3 weeks	Unclear
Scherk_2007	Acute mania	BAS	37-41 years (mean)	OR	*	*	1.85	1.24 - 2.76	507	2	*	*	*	15-30 mg/d	3 weeks	Unclear
Tan_2015	Dementia	Somnolence	77-84 years	OR	*	*	3.51	1.64 - 7.5	*	*	*	*	*	2-10 mg/d	6-26 weeks	Nursing home or outpatient
Tan_2015	Dementia	Injuries or Falls	77-84 years	OR	*	*	0.86	0.58 - 1.28	*	*	*	*	*	2-10 mg/d	6-26 weeks	Nursing home or outpatient
Tan_2015	Dementia	Urinary Tract Infection	77-84 years	OR	*	*	1.2	0.78 - 1.87	*	*	*	*	*	2-10 mg/d	6-26 weeks	Nursing home or outpatient
Tan_2015	Dementia	Stroke	77-84 years	OR	*	*	1.58	0.38 - 6.55	*	*	*	*	*	2-10 mg/d	6-26 weeks	Nursing home or outpatient
Thomas_2015	Schizophrenia	Akathisia	=>18 years	*	RR	*	1.55	1.05 - 2.29	*	12	*	*	*	10-30 mg/d	4-26 weeks	Unclear
Thomas_2015	Schizophrenia	BMI	=>18 years	*	*	Mean difference	1.69	0.81 - 2.56	*	2	*	*	*	10-30 mg/d	4-26 weeks	Unclear
CHLORPROMAZINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Acute Movement Disorders (Dystonia)	18-64 years	*	RR	*	3.47	1.5 - 8.03	942	5	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Parkinsonism (Includes EPS)	18-64 years	*	RR	*	2.11	1.59 - 2.8	1468	15	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Tremor	18-64 years	*	RR	*	1.66	1.01 - 2.73	392	7	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Rigidity	18-64 years	*	RR	*	2.24	1.42 - 3.54	412	7	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting

Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Akathisia	18-64 years	*	RR	*	0.78	0.54 - 1.11	1164	9	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Sleepiness	18-64 years	*	RR	*	2.79	2.25 - 3.45	1627	23	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Fits/ Loss of Consciousnes s	18-64 years	*	RR	*	3.11	1.05 - 9.18	695	3	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weakness	18-64 years	*	RR	*	3.33	1.02 - 10.88	92	3	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Blood Problems (Agranulocyt osis, Leukopenia)	18-64 years	*	RR	*	2.08	0.74 - 5.83	394	7	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Rashes/Itchin g/Skin Disorders	18-64 years	*	RR	*	1.45	0.92 - 2.29	1313	13	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Liver Problems	18-64 years	*	RR	*	4.31	0.98 - 18.95	249	4	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Photosensitiv ity	18-64 years	*	RR	*	6.04	3.22 - 11.32	799	6	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Eye Opacity/Eye Pigment Problems	18-64 years	*	RR	*	3.09	1.87 - 5.11	657	2	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Blood Pressure - Low/ Dizziness/ Syncope	18-64 years	*	RR	*	2.38	1.74 - 3.25	1488	18	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Constipation	18-64 years	*	RR	*	2.05	1.33 - 3.15	1117	10	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting

Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Urinary Problems	18-64 years	*	RR	*	1.73	0.7 - 4.3	926	5	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Blurred Vision	18-64 years	*	RR	*	1.16	0.51 - 2.65	962	7	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Dry Mouth	18-64 years	*	RR	*	4.56	2.35 - 8.85	1015	7	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weight Increase	18-64 years	*	RR	*	4.92	2.32 - 10.43	165	5	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Weight Decrease	18-64 years	*	RR	*	0.38	0.22 - 0.66	165	5	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Nausea/Vomiting	18-64 years	*	RR	*	2.07	1.14 - 3.73	1024	5	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Salivation	18-64 years	*	RR	*	3.37	1.07 - 10.57	830	3	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Menorrhagia/ Abnormal Menstruation	18-64 years	*	RR	*	1.39	0.62 - 3.13	46	2	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
Adams, 2014	Schizophrenia or Non-Affective Serious/Chronic Mental Illness	Lactation	18-64 years	*	RR	*	1.48	0.57 - 3.81	192	2	*	*	*	25-1200mg/d	5 days -3 months	Inpatients and community setting
CLOZAPINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**

Cohen, 2012	Schizophrenia, Bipolar Disorder, Behavioral Disorders, Autism, Intellectual Disability, Tourette Syndrome or Conduct Disorder	Weight Gain (kg)	8-17 years	*	*	Mean difference	2.38	0.19 - 4.62	1019	*	*	*	*	26-403 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia, Bipolar Disorder, Behavioral Disorders, Autism, Intellectual Disability, Tourette Syndrome or Conduct Disorder	Weight Gain (kg)	8-17 years	OR	*	*	13.83	2.21 - 49.21	915	*	*	*	*	26-403 mg/d	3-12 weeks	Unclear
FLUPHENAZINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Matar, 2013	Schizophrenia	Akathisia	16-58 years	*	RR	*	3.43	1.23 - 9.56	227	2	*	*	*	2.5-20 mg/d	6 weeks-2 years	Inpatients and outpatients
Matar, 2013	Schizophrenia	Rigidity	16-58 years	*	RR	*	3.54	1.76 - 7.14	227	2	*	*	*	2.5-20 mg/d	6 weeks-2 years	Inpatients and outpatients
Matar, 2013	Schizophrenia	Tremor	16-58 years	*	RR	*	3.19	1.25 - 8.11	227	2	*	*	*	2.5-20 mg/d	6 weeks-2 years	Inpatients and outpatients
Matar, 2013	Schizophrenia	Rash	16-58 years	*	RR	*	0.76	0.15 - 3.78	227	2	*	*	*	2.5-20 mg/d	6 weeks-2 years	Inpatients and outpatients
HALOPERIDOL																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Adams, 2013	Schizophrenia	Dystonia	<18-65 years	*	RR	*	11.49	3.23 - 40.85	471	5	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Akathisia	<18-65 years	*	RR	*	3.66	2.24 - 5.97	695	6	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Dyskinesia and Tardive Dyskinesia	<18-65 years	*	RR	*	1	0.14 - 7.13	157	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed

Adams, 2013	Schizophrenia	Parkinsonism	<18-65 years	*	RR	*	5.48	2.68 - 11.22	485	5	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Needing Antiparkinson Medication	<18-65 years	*	RR	*	3.23	2.2 - 4.72	480	4	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Blurred Vision	<18-65 years	*	RR	*	3.96	1.21 - 12.93	240	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Tremor	<18-65 years	*	RR	*	3.93	1.96 - 7.91	447	5	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Blood Pressure - Low/Dizziness	<18-65 years	*	RR	*	1.01	0.36 - 2.79	245	3	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Rigidity	<18-65 years	*	RR	*	4.98	2.74 - 9.05	461	5	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Agitation	<18-65 years	*	RR	*	1.07	0.54 - 2.12	362	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Anxiety	<18-65 years	*	RR	*	0.84	0.33 - 2.16	362	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Drooling	<=65 years	*	RR	*	4	0.88 - 18.21	207	3	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Headache	<=65 years	*	RR	*	0.93	0.62 - 1.39	593	4	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Insomnia	<=65 years	*	RR	*	1.11	0.76 - 1.63	629	4	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Oculogyric Crises	<=65 years	*	RR	*	0.97	0.14 - 6.57	83	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Nausea/vomiting	<=65 years	*	RR	*	0.9	0.49 - 1.65	231	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Perspiration	<=65 years	*	RR	*	4.74	0.58 - 38.81	93	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Sleepiness	<=65 years	*	RR	*	3.09	1.51 - 6.31	686	7	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed

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Adams, 2013	Schizophrenia	Weight gain (kg)	<=65 years	*	RR	*	4.89	1.41 - 16.95	441	2	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Adams, 2013	Schizophrenia	Weight loss	<=65 years	*	RR	*	0.77	0.36 - 1.64	385	3	*	*	*	0.5-200mg/d	10 days - 3 years	Inpatients, outpatients and mixed
Ballard, 2006	Alzheimer's Disease	EPS	>60 years	OR	*	*	2.34	1.25 - 4.38	204	36	*	*	*	0.5-2 mg/d	>=6 weeks	Outpatients or people in a care facility
Ballard, 2006	Alzheimer's Disease	Drowsiness	>60 years	OR	*	*	4.2	1.78 - 9.9	229	36	*	*	*	0.5-2 mg/d	>=6 weeks	Outpatients or people in a care facility
Cipriani, 2006	Bipolar or Schizoaffective Disorder	Extrapyramidal Disorder	18-68 years	*	RR	*	4.17	2.88 - 6.03	474	2	*	*		3-85 mg/d	6 days - 12 weeks	Inpatients and mixed
Cipriani, 2006	Bipolar or Schizoaffective Disorder	Somnolence	18-68 years	*	RR	*	2.01	0.83 - 4.87	484	2	*	*	*	3-85 mg/d	6 days - 12 weeks	Inpatients and mixed
Cipriani, 2006	Bipolar or Schizoaffective Disorder	Tremor	18-68 years	*	RR	*	3.28	1.86 - 5.79	484	2	*	*	*	3-85 mg/d	6 days - 12 weeks	Inpatients and mixed
Cipriani, 2006	Bipolar or Schizoaffective Disorder	Weight gain (kg)	18-68 years	*	*	Mean difference	0.38	-0.17 - 0.92	380	2	*	*	*	3-85 mg/d	6 days - 12 weeks	Inpatients and mixed
Gao, 2008	Schizophrenia	Akathisia	Unclear	OR	*	*	2.91	1.73 - 4.88	450	3	25.70%	10.50%	-7(-12, -5) NNTB/NNTH	8-12 mg/d	6 weeks	Unclear
Gao, 2008	Schizophrenia	Overall EPS	Unclear	OR	*	*	3.68	2.11 - 6.43	450	3	25.20%	8.30%	-4 (-7, -3) NNTB or NNTH	8-12 mg/d	6 weeks	Unclear
Gao, 2008	Schizophrenia	Anticholinergic Use	Unclear	OR	*	*	2.51	1.66 - 3.79	450	3	41.90%	22.40%	-5 (-8, -3) NNTB or NNTH	8-12 mg/d	6 weeks	Unclear
Gao, 2008	Bipolar Mania	Overall EPS	Unclear	OR	*	*	7.77	4.50 - 13.40	484	2	38.30%	7.50%	-3 (-4, -3) NNTB or NNTH	2-8mg/d	7 weeks	Unclear
Hulshof, 2015	Dementia or Delirium	Mortality	72-83 years	*	RR	*	1.25	0.59 - 2.65	1799	11	*	*	*	0.5-10 mg/d	0.7 -12 weeks	Hospital settings, nursing homes, community centers and memory clinics
Leucht, 2009	Schizophrenia	Use of Antiparkinson Medication	38 years (median)	*	RR	*	2.34	1.9 - 2.88	1608	11	*	*	*	Unclear	Unclear	Unclear

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Leucht, 2009	Schizophrenia	EPS	38 years (median)	OR	*	*	2.03	1.60 - 2.57	1004	7	*	*	*	Unclear	Unclear	Unclear
Leucht, 2009	Schizophrenia	Sedation	38 years (median)	*	RR	*	2.28	1.11 - 4.67	970	6	*	*	*	Unclear	Unclear	Unclear
Leucht, 2009	Schizophrenia	Somnolence	38 years (median)	OR		*	2.26	1.51 - 3.39	970	6	16.50%	8.10%	12 (7-44) NNH	Unclear	Unclear	Unclear
Powney, 2012	Psychosis-induced Aggression or Agitation	Over Sedated	18-73 years	*	RR	*	3.36	1.42 - 7.99	313	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	Somnolence During 24 hours	18-73 years	*	RR	*	2.28	0.97 - 5.36	615	4	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	Dizziness During 24 Hours (If Reported In =>5%)	18-73 years	*	RR	*	1.33	0.48 - 3.65	392	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	Hypotension During 24 Hours	18-73 years	*	RR	*	1.2	0.05 - 27.44	125	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	QTc Interval (Avg Change At 24 Hours)	18-73 years	*	*	Mean difference	3.63	-2.67 - 9.93	265	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	EPS During 24 Hours	18-73 years	*	RR	*	6.79	2.19 - 21.07	398	3	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	Agitation During 24 Hours (If Reported In =>5%)	18-73 years	*	RR	*	0.8	0.29 - 2.19	395	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
Powney, 2012	Psychosis-induced Aggression or Agitation	Headache During 24 Hours (If Reported In =>5%)	18-73 years	*	RR	*	1.28	0.55 - 3	395	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings

Powney, 2012	Psychosis-induced Aggression or Agitation	Nausea During 24 Hours	18-73 years	*	RR	*	0.69	0.13 - 3.67	395	2	*	*	*	5-10 mg/d IM	2 hours - 21 days	Inpatients, outpatients and emergency settings
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Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Almandil, 2013	Conduct Disorder, Behavioral Disorder, Autism, Pervasive Developmental Disorder, Bipolar Disorder, Mania, Schizophrenia or Attention Deficit Hyperactivity Disorder	Weight Gain	<=18 years	*	*	Mean difference	3.45	2.93 - 3.98	183	3	*	*	*	0.01-30mg/d	3-26 weeks	Unclear
Ballard, 2006	Alzheimer's Disease	Abnormal Gait	>60 years	OR	*	*	4.76	1.67 - 13.57	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Nervousness	>60 years	OR	*	*	1.09	0.52 - 2.27	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Fever	>60 years	OR	*	*	4.55	1.04 - 19.84	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Peripheral Edema	>60 years	OR	*	*	2.24	0.74 - 6.72	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Falls	>60 years	OR	*	*	1.52	0.79 - 2.91	685	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Injury	>60 years	OR	*	*	1.05	0.61 - 1.82	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Anxiety	>60 years	OR	*	*	0.92	0.39 - 2.16	631	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Agitation	>60 years	OR	*	*	1.07	0.65 - 1.75	838	3	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility

Ballard, 2006	Alzheimer's Disease	Weight Gain	>60 years	OR	*	*	4.7	1.09 - 20.39	685	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Anorexia	>60 years	OR	*	*	0.71	0.34 - 1.47	838	3	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Ballard, 2006	Alzheimer's Disease	Somnolence	>60 years	OR	*	*	3.72	1.9 - 7.25	450	2	*	*	*	1-15 mg/d	6-10 weeks	Outpatients and people in a care facility
Belgamwar, 2005	Acutely Disturbed/Agitated People with Suspected Serious Mental Illnesses	EPS - Requiring Anticholinergic Medication By 24 Hours	18-97 years	*	RR	*	1.27	0.49 - 3.26	570	3	*	*	*	1-15 mg/d	Unclear	Inpatient/ outpatient clinics, community centres, day hospitals and emergency settings attended by psychiatric teams
Cohen, 2012	Schizophrenia or Bipolar Disorder	Weight Gain (kg)	8-17 years	OR	*	*	15.1	6.56 - 31.1	242	9	*	*	*	72-107 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	Weight Gain (kg)	8-17 years	*	*	Mean difference	3.99	3.17 - 4.84	1222		*	*	*	72-107 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	*	8.49	3.97 - 16.55	1291	*	*	*	*	72-107 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	EPS	8-17 years	OR	*	*	6.36	2.43 - 13.84	1014	*	*	*	*	72-107 mg/d	3-12 weeks	Unclear
DeHert, 2011	Pervasive Developmental Disorder, Bipolar Disorder or Schizophrenia	Weight Gain (kg)	6-17 years	*	*	Mean Difference	3.45	2.93 - 3.97	276	2	*	*	*	2.5-20 mg/d	4-8 weeks	Unclear
Duggan, 2009	Schizophrenia	Agitation	18-70 years	*	RR	*	1.2	0.7 - 2.07	418	2	*	*	*	1-20 mg/d	4-18 weeks	Inpatients, outpatients and mixed
Duggan, 2009	Schizophrenia	Hostility	18-70 years	*	RR	*	0.97	0.57 - 1.63	418	2	*	*	*	1-20 mg/d	4-18 weeks	Inpatients, outpatients and mixed
Duggan, 2009	Schizophrenia	Requiring Anticholinergic Medication	18-70 years	*	RR	*	0.9	0.29 - 2.79	418	2	*	*	*	1-20 mg/d	4-18 weeks	Inpatients, outpatients and mixed
Duggan, 2009	Schizophrenia	Weight Gain (kg)	18-70 years	*	*	Mean difference	3.58	-1.18 - 8.34	227	2	*	*	*	1-20 mg/d	4-18 weeks	Inpatients, outpatients and mixed

Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Urinary Problems	4-17 years	*	*	*	*	*	*	4	8%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Anxiety	4-17 years	*	*	*	*	*	*	3	2%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Constipation	4-17 years	*	*	*	*	*	*	3	24%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Gastrointestinal Problems	4-17 years	*	*	*	*	*	*	4	25%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Hypersalivation	4-17 years	*	*	*	*	*	*	3	15%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Akathisia	4-17 years	*	*	*	*	*	*	4	9%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Flu Symptoms	4-17 years	*	*	*	*	*	*	3	29%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Dry mouth	4-17 years	*	*	*	*	*	*	4	8%	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Headache	4-17 years	*	*	*	*	*	*	4	25%	*	*	Unclear	8 weeks	Unclear

Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Extrapyramidal Symptoms	4-17 years	*	*	Proportion	0.05	0.01 - 0.34	*	2	*	*	*	Unclear	8 weeks	Unclear
Flank, 2014	Pervasive Developmental Disorder or Childhood-Onset Schizophrenia	Sedation	4-17 years	*	*	Proportion	0.36	0.09 - 1.49	*	2	*	*	*	Unclear	8 weeks	Unclear
Jensen, 2015	Schizophrenia, Acute Mania or Mixed Episode, or Psychosis	QTc Interval Change (QTc)	11-19 years	OR	*	*	0.93	0.55 - 1.57	148	2	*	*	*	10-13 mg/d	3-10 weeks	Unclear
Kishi, 2012	Anorexia Nervosa	Drowsiness/ Sedation/ Somnolence	12-37 years	*	RR	*	11.45	2.94 - 44.54		3	*	*	*	2.5-10 mg/d	8-12 weeks	Inpatients and outpatients
Kishi, 2012	Anorexia Nervosa	Change in BMI	12-37 years	OR	*	*	1.44	0.72 - 2.92	106	4	*	*	*	2.5-10 mg/d	8-12 weeks	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophreniform Disorder or Schizoaffective Disorder	Use of Anticholinergic Drugs	20-60 years	*	RR	*	0.46	0.25 - 0.83	1055	7	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophreniform Disorder or Schizoaffective Disorder	Use of Benzodiazepines	20-60 years	*	RR	*	0.53	0.3 - 0.95	1055	7	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients

Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	Akathisia	20-60 years	*	RR	*	0.61	0.15 - 2.57	1038	7	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	EPS	20-60 years	*	RR	*	1.12	0.47 - 2.66	1002	7	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	Dyskinesia	20-60 years	*	RR	*	1.25	0.06 - 25.4	286	3	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients

Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	SAS/DIEPSS	20-60 years	OR	*	*	1	0.75 - 1.36	627	6	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	BAS/ DIEPSS	20-60 years	OR	*	*	0.85	0.61 - 1.20	504	5	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	Orthostatic Hypotension/ Dizziness	20-60 years	*	RR	*	1.82	0.72 - 4.55	1049	7	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	QT Prolongation	20-60 years	*	RR	*	0.34	0.16 - 0.7	869	6	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients

Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	Agitation and Calmness Score	20-60 years	*	RR	*	2.39	0.89 - 6.43	757	6	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Kishi, 2015	Schizophrenia, Mania, Depression, Acute Psychosis, Mental Retardation with Psychosis, Substance Induced Psychosis, Schizophrenia, Schizophreniform Disorder or Schizoaffective Disorder	QTc Interval Change (QTc)	20-60 years	OR	*	*	0.78	0.59 - 1.02	*	*	*	*	*	2.5-10 mg/d	1.5-24 hours	Inpatients and outpatients
Leucht, 2009	Schizophrenia	Use of antiparkinson medication	38 years (median)	*	*	*	1.69	0.98 - 2.92	481	3	15.60%	9.80%	*	2.5-20 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	Use of antiparkinson medication	38 years (median)		RR	*	1.23	0.52 - 2.93	481	3	*	*	*	2.5-20 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	EPS	38 years (median)	OR*	*	*	1.04	0.61 - 1.06	185	2	*	*	*	2.5-20 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	Sedation	38 years (median)	*	RR	*	8.26	1.15 - 59.61	408	3	*	*	*	2.5-20 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	Somnolence	38 years (median)	*	*	Risk Difference	0.13	-0.01 - 0.26	408	3	27.10%	12.40%	*	2.5-20 mg/d	2-28 weeks	Unclear
Maher, 2011	Dementia	Cerebrovascular accident	Unclear	OR	*	*	1.5	0.33 - 7.44	510	2	1.70%	2.20%	*	2-20 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	Increased appetite or weight increase	Unclear	OR	*	*	4.7	1.87 - 14.14	808	3	1.80%	7.10%		2-20 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	Sedation	Unclear	OR	*	*	4.6	2.87 - 7.55	1218	5	5.70%	20.30%		2-20 mg/d	6-12 weeks	Unclear

Pringsheim, 2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Change in BMI	=<18 years	*	*	Mean Difference	1.28	0.96 - 1.59	267	2	*	*	*	Unclear	3-8 weeks	Unclear
Pringsheim, 2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Weight gain in kg	=<18 years	*	*	Mean Difference	3.47	2.94 - 3.99	278	3	*	*	*	Unclear	3-8 weeks	Unclear
Rendell, 2003	Acute Mania (Bipolar or Schizoaffective Disorder)	Depression	18-86 years	*	RR	*	0.84	0.44 - 1.6	249	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Acute Mania (Bipolar or Schizoaffective Disorder)	SAS Scale	18-86 years	*	*	Mean Difference	-0.33	-0.74 - 0.09	241	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Acute Mania (Bipolar or Schizoaffective Disorder)	Barnes Akathisia Scale	18-86 years	*	*	Mean Difference	-0.13	-0.32 - 0.06	246	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Acute Mania (Bipolar or Schizoaffective Disorder)	Weight gain in kg	18-86 years	*	*	Mean Difference	1.91	1.29 - 2.53	149	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Somnolence	18-86 years	*	RR	1	2.65	1.61 - 4.38	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Dry mouth	18-86 years	*	RR	*	3.06	1.5 - 6.22	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Dizziness	18-86 years	*	RR	*	2.95	1.37 - 6.38	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Agitation	18-86 years	*	RR	*	0.59	0.35 - 1.01	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Asthenia	18-86 years	*	RR	*	2.42	1.1 - 5.33	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Headache	18-86 years	*	RR	*	0.95	0.56 - 1.61	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Anxiety	18-86 years	*	RR	*	0.65	0.11 - 3.67	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear

Rendell, 2003	Bipolar or Schizoaffective Disorder	Constipation	18-86 years	*	RR	*	2.09	0.87 - 5.04	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Hostility	18-86 years	*	RR	*	0.51	0.21 - 1.22	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Nervousness	18-86 years	*	RR	*	0.54	0.27 - 1.08	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Personality Disorder	18-86 years	*	RR	*	0.41	0.16 - 1.02	254	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Rendell, 2003	Bipolar or Schizoaffective Disorder	Weight gain	18-86 years	OR	*	*	31.96	1.69 - 98.40	249	2	*	*	*	5-20 mg/d	2-6 weeks	Unclear
Scherk, 2007	Acute Mania	Weight gain in kg	37-40 years (mean)	OR	*	*	3.9	2.43 - 6.25	246	2	*	*	*	5-800 mg/d	3-4 weeks	Unclear
Scherk, 2007	Acute Mania	SAS/ESRS	37-40 years (mean)	OR	*	*	0.72	0.46 - 1.14	246	2	*	*	*	5-800 mg/d	3-4 weeks	Unclear
Scherk, 2007	Acute Mania	BAS	37-40 years (mean)	OR	*	*	0.72	0.46 - 1.14	251	2	*	*	*	5-800 mg/d	3-4 weeks	Unclear
Stoffers, 2010	Borderline Personality Disorder	Body weight change in kg	23-33 years	OR	*	*	6.72	5.12 - 8.82	752	6	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Increased appetite	23-33 years	*	RR	*	2.76	1.75 - 4.34	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Headache	23-33 years	*	RR	*	0.91	0.43 - 1.92	615	2	*	*	*	2.5-20 mg/d	6 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Fatigue	23-33 years	*	RR	*	2.04	0.79 - 5.23	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Somnolence	23-33 years	*	RR	*	2.97	1.75 - 5.03	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Insomnia	23-33 years	*	RR	*	0.68	0.33 - 1.37	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Nausea	23-33 years	*	RR	*	0.83	0.43 - 1.59	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Stoffers, 2010	Borderline Personality Disorder	Dry mouth	23-33 years	*	RR	*	2.24	1.08 - 4.67	615	2	*	*	*	2.5-20 mg/d	5 weeks - 6 months	Unclear
Tan, 2015	Dementia	Somnolence	77-84 years	OR	*	*	3.61	1.83 - 7.13	*	*	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients
Tan, 2015	Dementia	Injuries or falls	77-84 years	OR	*	*	1.13	0.72 - 1.76	*	*	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients

Tan, 2015	Dementia	Abnormal gait	77-84 years	OR	*	*	3.84	1.64 - 8.95	*	3	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients
Tan, 2015	Dementia	Edema	77-84 years	OR	*	*	0.52	0.16 - 1.69	*	2	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients
Tan, 2015	Dementia	Urinary infection	77-84 years	OR	*	*	6.93	1.33 - 35.96	*	*	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients
Tan, 2015	Dementia	Stroke	77-84 years	OR	*	*	3.93	0.62 - 25.1	*	2	*	*	*	5 mg/d	6-26 weeks	Nursing home and outpatients
QUETIAPINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Cohen, 2012	Schizophrenia or Bipolar Disorder	Weight gain in kg	8-17 years	*	*	Mean difference	1.74	0.99 - 2.5	1267	*	*	*	*	17-611 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	Significant weight gain	8-17 years	OR	*	*	6.2	2.61 - 13.56	1343	*	*	*	*	17-611 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	*	5.44	2.91 - 9.26	1424	*	*	*	*	17-611 mg/d	3-12 weeks	Unclear
Cohen, 2012	Schizophrenia or Bipolar Disorder	EPS	8-17 years	OR	*	*	2.54	0.88 - 6.07	1250	*	*	*	*	17-611 mg/d	3-12 weeks	Unclear
DeFruyt, 2012	Bipolar Depression	Somnolence	18-65 years	*	RR	*	3.91	2.77 - 5.53	1732	5	24%	6%	5 (4, 6) NNH	300mg/d	8 weeks	Outpatients
DeFruyt, 2012	Bipolar Depression	Weight gain	18-65 years	*	RR	*	2.37	1.22 - 4.59	1701	5	6%	2%	27 (18, 58) NNH	300mg/d	8 weeks	Outpatients
DeFruyt, 2012	Bipolar Depression	Fatigue	18-65 years	*	RR	*	1.44	0.94 - 2.2	1341	4	8%	5%	*	300mg/d	8 weeks	Outpatients
DeFruyt, 2012	Bipolar Depression	Sedation	18-65 years	*	RR	*	4.49	2.57 - 4.74	1732	5	19%	6%	6 (5, 8) NNH	300mg/d	8 weeks	Outpatients
DeFruyt, 2012	Bipolar Depression	EPS	18-65 years	*	RR	*	1.93	0.89 - 4.16	1743	5	7%	4%	*	300mg/d	8 weeks	Outpatients
DeFruyt, 2012	Bipolar Depression	Mania	18-65 years	*	RR	*	0.62	0.26 - 1.47	1743	5	3%	5%	*	300mg/d	8 weeks	Outpatients
DeHert, 2011	Schizophrenia or Bipolar Disorder	Weight change in kg	10-18 years	*	*	Mean difference	1.43	1.17 - 1.69	691	5	*	*	*	300-800 mg/d	3-12 weeks	Unclear
Depping, 2010	Generalised Anxiety Disorder	EPS (Short-term)	=>18 years	OR	*	*	1.8	1.12 - 2.9	2262	4	*	*	*	25-400 mg/d	8 weeks	Unclear
Depping, 2010	Generalised Anxiety Disorder	Weight change (sig)	=>18 years	OR	*	*	2.39	1.23 - 4.65	2262	4	*	*	*	25-400 mg/d	8 weeks	Unclear
Depping, 2010	Generalised Anxiety Disorder	Weight change in kg	=>18 years	*	*	Mean difference	0.63	0.4 - 0.86	2201	4	*	*	*	25-400 mg/d	8 weeks	Unclear
Depping, 2010	Generalised Anxiety Disorder	Sedation in short term	=>18 years	OR	*	*	4.48	2.65 - 7.59	2262	4	*	*	*	25-400 mg/d	8 weeks	Unclear

Hutton, 2015	Schizophrenia	Simpson-Angus Scale	>12 years	*	RR	*	0.97	0.73 - 1.29	1465	7	14.70%	13.90%	Absolute difference 0.007 (-0.033, 0.047)	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Abnormal Involuntary Movements Scale	>12 years	*	RR	*	0.694	0.52 - 0.92	799	4	16.50%	21.10%	21 (8, 27) NNB	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Barnes Akathisia Scale	>12 years	*	RR	*	0.866	0.60 - 1.23	1616	7	6.90%	7.60%	200 (33, 50) NNB	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Needing medication for EPS	>12 years	*	RR	*	0.838	0.60 - 1.18	1769	*	9.10%	9.30%	250 (40,21) NNH	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Mean weight change	>12 years	*	*	Mean difference	1.753	1.10 - 2.40	2358	12	*	*	*	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Significant weight change (=>7% of weight)	>12 years	OR	*	*	2.988	2.05 - 4.36	2083	10	11.50%	3.70%	13 (23, 9) NNH	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Schizophrenia	Sedation or somnolence	>12 years	*	RR	*	2.581	1.95 - 3.41	2377	12	*	*	9 (7, 13) NNH	>250 mg/d	6-52 weeks	Inpatients and mixed
Hutton, 2015	Major Depression	EPS	>12 years	OR	*	*	1.84	0.94 - 3.6	1342	3	*	*	*	>250 mg/d	6-52 weeks	Inpatients and mixed
Komossa, 2010	Major Depression	Significant weight gain =>7% from baseline short term	18-70 years	OR	*	*	2.12	1.13 - 3.99	2118	4	*	*	*	0-300 mg/d	4-52 weeks	Inpatients, outpatients and mixed
Komossa, 2010	Major Depression	Weight change from baseline in kg in short term	18-70 years		*	Mean difference	0.65	0.11 - 1.18	2027	4	*	*	*	0-300 mg/d	4-52 weeks	Inpatients, outpatients and mixed
Komossa, 2010	Major Depression	Sedation	18-70 years	OR	*	*	5.76	2.32 - 14.32	2118	4	*	*	*	0-300 mg/d	4-52 weeks	Inpatients, outpatients and mixed
Leucht, 2009	Schizophrenia	Use of antiparkinson medication	38 years (median)	*	*	Mean difference	-0.02	-0.08 - 0.03	521	4	9.50%	11.20%	*	75-750 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	Use of antiparkinson medication	38 years (median)	*	RR	*	0.79	0.46 - 1.35	509	3	*	*	*	75-750 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	EPS	38 years (median)	OR	*	*	0.85	0.55 - 1.31	529	3	*	*	*	75-750 mg/d	2-28 weeks	Unclear
Leucht, 2009	Schizophrenia	Sedation	38 years (median)	*	RR	*	2.02	1.18 - 3.47	750	5	*	*	*	75-750 mg/d	2-28 weeks	Unclear

Leucht, 2009	Schizophrenia	Somnolence	38 years (median)	*	*	Risk difference	0.13	0.01 - 0.24	750	5	16.80%	9.70%	8 (4-74) NNH	75-750 mg/d	2-28 weeks	Unclear
Maher, 2011	Dementia	Cardiovascular event	Unclear	OR	*	*	1.1	0.53 - 2.3	609	3	5.90%	8.20%	*	50-150 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	Cerebrovascular accident	Unclear	OR	*	*	0.7	0.1 - 3.08	426	6	0.80%	1.60%	*	50-150 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	Sedation	Unclear	OR	*	*	5.2	2.93 - 9.51	799	4	5.10%	18.80%	*	50-150 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	EPS	Unclear	OR	*	*	1.2	0.46 - 3.08	609	3	3.50%	5.10%	*	50-150 mg/d	6-12 weeks	Unclear
Maher, 2011	Dementia	Urinary tract symptoms	Unclear	OR	*	*	2.4	1.16 - 5.15	523	2	6.30%	13.30%	*	50-150 mg/d	6-12 weeks	Unclear
Pringsheim, 2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Weight gain (kg)	=<18 years		*	Mean difference	1.41	1.01 - 1.81	81	3	*	*	*	Unclear	6-8 weeks	Unclear
Schneider, 2005	Alzheimer's with agitation or Dementia with agitation	Deaths	66-99 years	OR	*		1.67	0.7 - 4.03	637	3	5.40%	2.80%	*	25-600 mg/d	10 weeks	Nursing home
Schneider, 2006	Alzheimer's with agitation or psychosis	EPS	66-99 years	OR	*	*	0.92	0.43 - 1.98	582	2	5.20%	6%	*	25-600 mg/d	10-26 weeks	Nursing home
Schneider, 2006	Alzheimer's with agitation or psychosis	Urinary tract infection	66-99 years	OR	*	*	1.73	0.57 - 5.26	582	2	3.60%	9.20%	*	25-600 mg/d	10-26 weeks	Nursing home
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Patients receiving medications for extrapyramidal AE	=>18 years	*	RR	*	0.63	0.34 - 1.15	395	2	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Parkinsonism	=>18 years	*	RR	*	0.52	0.26 - 1.06	595	2	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Constipation	=>18 years	*	RR	*	1.88	0.95 - 3.74	704	3	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Dizziness	=>18 years	*	RR	*	2.23	1.12 - 4.42	716	4	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Low blood pressure (postural)	=>18 years	*	RR	*	1.92	0.79 - 4.7	418	2	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear
Srisurapanont, 2004	Schizophrenia or Schizoaffective Disorder	Sleepiness	=>18 years	*	RR	*	2	1.32 - 3.04	716	4	*	*	*	75-750 mg/d	3 weeks - 16 months	Unclear

Suttajit, 2014	Acute Bipolar Depression	EPS	10-65 years	*	RR	*	2.77	2.12 - 3.62	*	6	*	*	8 (7, 10) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Sedation	10-65 years	*	RR	*	3.32	2.71 - 4.06	*	6	*	*	8 (7, 9)	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Somnolence	10-65 years	*	RR	*	3.74	2.86 - 4.9	*	5	*	*	7 (6, 8) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Dizziness	10-65 years	*	RR	*	2.18	1.73 - 2.74	*	6	*	*	14 (11, 20) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Constipation	10-65 years	*	RR	*	2.05	1.5 - 2.81	*	5	*	*	25 (18, 41) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Dry mouth	10-65 years	*	RR	*	3.65	3.04 - 4.4	*	6	*	*	*	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Mania	10-65 years	*	RR	*	0.58	0.37 - 0.92	*	6	*	*	*	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Increased appetite	10-65 years	*	RR	*	2.81	1.58 - 5.01	*	4	*	*	26 (18, 48) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Weight gain	10-65 years	*	RR	*	2.33	1.34 - 4.03	*	4	*	*	29 (19, 57) NNH	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Headache	10-65 years	*	RR	*	0.68	0.53 - 0.86	*	6	*	*	*	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Nausea	10-65 years	*	RR	*	0.77	0.56 - 1.07	*	5	*	*	*	50-600 mg/d	1-12 weeks	Unclear
Suttajit, 2014	Acute Bipolar Depression	Diarrhoea	10-65 years	*	RR	*	0.64	0.4 - 1.01	*	2	*	*	*	50-600 mg/d	1-12 weeks	Unclear
Tan, 2015	Dementia	Somnolence	77-84 years	OR	*	*	5.88	2.39 - 14.47	*	*	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
Tan, 2015	Dementia	Injuries or falls	77-84 years	OR	*	*	0.85	0.57 - 1.29	*	*	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
Tan, 2015	Dementia	Abnormal gait	77-84 years	OR	*	*	1.98	0.73 - 5.39	*	3	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
Tan, 2015	Dementia	Edema	77-84 years	OR	*	*	1.51	0.55 - 4.19	*	2	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
Tan, 2015	Dementia	Urinary infection	77-84 years	OR	*	*	1.9	0.95 - 3.8	*	*	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
Tan, 2015	Dementia	Stroke	77-84 years	OR	*	*	1.13	0.36 - 3.56	*	4	*	*	*	50-100 mg/d	6-26 weeks	Nursing home or outpatients
RISPERIDONE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**

Almandil, 2013	Conduct Disorder, Behavioral Disorder, Autism, Pervasive Developmental Disorder, Bipolar Disorder, Mania, Schizophrenia or Attention Deficit Hyperactivity Disorder	Weight gain	<=18 years	*	*	Mean difference	1.77	1.35 - 2.2	712	4	*	*	*	0.01-30mg/d	4-52 weeks	Unclear
Aleman, 2001	Schizophrenia	Aggression	Unclear	*	*	Mean weighted effect size	0.28	0.07 - 0.49	456	2	*	*	*	2.5-8.5 mg/d	8 weeks	Unclear
Ballard_2006	Alzheimer's Disease	EPS	>60 years	OR	*	*	1.78	1.0 - 3.17	1121	3	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Agitation	>60 years	OR	*	*	0.86	0.62 - 1.19	1413	*	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Injury	>60 years	OR	*	*	0.74	0.53 - 1.04	1074	3	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Cerebrovascular events	>60 years	OR	*	*	3.64	1.72 - 7.69	1954	5	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Mortality	>60 years	OR	*	*	1.25	0.73 - 2.16	1954	5	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Abnormal gait	>60 years	OR	*	*	5.31	2.24 - 12.62	1100	3	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	URTI	>60 years	OR	*	*	1.15	0.69 - 1.93	784	2	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Falls	>60 years	OR	*	*	0.84	0.63 - 1.14	1411	4	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Peripheral edema	>60 years	OR	*	*	2.75	1.51 - 5.03	938	3	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Urinary tract infection	>60 years	OR	*	*	1.4	0.92 - 2.13	648	2	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Fever	>60 years	OR	*	*	1.22	0.63 - 2.34	938	3	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Tremor	>60 years	OR	*	*	2.43	0.8 - 7.42	810	2	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Ballard_2006	Alzheimer's Disease	Somnolence	>60 years	OR	*	*	2.38	1.76 - 3.2	1640	5	*	*	*	0.5-2.0 mg/d	10-13 weeks	Unclear
Cohen_2012	Schizophrenia or Bipolar Disorder	Weight gain in kg	8-17 years	*	*	Mean difference	2.02	1.39 - 2.66	1545	*	*	*	*	1.5-6 mg/d	3-12 weeks	Unclear
Cohen_2012	Schizophrenia or Bipolar Disorder	Significant weight gain	8-17 years	OR	*	*	6.03	3.02 - 11.4	1756	*	*	*	*	1.5-6 mg/d	3-12 weeks	Unclear
Cohen_2012	Schizophrenia or Bipolar Disorder	Somnolence	8-17 years	OR	*	*	7.3	4.63 - 11.19	1827	*	*	*	*	1.5-6 mg/d	3-12 weeks	Unclear
Cohen_2012	Schizophrenia or Bipolar Disorder	EPS	8-17 years	OR	*	*	3.71	2.18 - 6.02	1946	*	*	*	*	1.5-6 mg/d	3-12 weeks	Unclear

Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	Significant weight gain	7-14 years	OR	*	*	7.76	1.88 - 25.2	470	*	*	*	*	2-15 mg/d	6-10 weeks	Unclear
Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	EPS	7-14 years	OR	*	*	3.72	1.73 - 7.22	569	*	*	*	*	2-15 mg/d	6-10 weeks	Unclear
Cohen_2013	Pervasive Developmental Disorder or Intellectual Disability	Somnolence	7-14 years	OR	*	*	9.63	3.52 - 22.79	569	*	16.60%	9%	*	2-15 mg/d	6-10 weeks	Unclear
Davidson_2000	Dementia or Alzheimer's	EPS	75-81 years	OR	*	*	1.91	1.22 - 2.98	705	*	*	*	*	Unclear	6-12 weeks	Unclear
Davidson_2000	Dementia or Alzheimer's	Somnolence	75-81 years	OR	*	*	1.37	0.9 - 2.06	705	2	*	*	*	Unclear	6-12 weeks	Unclear
De Hert_2011	Conduct Disorder, Behavioral Problem, Autism, Conduct Disorder, Tourette's, Autism, ADHD, Bipolar or Schizophrenia	Weight change in kg	5-62 years	*	*	Mean difference	1.76	1.27 - 2.25	946	12	*	*		0.15-6 mg/d	3-24 weeks	Unclear
Gao_2008a	Schizophrenia	Overall EPS	Unclear	OR	*	*	1.1	0.47 - 2.55	376	3	6.50%	5.80%	-137 (23,-17) NNTB or NNTH	6 mg/d	6 weeks	Unclear
Gao_2008a	Schizophrenia	Anticholinergic Use	Unclear	OR	*	*	1.14	0.56 - 2.35	174	2	23.30%	20.50%	-36 (11, -7) NNTB or NNTH	6 mg/d	6 weeks	Unclear
Gao_2008b	Bipolar Disorder	Overall EPS	Unclear	OR	*	*	4.24	2.55 - 7.05	584	2	25.70%	7.40%	-5 (-8, -4) NNTB or NNTH	4.1-5.6 mg/d	6 weeks	Unclear
Gao_2008b	Bipolar Disorder	Anticholinergic Use	Unclear	OR	*	*	4.44	2.72 - 7.27	549	2	29.90%	8.60%	-5 (-7, -4) NNTB or NNTH	4.1-5.6 mg/d	6 weeks	Unclear
Jensen_2015	Bipolar Spectrum Disorders, Schizophrenia, Behavioural Problems in Autism, Oppositional Defiant Disorder or Psychosis	Qtc interval change	9-15 years	OR	*	*	0.98	0.78 - 1.22	573	12	*	*	*	0.5-3.5 mg/d+D163:Z163	24-34 weeks	Unclear
Leucht_2009	Schizophrenia	Use of antiparkinson medication	38 years (median)	OR	*	*	1.35	0.83 - 2.19	323	4	32.30%	25.90%	*	75-750 mg/d	2-28 weeks	Unclear
Leucht_2009	Schizophrenia	Use of antiparkinson medication	38 years (median)		RR	*	1.24	0.89 - 1.71	323	4	*	*	*	75-750 mg/d	2-28 weeks	Unclear

Leucht_2009	Schizophrenia	EPS	38 years (median)	OR	*	*	1.29	0.98 - 1.72	642	5	*	*	*	75-750 mg/d	2-28 weeks	Unclear
Leucht_2009	Schizophrenia	Sedation	38 years (median)	*	RR	*	1.29	0.73 - 2.29	665	4	*	*	*	75-750 mg/d	2-28 weeks	Unclear
Leucht_2009	Schizophrenia	Somnolence/ sedation	38 years (median)	OR	*	*	1.34	0.72 - 2.49	665	4	7.60%	5.70%	*	75-750 mg/d	2-28 weeks	Unclear
Maher_2011	Dementia	Cardiovascular event	Unclear	OR	*	*	2.1	1.38 - 3.22	2767	6	3.40%	6.80%	*	0.5-2.25 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Cerebrovascular accident	Unclear	OR	*	*	3.12	1.32 - 8.21	1852	4	1.10%	2.20%	*	0.5-2.25 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Increased appetite or weight increase	Unclear	OR	*	*	3.4	1.08 - 12.75	517	2	2.10%	5%	*	0.5-2.25 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	EPS	Unclear	OR	*	*	3	1.96 - 4.7	2477	5	3.40%	8.30%		0.5-2.25 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Sedation	Unclear	OR	*	*	2.3	1.79 - 3.05	2182	6	11.10%	21%	*	0.5-2.25 mg/d	6-12 weeks	Unclear
Maher_2011	Dementia	Urinary tract symptoms	Unclear	OR	*	*	1.6	1.13 - 2.13	1725	4	10.70%	15.50%		0.5-2.25 mg/d	6-12 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Weight change in kg	=<18 years	OR	*	*	4.43	2.81 - 6.84	*	3	*	*	*	1-1.8 mg/d	6-12 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Significant weight change	=<18 years	*	RR	*	0.91	0.85 - 0.96	*	5	*	*	*	1-1.8 mg/d	6-12 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Sedation	=<18 years	*	RR	*	0.53	0.42 - 0.68	*	5	*	*	*	1-1.8 mg/d	6-12 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Mean weight gain (kg)	=<18 years	*	*	Mean difference	1.72	1.17 - 2.26	833	10	*	*	*	Unclear	3-10 weeks	Unclear
Pringsheim_2011	Autism, Conduct Disorder, Disruptive Behaviour Disorder, Aggression, Bipolar Disorder I or Schizophrenia	Extrapyramidal disorder	=<18 years	OR	*	*	3.35	2.04 - 5.48	773	7	*	*	*	1-6 mg/d	3-10 weeks	Unclear
Scherk_2007	Mania	Weight gain in kg	34-41 years (mean)	OR	*	*	1.69	0.71 - 4.12	824	3	*	*	*	1-6 mg/d	3 weeks	Unclear

Schneider_2005	Dementia with aggression	Death	56-97 years	OR	*	*	1.3	0.76 - 2.23	1954	5	3.80%	2.80%	*	0.5-4 mg/d	8-12 weeks	Nursing home
Schneider_2006	Dementia with aggression	Somnolence	81-83 years	OR	*	*	2.43	1.78 - 3.32	1954	5	*	*	*	0.5-4 mg/d	8-12 weeks	Nursing home and outpatients
Schneider_2006	Dementia with aggression	Injury and Accidental Injury	81-83 years	OR	*	*	0.83	0.65 - 1.06	1725	4	22.70%	23.90%	*	0.5-4 mg/d	8-12 weeks	Nursing home and outpatients
Schneider_2006	Dementia with aggression	EPS	81-83 years	OR	*	*	1.8	1.35 - 2.42	1954	5	*	*		0.5-4 mg/d	8-12 weeks	Nursing home and outpatients
Schneider_2006	Dementia with aggression	Urinary tract infection	81-83 years	OR	*	*	1.54	0.88 - 2.7	*	*	15.50%	10.70%	*	0.5-4 mg/d	8-12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Somnolence	77-84 years	OR	*	*	3.57	2.72 - 4.67	*	*	*	*	*	Unclear	12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Injuries or falls	77-84 years	OR	*	*	0.85	0.68 - 1.08	*	*	*	*	*	Unclear	12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Abnormal gait	77-84 years	OR	*	*	1.21	0.73 - 1.99	*	3	*	*	*	Unclear	12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Edema	77-84 years	OR	*	*	0.49	0.3 - 0.78	*	4	*	*	*	Unclear	12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Urinary infection	77-84 years	OR	*	*	2.28	1.58 - 3.3	*	4	*	*	*	Unclear	12 weeks	Nursing home and outpatients
Tan_2015	Dementia	Stroke	77-84 years	OR	*	*	4.53	1.75 - 11.72	*	4	*	*	*	Unclear	12 weeks	Nursing home and outpatients
MOODSTABILISERS																
LITHIUM																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Burgess_2001	Any Mood Disorder	Hypothyroidism	All ages	OR	*	*	7.19	0.6 - 32.32	310	3	*	*	*	900-1250mg	11 months - 4 years	Mixed
Geddes_2004	Bipolar Disorder	Somnolence	Unclear	*	RR	*	1.98	1.02 - 3.84	770	5	*	*	*	Unclear	>=3 months	Unclear
Geddes_2004	Bipolar Disorder	Nausea	Unclear	*	RR	*	1.76	1.07 - 2.92	770	5	*	*	*	Unclear	>=3 months	Unclear
Geddes_2004	Bipolar Disorder	Diarrhoea	Unclear	*	RR	*	2.35	1.35 - 4.1	770	5	*	*	*	Unclear	>=3 months	Unclear
Geddes_2004	Bipolar Disorder	Hypothyroidism	Unclear	*	RR	*	9.26	0.51 - 169.91	770	5	*	*	*	Unclear	>=3 months	Unclear
Geddes_2004	Bipolar Disorder	Suicide	Unclear	*	RR	*	0.32	0.03 - 2.98	565	*	0%	0.70%	*	Unclear	>=3 months	Unclear

McKnight_2012	Depression or Bipolar Disorder	Weight gain	Unclear	OR	*	*	1.89	1.27 - 2.82	1224	5	10%	5.60%	23 (12, 71) NNH	Unclear	Unclear	Unclear
McKnight_2012	Depression or Bipolar Disorder	Skin disorders	Unclear	OR	*	*	1.28	0.49 - 3.36	213	2	*	*	23 (12, 71) NNH	Unclear	Unclear	Unclear
VALPROATE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Cipriani_2013	Bipolar Disorder	Alopecia	All ages	*	RR	*	2.51	1.15 - 5.51	312	2	*	*	*	Within the therapeutic dose range	6-12 months	Outpatients and mixed
Cipriani_2013	Bipolar Disorder	Tremor	All ages	*	RR	*	2.41	1.58 - 3.67	312	2	*	*	*	Within the therapeutic dose range	6-12 months	Outpatients and mixed
Cipriani_2013	Bipolar Disorder	Weight gain	All ages	*	RR	*	2.04	1.07 - 3.86	312	2	*	*	*	Within the therapeutic dose range	6-12 months	Outpatients and mixed
Hirsch_2012	Epilepsy and Non-epilepsy Indications	Infections	Unclear	*	*	*	*	*	278	*	16.80%	5.70%	*	Unclear	Unclear	Unclear
Huband_2010	Any individual experiencing recurrent aggressive outbursts or episodes	Headache	=> 5 years	OR	*	*	0.76	0.44 - 1.32	276	2	*	*	*	80-1500 mg/d	2-24 weeks	Inpatients, outpatients, community and custodial settings
Huband_2010	Any individual experiencing recurrent aggressive outbursts or episodes	Weight gain	=> 5 years	OR	*	*	2.42	1.1 - 5.31	276	2	*	*	*	80-1500 mg/d	2-24 weeks	Inpatients, outpatients, community and custodial settings
Lonergan_2009	Dementia	Sedation	=> 49 years	OR	*	*	2.48	1.37 - 4.47	241	3	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	GI problems	=> 49 years	OR	*	*	7.09	1.73 - 29.02	208	2	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	Urinary tract infection	=> 49 years	OR	*	*	3.02	1.04 - 8.8	227	2	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	Falls without injury	=> 49 years	OR	*	*	1.7	0.84 - 3.44	222	3	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	Falls with injury	=> 49 years	OR	*	*	1.57	0.38 - 6.41	82	2	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients

Lonergan_2009	Dementia	Skin problem	=> 49 years	OR	*	*	1.27	0.45 - 3.58	227	2	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	Infection	=> 49 years	OR	*	*	1.2	0.7 - 2.45	380	3	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Lonergan_2009	Dementia	Thrombocytopenia	=> 49 years	OR	*	*	7.91	1.92 - 32.57	186	2	*	*	*	480-1000 mg/d	3-6 weeks	Inpatients and outpatients
Macritchie_2003	Bipolar Disorder	Constipation	18-75 years	*	RR	*	0.95	0.37 - 2.45	185	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Diarrhoea	18-75 years	*	RR	*	0.65	0.3 - 1.4	185	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Pain	18-75 years	*	RR	*	0.89	0.47 - 1.68	185	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Sedation	18-75 years	*	RR	*	1.58	0.81 - 3.08	321	3	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Asthenia	18-75 years	*	RR	*	1.55	0.72 - 3.34	279	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Dizziness	18-75 years	*	RR	*	3.17	1.13 - 8.88	279	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Nausea	18-75 years	*	RR	*	1.45	0.82 - 2.56	323	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Vomiting	18-75 years	*	RR	*	2.37	0.85 - 6.61	185	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
Macritchie_2003	Bipolar Disorder	Headache	18-75 years	*	RR	*	0.67	0.38 - 1.17	145	2	*	*	*	750-1040 mg/d	6 days - 12 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Sedation	=<18 years	*	RR	*	1.19	0.9 - 1.56	*	2	*	*	*	20-375 mg/d	6-8 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Weight gain	=<18 years	OR	*	*	1.69	0.65 - 4.43	*	2	*	*	*	20-375 mg/d	6-8 weeks	Unclear
McQuire_2015	Autism Spectrum Disorder or Intellectual Disability	Dysarthria	=<18 years	*	*	*	*	*	189	7	0.50%	*	*	20-375 mg/d	6-8 weeks	Unclear
Schwarz_2008	Schizophrenia or Schizoaffective Disorder	Sedation	28-45 years	*	RR	*	1.52	1.04 - 2.22	296	2	*	*	*	300-1500 mg/d	21 days - 12 weeks	Unclear
Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Diarrhoea	22-57 years	*	RR	*	1.6	0.68 - 3.77	70	3	19%	11.90%	*	250-2500 mg/d	6-8 weeks	Outpatients
Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Dizziness	22-57 years	*	RR	*	0.84	0.19 - 3.75	66	2	11.40%	16.10%	*	250-2500 mg/d	6-8 weeks	Outpatients

Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Dry mouth	22-57 years	*	RR	*	1.56	0.4 - 6.09	72	2	14.30%	8.10%	*	250-2500 mg/d	6-8 weeks	Outpatients
Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Fatigue or myalgia/weakness	22-57 years	*	RR	*	1.48	0.61 - 3.57	117	3	1.70%	11.90%	*	250-2500 mg/d	6-8 weeks	Outpatients
Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Headache	22-57 years	*	RR	*	1.48	0.25 - 8.92	63	2	18.80%	13.20%	*	250-2500 mg/d	6-8 weeks	Outpatients
Smith_2010	Bipolar I or II or NOS with or without rapid cycling	Nausea	22-57 years	*	RR	*	2.01	0.98 - 4.11	117	3	13.10%	15.30%	*	250-2500 mg/d	6-8 weeks	Outpatients
ANXIOLYTICS																
BUSPIRONE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Chessick_2006	Generalised Anxiety Disorder	Drowsiness	=>18 years	*	RR	*	1.44	0.84 - 2.49	481	2	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
Chessick_2006	Generalised Anxiety Disorder	Dizziness	=>18 years	*	RR	*	3.18	1.82 - 5.56	635	3	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
Chessick_2006	Generalised Anxiety Disorder	Dry mouth	=>18 years	*	RR	*	1.55	0.79 - 3.05	437	3	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
Chessick_2006	Generalised Anxiety Disorder	Nausea	=>18 years	*	RR	*	2.16	1.14 - 4.1	429	3	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
Chessick_2006	Generalised Anxiety Disorder	Headache	=>18 years	*	RR	*	1.48	0.36 - 6.02	416	2	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
Chessick_2006	Generalised Anxiety Disorder	Somnolence	=>18 years	*	RR	*	2.15	0.97 - 4.79	183	2	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or

																the community
Chessick_2006	Generalised Anxiety Disorder	Tinnitus	=>18 years	*	RR	*	1.65	0.64 - 4.22	183	2	*	*	*	5-60 mg/d	4-14 weeks	Outpatients from psychiatric clinics or the community
HYDROXYZINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Guaiana_2010	Generalised Anxiety Disorder	Agitation/anxiety/ nervousness/ tension	18-65 years	OR	*	*	1.43	0.36 - 5.76	203	2	*	*	*	>=25 mg/d	<=12 weeks	Psychiatric inpatients, psychiatric outpatients and primary care
Guaiana_2010	Generalised Anxiety Disorder	Dizziness	18-65 years	OR	*	*	1.15	0.06 - 24.03	242	2	*	*	*	>=25 mg/d	<=12 weeks	Inpatients, outpatients and primary care
Guaiana_2010	Generalised Anxiety Disorder	Dry mouth	18-65 years	OR	*	*	1.07	0.41 - 2.82	203	2	*	*	*	>=25 mg/d	<=12 weeks	Inpatients, outpatients and primary care
Guaiana_2010	Generalised Anxiety Disorder	Insomnia	18-65 years	OR	*	*	1.09	0.32 - 3.73	203	2	*	*	*	>=25 mg/d	<=12 weeks	Inpatients, outpatients and primary care
Guaiana_2010	Generalised Anxiety Disorder	Sleepiness/ drowsiness/ somnolence	18-65 years	OR	*	*	2.15	0.76 - 6.07	584	4	*	*	*	>=25 mg/d	<=12 weeks	Inpatients, outpatients and primary care
STIMULANTS																
AMPHETAMINE SALTS																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Punja_2016	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	*	6.42	1.56 - 26.52	1124	5	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Insomnia/trouble sleeping	6-17 years	*	RR	*	3.34	1.25 - 8.96	1280	5	*	*	*	10-70 mg/d	14-63 days	Unclear

Punja_2016	Attention Deficit Hyperactivity Disorder	Abdominal pain	6-17 years	*	RR	*	1.69	1.17 - 2.45	1318	6	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Headaches	6-17 years	*	RR	*	0.85	0.64 - 1.14	918	3	*	*	*	10-70 mg/d	14-63 days	Unclear
LISDEXAMFETAMINE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Citrome_2015	Binge Eating Disorder	Dry mouth	18-55 years	*	RR	*	4.94	3.77 - 6.24	1004	3	36.40%	7.40%	4 (3-5) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Decreased appetite	18-55 years	*	RR	*	4.12	2.38 - 6.84	1004	3	12.30%	3%	11 (8-17) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Insomnia	18-55 years	*	RR	*	2.88	1.85 - 4.35	1004	3	13.90%	4.80%	11 (8-18) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Headache	18-55 years	*	RR	*	1.59	1.11 - 2.22	1004	3	14.20%	9%	19 (11-75) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Constipation	18-55 years	*	RR	*	4.47	1.93 - 9.84	1004	3	6.20%	1.40%	21 (15-40) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Feeling jittery	18-55 years	*	RR	*	11.42	2.37 - 40.61	1004	3	5.30%	0.50%	21 (15-35) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Nausea	18-55 years	*	RR	*	1.63	1.00 - 2.60	1004	3	8.30%	5.10%	32 (16-696) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Irritability	18-55 years	*	RR	*	1.20	0.72 - 1.96	1004	3	6.30%	5.30%	97 (ns) NNH	20-70 mg/d	11-104 weeks	Unclear
Citrome_2015	Binge Eating Disorder	Fatigue	18-55 years	*	RR	*	1.13	0.66 - 1.91	1004	3	5.40%	4.80%	162 (ns) NNH	20-70 mg/d	11-104 weeks	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	*	9.83	5.08 - 19.02	1081	4	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Insomnia/trouble sleeping	6-17 years	*	RR	*	5.91	2.84 - 12.29	1081	4	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Abdominal pain	6-17 years	*	RR	*	1.29	0.76 - 2.19	769	3	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Nausea/vomiting	6-17 years	*	RR	*	1.48	0.61 - 3.61	927	4	*	*	*	10-70 mg/d	14-63 days	Unclear
Punja_2016	Attention Deficit Hyperactivity Disorder	Headaches	6-17 years	*	RR	*	1.07	0.73 - 1.57	1077	5	*	*	*	10-70 mg/d	14-63 days	Unclear

METHYLPHENIDATE																
Author & Year	**Diagnosis**	**Adverse Events**	**Age**	**OR**	**RR**	**Other**	**Effect**	**95% CI**	**N**	**k**	**Drug %**	**Placebo %**	**NNH/NNT**	**Dose**	**Duration**	**Setting**
Schacter_2001	Attention Deficit Disorder	Decreased appetite	=<18 years	*	RR	*	3.09	2.47 - 3.73	675	10	44.80%	14.40%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Insomnia	=<18 years	*	RR	*	1.55	1.30 - 1.81	663	9	47.70%	30.70%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Headache	=<18 years	*	RR	*	1.50	1.02 - 2.14	581	8	18.40%	12.50%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Stomach ache	=<18 years	*	RR	*	1.60	0.99 - 2.42	290	7	24%	14.90%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Drowsiness	=<18 years	*	RR	*	1.67	0.94 - 2.72	201	4	24.30%	14.50%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Anxiety	=<18 years	*	RR	*	0.81	0.61 - 1.03	482	7	31.10%	38.40%	*	Unclear	Unclear	Unclear
Schacter_2001	Attention Deficit Disorder	Dizziness	=<18 years	*	RR	*	3.49	1.19 - 9.31	383	4	7.30%	2.20%	*	Unclear	Unclear	Unclear
Storebo_2015	Attention Deficit Hyperactivity Disorder	Psychosis	6-17 years	*	RR	*	1.78	0.19 - 16.96	712	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Syncope	6-17 years	*	RR	*	2.92	0.07 - 4.11	1246	8	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Affective nervous system AE	6-17 years	*	RR	*	2.39	0.48 - 11.96	390	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Aggression	6-17 years	*	RR	*	1.16	0.17 - 7.8	417	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Confusion	6-17 years	*	RR	*	1.01	0.22 - 4.73	548	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Dizziness	6-17 years	*	RR	*	2.5	0.7 - 8.99	683	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients

Storebo_2015	Attention Deficit Hyperactivity Disorder	Drowsiness	6-17 years	*	RR	*	1.27	0.82 - 1.98	811	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Fatigue	6-17 years	*	RR	*	0.76	0.36 - 1.63	858	7	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Headache	6-17 years	*	RR	*	1.22	0.9 - 1.64	2724	17	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Insomnia	6-17 years	*	RR	*	1.31	0.35 - 4.93	349	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Irritability	6-17 years	*	RR	*	1.11	0.77 - 1.6	1721	11	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Nervousness	6-17 years	*	RR	*	2.52	0.82 - 7.76	362	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Sad/Tearful/ Depressed	6-17 years	*	RR	*	1.41	0.86 - 2.29	707	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Somnolence	6-17 years	*	RR	*	0.59	0.11 - 3.11	173	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Trouble sleeping or sleep problems	6-17 years	*	RR	*	1.6	1.15 - 2.23	2416	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Tics or nervous movements	6-17 years	*	RR	*	0.85	0.26 - 2.79	1231	8	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Worried or anxious	6-17 years	*	RR	*	1.37	0.84 - 2.25	596	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Decreased appetite	6-17 years	*	RR	*	3.66	2.56 - 5.23	2962	16	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Decreased weight	6-17 years	*	RR	*	3.89	1.43 - 10.59	859	6	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Diarrhoea	6-17 years	*	RR	*	1.07	0.41 - 2.74	857	5	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Dyspepsia	6-17 years	*	RR	*	1.8	0.71 - 4.54	159	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients

Storebo_2015	Attention Deficit Hyperactivity Disorder	Nausea	6-17 years	*	RR	*	1.3	0.85 - 1.99	1995	11	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Stomachache	6-17 years	*	RR	*	1.3	1.0 - 1.69	2341	13	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Vomiting	6-17 years	*	RR	*	1.17	0.76 - 1.79	1916	11	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Prolonged QT-interval	6-17 years	*	RR	*	0.81	0.13 - 5	466	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Cough	6-17 years	*	RR	*	0.95	0.41 - 2.18	996	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Nasal congestion	6-17 years	*	RR	*	1.19	0.59 - 2.41	479	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Gastroenteritis	6-17 years	*	RR	*	4.63	0.99 - 21.72	435	4	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Influenza	6-17 years	*	RR	*	0.65	0.2 - 2.1	624	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Nasopharyngitis	6-17 years	*	RR	*	1.15	0.7 - 1.87	979	5	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Pharyngitis	6-17 years	*	RR	*	2.43	0.49 - 12.05	293	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Pyrexia	6-17 years	*	RR	*	1.02	0.01 - 87.72	400	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Upper respiratory tract infection (NOS)	6-17 years	*	RR	*	1.19	0.68 - 2.06	917	5	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Viral infection	6-17 years	*	RR	*	0.7	0.23 - 2.15	614	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Weight gain	6-17 years	OR	*	*	0.13	0.06 - 0.28	805	5	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Diastolic blood pressure	6-17 years		RR	*	0.94	-0.12 - 2.01	1067	8	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients

Storebo_2015	Attention Deficit Hyperactivity Disorder	Systolic blood pressure	6-17 years		RR	*	-0.05	-1.25 - 0.16	1067	8	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Pulse or heart rate	6-17 years		RR	*	3.41	0.87 - 5.94	1240	8	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Accidental injury	6-17 years		RR	*	0.99	0.48 - 2.07	656	3	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients
Storebo_2015	Attention Deficit Hyperactivity Disorder	Skin Disorder (rash)	6-17 years		RR	*	0.52	0.01 - 26.44	200	2	*	*	*	5-70 mg/d	1 week - 6 months	Inpatients and outpatients

Appendix E – Secondary Results

E.1 Main Results of Ten Most Reported Medications

E.1.1 Amitriptyline

The only antidepressant with more than 10 outcomes reported was amitriptyline. There were other antidepressants, such as paroxetine (7 studies) and fluoxetine (6 studies), that were reported in many reviews. Although only one review reported data on amitriptyline, it calculated effect sizes for 23 unique adverse events.[20] The review performed subgroup analyses and found no difference between industry-sponsored and non-industry sponsored trials, inpatient versus outpatient trials, or two-arm versus three-arm trials. The most common adverse events reported in descending order of prevalence were 'Other,' neurological, gastrointestinal and constitutional.

Other

The results documented amitriptyline's known adverse events including nasal congestion, urination problems, vision problems, tachycardia, sexual dysfunction among others. The data indicated a significant association between amitriptyline and sexual dysfunction (OR 16.6 95% CI 4.5 to 60.6), increased appetite (OR 4.0 95% CI 2.0 to 8.2), tachycardia (OR 2.4 95% CI 1.5 to 3.9), urinary problems (OR 8.7 95% CI 2.0 to 39.1), low blood pressure, blurred vision or ambloyopia (OR 13.5 95% CI 9.4 to 19.4) and anticholinergic adverse events (OR 6.3 95% CI 3.4 to 11.7). No significant differences were found in dermal rash (N=140, k=2), gastralgia (N=172, k=2) or headaches (N=1173, k=9). The data on mortality were so seldom reported that it was deemed not estimable.

Neurology

There is evidence that amitriptyline significantly increased individuals' chances of experiencing sedation, sleepiness, somnolence or drowsiness (OR 5.5 95% CI 3.69 to 8.2), tremor (OR 5.7

95% CI 3.2 to 10.1), dizziness or syncope (OR 2.9 95% CI 2.1 to 4.1). No significant differences were found in agitation (N=339, k=2), confusion (N=228, k=4) or nervousness (N=449, k=4).

Gastrointestinal

Dyspepsia (OR 6.8 95% CI 2.5 to 18.5), dry mouth (OR 13.5 95% CI 9.4 to 19.4) and constipation (OR 3.4 95% CI 2.4 to 4.9) were experienced more often by the amitriptyline group than placebo. However, no significant differences were reported in nausea (N=749, k=6) or diarrhoea (N=339, k=2) although the review reported moderate heterogeneity between studies (I^2=47%) for nausea.

Constitutional

Sweating did not occur more frequently in the amitriptyline group than placebo (N=339, k=2), nor did insomnia (N=923, k=5).

E.1.2 Aripiprazole

Aripiprazole and risperidone were the two antipsychotic drugs that were reported the most frequently. Specifically, 18 studies provided data on these medications.[4,6,8,21-34] A total of 61 outcomes was reported for aripiprazole. Data were often insufficient for the included systematic reviews to perform subgroup analysis. One review initially planned to assess whether individuals with psychotic mania had different responses to aripiprazole than those with non-psychotic mania but could not due to a lack of data.[22] The most commonly reported adverse events for aripiprazole, in descending order of prevalence, were neurological, constitutional, 'Other' and gastrointestinal.

Neurology

One review provided evidence that aripiprazole increased the chances of an individual with either autism spectrum disorder or pervasive developmental disorder of experiencing sedation (RR 4.3 95% CI 1.6 to 11.6). Other reviews that analysed individuals with either pervasive

developmental disorder or intellectual disability (RR 2.4 95% CI 1.1 to 5.5), dementia (OR 2.6 95% CI 1.6 to 4.5) or bipolar disorder (RR 2.6 95% CI 1.7 to 3.9) concluded that aripiprazole was associated with sedation. However, the data extracted from reviews that analysed individuals with either schizophrenia, schizoaffective disorder or acute relapse of schizophrenia (N=1,107, k=4) or those with either autism spectrum disorder or intellectual disability (k=2) indicated no significant difference in sedation. Parkinsonism (N=1,233, k=4), tremor (N=1,105, k=3) and mania (N=727, k=2) demonstrated no association to amitriptyline.

Somnolence did not occur more frequently in the aripiprazole group than placebo in reviews analysing individuals with bipolar or schizoaffective disorder (N=970, k=3) or bipolar depression (N=727, k=2). However, in other reviews aripiprazole was linked to somnolence where individuals had a diagnosis of either attention deficit hyperactivity disorder, schizophrenia, behavioral disorder, pervasive developmental disorder or intellectual disability (OR 6.1 95% CI 2.8 to 12.2), pervasive developmental disorder or intellectual disability (OR 25.8 95% CI 1.3 to 112.3) or dementia (OR 3.5 95% CI 1.6 to 7.5).

Tremor (N=313, k=2) occurred more frequently in the aripiprazole group than placebo. Extrapyramidal symptoms were experienced by participants more often in the aripiprazole group when they had bipolar disorder or schizoaffective disorder (RR 2.2 95% CI 1.5 to 3.4), schizophrenia spectrum disorders (RR 1.1 95% CI 0.8 to 1.4) but not when they had dementia as a diagnosis (N=1,080, k=4). One review whose participants either attention deficit hyperactivity disorder, schizophrenia behavioral disorder, pervasive developmental disorder or intellectual disability indicated a significant association between aripiprazole and extrapyramidal symptoms. Other reviews involving participants with either pervasive developmental disorder or intellectual

disability (N=556), another with either autism spectrum disorder, Asperger's disorder or pervasive developmental disorder (N=313, k=2) or schizophrenia (OR 1.1 95% CI 0.6 to 2.0) found no significant differences in extrapyramidal symptoms. The wide inclusion of diagnoses makes it challenging to generate any inferences or hypotheses regarding extrapyramidal symptoms and aripiprazole.

Akathisia occurred more frequently in the aripiprazole group in participants with acute mania, bipolar disorder or schizoaffective disorder (RR 3.2 95% CI 2.3 to 4.4; RR 25.6 95% CI 3.4 to 9.3; RR 3.7 95% CI 2.5 to 5.4; OR 4.8 95% CI 2.3 to 10.1; OR 1.9 95% CI 1.2 to 2.8). Additionally, one review reported a significant association to akathisia in adults with schizophrenia (RR 1.6 95% CI 1.1 to 2.3) while a second review reported no significant difference in participants with the same diagnosis but in an unspecified age group (OR 1.7 95% CI 0.9 to 3.0).

One review found no significant difference in the use of antiparkinson medication when their study population included individuals with either schizophrenia, schizoaffective disorder or acute relapse of schizophrenia (N=1,310, k=6). Another review that included individuals with bipolar or schizoaffective disorder (RR 3.3 95% CI 1.8 to 5.9) and a second review that included individuals with schizophrenia (RR 1.5 95% CI 1.0 to 2.2) indicated that aripiprazole was linked to the need to use anticholinergic medication.

Constitutional

Fatigue was linked to aripiprazole (RR 1.9 95% CI 1.2 to 3.2). One review that focused on individuals with pervasive developmental disorder or intellectual disability found that significant weight gain occurred more frequently in the aripiprazole group than placebo (OR 6.3 95% CI 1.6

to 17.1). However, weight gain occurred just as often in the aripiprazole group and control group in other reviews where participants had either bipolar or schizoaffective disorder (N=1,596, k=5), autism spectrum disorder or pervasive developmental disorder (N=308, k=2), bipolar depression (N=727, k=2) autism spectrum disorder or intellectual disability, schizophrenia, bipolar disorder (N=1,621, k=6), or acute mania (OR 1.3 95% CI 0.95 to 1.8). No significant differences were found in insomnia.

Other

Pain extremity (RR 2.0 95% CI 1.1 to 3.8) occurred more frequently in the aripiprazole group than placebo. However, no significant differences were found in cerebrovascular accidents (N=593, k=3), urinary tract symptoms (N=951, k=3), activation symptoms (N=1,489, k=5), injection site pain, injuries or falls, stroke or drooling (N=313, k=2). Additionally, Jensen reported no significant association between a change in the corrected QT and aripiprazole (N=571, k=8).[5]

Gastrointestinal

Nausea (RR 1.5 95% CI 1.2 to 1.9) occurred more often in the aripiprazole group than placebo however gastroenteric disturbance did not (N=1,488, k=5).

One forest plot was generated for most of the 31 medications and a distinction was made whether the outcome was measured as either an RR or OR. Occasionally, there were enough ORs and RRs for a single medication to allow for separate forest plots to be created comprising exclusively of ORs or RRs, which then increased the clarity and comparability of the data within each plot. I made two forest plots for aripiprazole, olanzapine, quetiapine and valproate.

E.1.3 Risperidone

As previously mentioned, an equally high number of reviews reported on risperidone and its 50 outcomes.[3,5,6,8,24,26-29,32-33,35-39,] The AMSTAR appraisal of the risperidone reviews yielded scores ranging from 5/11 to 11/11, which indicated medium to high quality reviews. The most commonly reported adverse events for risperidone, in descending order of prevalence, were neurological, 'Other', constitutional and gastrointestinal.

Neurology

Somnolence was associated with risperidone in individuals with Alzheimer's disease (OR 2.4 95% CI 1.8 to 3.2), pervasive developmental disorder or intellectual disability (OR 9.6 95% CI 3.5 to 22.8), schizophrenia or bipolar disorder (OR 7.3 95% CI 4.6 to 11.2), dementia with aggression (OR 2.4 95% CI 1.8 to 3.3) and dementia alone (OR 3.6 95% CI 2.7 to 4.7; OR 3.0 95% CI 2.0 to 4.7). However, in another review comprised of individuals with dementia (either dementia of the Alzheimer's type, vascular dementia or mixed dementia) and another comprised of individuals with schizophrenia (N=665, k=4) somnolence showed no association to the drug. The evidence suggested that risperidone caused sedation in individuals with autism spectrum disorder or intellectual disability (RR 0.5 95% CI 0.4 to 0.7) and dementia (OR 2.3 95% CI 1.8 to 3.1) but not in individuals with schizophrenia (N=665, k=4).

The results for extrapyramidal symptoms were varied. Extrapyramidal symptoms were seen more frequently in the risperidone group than placebo when individuals had a diagnosis of dementia or Alzheimer's (OR 1.9 95% CI 1.2 to 3.0), Alzheimer's alone (OR 1.8 95% CI 1.0 to 3.2), dementia with aggression (OR 1.8 95% CI 1.4 to 2.4), pervasive developmental disorder or intellectual disability (OR 3.7 95% CI 1.7 to 7.2) or schizophrenia or bipolar disorder (OR 3.7 95% CI 2.2 to 6.0). However, Leucht found no significant differences in extrapyramidal

symptoms (N=642, k=5) in his review.[27] Gao reported the incidence of extrapyramidal symptoms as well as the use of anticholinergic medications more often in the treatment group than placebo when the patient population had a diagnosis of bipolar disorder (OR 4.2 95% CI 2.6 to 7.1; OR 4.4 95% CI 2.7 to 7.3) but not schizophrenia (N=376, k=3; N=174, k=2).[26] No significant differences were found in agitation (N=1,413) or tremor (N=810, k=2).

Other

The evidence suggested that risperidone associated with stroke (OR 4.5 95% CI 1.8 to 11.7), cerebrovascular events (OR 3.6 95% CI 1.7 to 7.6; OR 3.1 95% CI 1.3 to 8.2) and cardiovascular event (OR 2.1 95% CI 1.4 to 3.2). Interestingly, the results also indicated a significant association between risperidone and abnormal gait in individuals with a diagnosis of Alzheimer's disease (OR 5.3 95% CI 2.2 to 12.6) but not dementia (k=3). Similarly, peripheral edema occurred more frequently in the risperidone group when individuals had a diagnosis of Alzheimer's (OR 2.8 95% CI 1.5 to 5.0) and occurred moderately less frequently when the individuals had a diagnosis of dementia (OR 4.5 95% CI 1.8 to 11.7). The drug was linked to urinary tract symptoms in individuals with dementia (RR 0.5 95% CI 0.4 to 0.7; OR 2.3 95% CI 1.6 to 3.3) but not in individuals with Alzheimer's disease (N=648, k=2). No significant differences were found in death (N=1,954, k=5; N=1,954, k=5), injury (N=1,725, k=4; N=1,074, k=3), falls (N=1,411, k=4), upper respiratory tract infection (N=784, k=2) or changes in the corrected QT interval (N=573, k=12).

Constitutional

Weight gain occurred more often in the risperidone group than placebo when the study population had a diagnosis of pervasive developmental disorder or intellectual disability (OR 7.8 95% CI 1.9 to 25.2), autism spectrum disorder or intellectual disability (95% CI 2.8 to 6.9) or

schizophrenia or bipolar disorder (OR 6.0 95% CI 3.0 to 11.4). However, no significant difference was found in weight gain when the population had a diagnosis of mania (N=824, k=3). Fever was not linked to the drug (N=938, k=3).

Gastrointestinal

No gastrointestinal adverse events were reported for risperidone.

E.1.4 Olanzapine

There were 17 reviews included for olanzapine and a total of 69 outcomes reported.[5-6,24,27-28,34,36-37,40-46,] The most commonly reported adverse events in descending order of prevalence were neurological, 'Other', constitutional and gastrointestinal. Certain reviews mentioned their included trials only reported adverse events if the incidence was either statistically significant or had a frequency of 10% or greater.

Neurology

The evidence indicated a significant association between olanzapine and benzodiazepine use (RR 0.5 95% CI 0.3 to 1.0), cerebrovascular accidents (OR 1.5 95% CI 0.3 to 7.4), dizziness (RR 3.0 95% CI 1.4 to 6.4) and sedation (RR 8.3 95% CI 1.2 to 59.6; N=1,218, k=5, OR 4.6 95% CI 2.9 to 7.6). In fact, somnolence was experienced more frequently by treatment groups that had a diagnosis of dementia (OR 3.6 95% CI 1.8 to 7.1), borderline personality disorder (RR 3.0 95% CI 1.8 to 5.0), Alzheimer's disease (OR 3.7 95% CI 1.9 to 7.3) and either schizophrenia or bipolar disorder (OR 8.5 95% CI 4.0 to 16.6) in comparison to placebo.

Extrapyramidal symptoms occurred more often in the olanzapine group than placebo when the participants' diagnosis was schizophrenia or bipolar disorder (OR 6.4 95% CI 2.4 to 13.8). The need to use anticholinergic medication within 24 hours of taking olanzapine was not linked to the drug when participants were acutely disturbed individuals with suspected serious mental illness

(N=570, k=3). Interestingly, a prolongation in the QT interval occurred less frequently in olanzapine group compared to placebo (RR 0.3 95% CI 0.2 to 0.7).

There were many reported outcomes that indicated no association with olanzapine. For instance, no significant differences were found in nervousness (450, k=2; N=254, k=2), anxiety (N=631, k=2; N=254, k=2), agitation (N=838, k=3; N=418, k=2; N=254, k=2), hostility (N=418, k=2; N=254, k=2), requiring anticholinergic medication (N=570, k=3; N=418, k=2; N=481, k=3), akathisia (N=1,038, k=7; N=504, k=5; N=251, k=2), extrapyramidal symptoms (N=1,002, k=7; N=627, k=6; N=185, k=2; N=246, k=2), dyskinesia (N=286, k=3), the Agitation and Calmness Score (N=757, k=6), depression (N=249, k=2), or personality disorder (N=254, k=2).

Other

Olanzapine was linked to abnormal gait (OR 4.8 95% CI 1.8 to 13.6; k=3, OR 3.8 95% CI 1.6 to 9.0) and urinary infection (OR 6.9, 95% CI 1.3 to 36.0). No significant differences were found in peripheral edema (N=450, k=2), injury (N=450, k=2), falls (N=685, k=2), stroke (k=2) or changes in the corrected QT interval (N=148, k=2).

Constitutional

A significant association was reported between olanzapine and fever (OR 4.6 95% CI 1.0 to 19.8), dry mouth (RR 3.1 95% CI 1.5 to 6.2; RR 2.2 95% CI 1.1 to 4.7) and asthenia (RR 2.4 95% CI 1.1 to 5.3). The link between significant weight gain and olanzapine is clearly well documented (OR 4.7 95% CI 1.1 to 20.4; OR 15.1 95% CI 6.6 to 31.1; OR 32.0 95% CI 1.7 to 98.4; OR 3.9 95% CI 2.4 to 6.3). No significant differences were found in fatigue (N=615, k=2) or insomnia (N=615, k=2).

Gastrointestinal

Olanzapine was linked to individuals having an increased appetite (RR 2.8 95% CI 1.8 to 4.3). Nausea (N=615, k=2), anorexia (N=838, k=3) and constipation (N=254, k=2) indicated no significant association to the drug.

E.1.5 Quetiapine

There were 13 reviews included for quetiapine and 56 outcomes reported.[3,8,24-25,27-28,32,34,39,47-51] The most common adverse events reported in descending order of prevalence were neurological, 'Other', constitutional and gastrointestinal. Additionally, the risks that were present in all of the systematic reviews on quetiapine are documented in my AMSTAR appraisal, which can be found in Appendix C.

Neurology

There was a large amount of evidence documenting the association between quetiapine and somnolence (OR 5.4 95% CI 2.9 to 9.2; RR 3.9 95% CI 2.8 to 5.5; RR 3.7 95% CI 2.9 to 4.9; OR 5.9 95% CI 2.4 to 14.5) as well as sedation (RR 4.5 95% CI 2.6 to 4.7; OR 4.5 95% CI 2.7 to 7.6; OR 5.8 95% CI 2.3 to 14.3; RR 2.0 95% CI 1.2 to 3.5; RR 2.0 95% CI 1.2 to 3.5; RR 3.3 95% CI 2.7 to 4.1). The drug also increased individuals' chances of experiencing dizziness (RR 2.2 95% CI 1.1 to 4.4; RR 2.2 95% CI 1.7 to 2.7). Interestingly, quetiapine was linked to extrapyramidal symptoms in people with generalised anxiety disorder (OR 1.8 95% CI 1.1 to 2.9) but not in those with schizophrenia or bipolar disorder (N=1,250), major depression (N=1,342, k=3), dementia (N=609, k=3) or Alzheimer's with agitation or psychosis (N=582, k=2). Also, extrapyramidal symptoms were experienced more often in the quetiapine group when individuals had acute bipolar depression (RR 2.8 95% CI 2.1 to 3.6) but not in other reviews when the diagnosis of the participants was general bipolar depression (N=1,743, k=5). Individuals taking

the drug reported a lower score on the Abnormal Involuntary Movements Scale compared to placebo (RR 0.7 95% CI 0.5 to 0.9). No associations of significance were indicated between quetiapine and mania (N=1,743, k=5; k=6), parkinsonism (N=595, k=2), the use of antiparkinson medication (N=1,769; N=509, k=3), the Barnes Akathisia Scale (N=1,616; k=7) or the Simpson Angus Scale (N=1,465, k=7).

Other

The evidence suggested that quetiapine increased individuals' chances of urinary tract symptoms. This was true when participants had dementia (OR 2.4 95% CI 1.2 to 5.2) but not when they had Alzheimer's disease (N=582, k=2). Sleepiness (RR 2.0 95% CI 1.3 to 3.0) and headaches (RR 0.7 95% CI 0.5 to 0.9) were linked to quetiapine However, injuries, abnormal gait (k=3), edema (k=2), urinary infection, stroke (k=4), low blood pressure (postural) (N=418, k=2), urinary tract infection (N=582, k=2), mortality (N=637, k=3), cardiovascular events (N=609, k=3) and cerebrovascular accidents (N=426, k=6) were not.

Constitutional

Quetiapine increased individuals' chances of weight gain and was extensively documented in my results (OR 6.2 95% CI 2.6 to 13.6; RR 2.4 95% CI 1.2 to 4.6; OR 2.4 95% CI 1.2 to 4.7; OR 3.0 95% CI 2.1 to 4.4; OR 2.1 95% CI 1.1 to 4.0; RR 2.3 95% CI 1.3 to 4.0). It was also linked to dry mouth (RR 3.7 95% CI 3.0 to 4.4) but not fatigue (N=1,341, k=4).

Gastrointestinal

Increased appetite was associated with the drug (RR 2.8 95% CI 1.6 to 5.0). Constipation occurred more frequently in the quetiapine group than placebo for people with acute bipolar depression (RR 2.1 95% CI 1.5 to 2.8) but not in those with schizophrenia or schizoaffective disorder (N=704, k=3). No significant differences were found in diarrhoea (k=2) or nausea (k=5).

E.1.6 Haloperidol

There were 8 reviews included for haloperidol and 39 outcomes reported.[26-27,36,52-56] The most commonly reported adverse events, in descending order of prevalence, were neurological, 'Other', constitutional and gastrointestinal.

Neurology

The evidence suggested that haloperidol was significantly linked to dystonia (RR 11.5 95% CI 3.2 to 40.9), akathisia (RR 3.7 95% CI 2.2 to 6.0; OR 2.9 95% CI 1.7 to 4.9), parkinsonism (RR 5.5 95% CI 2.7 to 11.2), the use of antiparkinson medication (RR 3.2 95% CI 2.2 to 4.7; RR 2.3 95% CI 1.9 to 2.9) and tremor (RR 3.9 95% CI 2.0 to 7.9; RR 3.3 95% CI 1.9 to 5.8). Although haloperidol is not well-documented as being a sedating antipsychotic, the drug was linked to sedation in our analysis (RR 2.3 95% CI 1.1 to 4.7; RR 3.4 95% CI 1.4 to 8.0).[52]

Interestingly, in one review extrapyramidal symptoms occurred less frequently in the haloperidol group than placebo when the participants had psychosis-induced aggression (RR 0.1 95% CI 0.0 to 0.4), however in a second review they occurred more frequently in the context of a study population with the same diagnostic inclusion criteria (RR 6.8 95% CI 2.2 to 21.1). Additionally, extrapyramidal symptoms generally were experienced more frequently when the study population had a diagnosis of Alzheimer's disease (OR 2.3 95% CI 1.3 to 4.4), schizophrenia or bipolar disorder (RR 4.2 95% CI 2.9 to 6.0; OR 2.0 95% CI 1.6 to 2.6; OR 3.7 95% CI 2.1 to 6.4; OR 7.8 95% CI 4.5 to 13.4). Somnolence was significantly linked to haloperidol in adults with schizophrenia (OR 2.3 95% CI 1.5 to 3.4) but not in individuals with either bipolar disorder or schizoaffective disorder (N=484, k=2), or those with psychosis-induced aggression or agitation (N=615, k=4).

Tardive dyskinesia (N=157, k=2), agitation (N=362, k=2; N=395, k=2), anxiety (N=362, k=2), and dizziness (N=245, k=3; N=125, k=2) were not associated with haloperidol. One review indicated the challenge of quantifying tardive dyskinesia with confidence due to the absence of long-term data.[52]

Other

The evidence associated haloperidol with blurred vision (RR 4.0 95% CI 1.2 to 12.9), rigidity (RR 5.0 95% CI 2.7 to 9.0), sleepiness (RR 3.1 95% CI 1.5 to 6.3) and drowsiness (OR 4.2 95% CI 1.8 to 9.9). No significant associations were found between haloperidol and drooling (N=207, k=3), headaches (N=593, k=4), oculogyric crises (N=83, k=2), perspiration (N=93, k=2), mortality (K=1,799, k=11), hypotension (N=125, k=2) or headaches (N=395, k=2).

Constitutional

Haloperidol was significantly linked to weight gain (RR 4.9 95% CI 1.4 to 17.0) but neither associated with insomnia (N=629, k=4) nor weight loss (N=385, k=3).

Gastrointestinal

No significant differences were found in nausea (N=395, k=2; N=231, k=2).

E.1.7 Chlorpromazine

One review on chlorpromazine was included and a total of 24 adverse events were reported.[57] The most commonly reported types of adverse events, in descending order of prevalence, were 'Other', neurological, gastrointestinal and constitutional. The included review explored the possible sources of bias in its methodology. Specifically, many of its trials were funded by the pharmaceutical industry and a couple of the trialists were imprisoned for research fraud.[57] Additionally, 47 of its included trials were judged as having a high risk of bias for selective reporting. It is relevant to consider the risks and quality of a review before analysing its results.

Other

Rigidity (RR 2.2 95% CI 1.4 to 3.5), sleepiness (RR 2.8 95% CI 2.3 to 3.5), weakness (RR 3.3 95% CI 1.0 to 10.9), photosensitivity (RR 6.0 95% CI 3.2 to 11.3), eye opacity (RR 3.1 95% CI 1.9 to 5.1) and salivation (RR 3.4 95% CI 1.1 to 10.6) occurred more frequently in the chlorpromazine group than placebo. Blood problems such as agranulocytosis and leukopenia (N=394, k=7), liver problems (N=249, k=4), urinary problems (N=926, k=5), blurred vision (N=962, k=7), menorrhagia (N=46, k=2) and lactation (N=192, k=2) were not associated with the drug.

Neurology

Chlorpromazine was associated with acute movement disorders such as dystonia (RR 3.5 95% CI 1.5 to 8.0), parkinsonism (RR 2.1 95% CI 1.6 to 2.8), tremor (RR 1.7 95% CI 1.0 to 2.7), a lowering of blood pressure with accompanying dizziness (RR 2.4 95% CI 1.7 to 3.3) and a loss of consciousness (RR 3.1 95% CI 1.1 to 9.2). No significant difference was found in akathisia (N=1,164, k=9).

Gastrointestinal

Constipation (RR 2.05 95% CI 1.33 to 3.15) and nausea (RR 2.1 95% CI 1.1 to 3.7) were linked to chlorpromazine.

Constitutional

The drug was linked to dry mouth (RR 4.6 95% CI 2.4 to 8.9) and weight gain (RR 4.9 95% CI 2.3 to 10.4).

E.1.8 Valproate

Seven reviews on valproate were included and 31 adverse events were reported in total.[29,58-63] The most commonly reported types of adverse events were neurological and 'Other', followed by gastrointestinal and constitutional adverse events. The documented adverse events of valproate include but are not limited to tremor, sedation, ataxia, alopecia, lethargy, dizziness,

haematological dysfunction, hepatic failure, polycystic ovaries and teratogenicity (i.e. neural tube defects, congenital heart lesions, oral clefts, craniofacial dysmorphic features).[58]

Neurology

Interestingly, sedation was observed more often in the valproate group than placebo when participants had a diagnosis of dementia (OR 2.5 95% CI 1.4 to 4.5) and schizophrenia or schizoaffective disorder (RR 1.5 95% CI 1.0 to 2.2) but not when individuals had bipolar disorder (N=321, k=3), or autism spectrum disorder or intellectual disability (k=2). Tremor (RR 2.4 95% CI 1.6 to 3.7) was linked to the drug, however, heterogeneity was quite high (I^2 90%).[58]

Other

Valproate was associated with urinary tract infection (OR 3.0 95% CI 1.0 to 8.8), thrombocytopenia (OR 7.9 95% CI 1.9 to 32.6) and alopecia (RR 2.0 95% CI 1.1 to 3.9). Headaches (N=63, k=2), falls with and without injury (N=82, k=2; N=222, k=3), skin problems (N=227, k=2), infection (N=380, k=3) and pain (N=185, k=2) were experienced as frequently by individuals assigned to placebo as individuals in the treatment group.

Gastrointestinal

A significant association was found between valproate and gastrointestinal problems (OR 7.1 95% CI 1.7 to 29.0). No significant differences were found in diarrhoea (N=70, k=3), nausea (N=117, k=3), vomiting (N=185, k=2) or constipation (N=185, k=2).

Constitutional

Valproate associated with asthenia (N=279, k=2, RR 1.6 95% CI 0.7 to 3.3). Interestingly, weight gain occurred more often in the valproate group than placebo when participants had aggression or bipolar disorder (OR=2.4 95% CI 1.1 to 5.3; RR 2.4 95% CI 1.6 to 3.7) but not autism spectrum disorder or intellectual disability (k=2). It was noted that heterogeneity was high in the review on individuals with bipolar disorder, however (I^2=80%).[58] No significant differences were found in fatigue (N=117, k=3) or dry mouth (N=72, k=2).

E.1.9 Lisdexamfetamine

Two reviews on lisdexamfetamine were included and a total of 14 outcomes was reported.[64-65] The most commonly reported types of adverse events, in descending order of prevalence, were gastrointestinal, 'Other', constitutional and neurological. The product label for lisdexamfetamine warns individuals that the drug can increase their chances of experiencing psychotic or manic symptoms and peripheral vasculopathy (i.e. Raynaud's phenomenon) among other adverse events.[64] Additionally, this drug has a well documented level of abuse and dependence similar to other central nervous system stimulants and for this reason the Drug Enforcement Administration has labeled it as a Schedule II medication.

Gastrointestinal

Decreased appetite (RR 9.8 95% CI 5.0 to 19.0; RR 4.1 95% CI 2.4 to 6.9), as well as dry mouth (RR 4.9 95% CI 3.8 to 6.2), constipation (RR 4.5 95% CI 1.9 to 9.8) and nausea (RR 1.6 95% CI 1.0 to 2.6) all associated with lisdexamfetamine. However, no significant associations were found for lisdexamfetamine and nausea or vomiting (N=927, k=4).

Other

Individuals taking the treatment felt jittery more often than placebo (RR 11.4 95% CI 2.4 to 40.6). Interestingly, headaches were linked to lisdexamfetamine when study participants had a diagnosis of binge eating disorder (RR 1.6 95% CI 1.1 to 2.2) but not when they had attention deficit hyperactivity disorder (N=927, k=4).

Constitutional

Insomnia was experienced more frequently by the lisdexamfetamine group than placebo (RR 5.9 95% CI 2.8 to 12.3; RR 2.9 95% CI 1.9 to 4.4). Fatigue was not associated with the drug (N=1,004, k=3).

Neurology

Irritability showed no significant association to methylphenidate (N=1,004, k=3).

E.1.10 Methylphenidate

Two reviews on methylphenidate were included and 44 outcomes were reported in total.[66-67] The most commonly reported types of adverse events, in descending order of prevalence, were 'Other', neurological, gastrointestinal and constitutional. Well-documented adverse events of methylphenidate include headaches, sleep problems, tiredness and decreased appetite. Psychotic symptoms, mood disorders and other serious adverse events were estimated to occur in approximately 3% of the children who take methylphenidate.[67]

Other

Abdominal pain occurred more frequently in the methylphenidate group than placebo (RR 1.3 95% CI 1.0 to 1.7) when the participants had a diagnosis of attention deficit hyperactivity disorder but not attention deficit disorder (N=290, k=7) while headaches occurred more frequently in the treatment group when the study population had a diagnosis of attention deficit disorder (RR 1.5 95% CI 1.0 to 2.1) but not attention deficit hyperactivity disorder (N=2,724, k=17). We found no evidence that linked the drug to skin disorders (N=200, k=2), accidental injury (N=656, k=3), pulse or heart rate change (N=1,240, k=8), diastolic blood pressure change (N=1,067, k=8), systolic blood pressure change (N=1,067, k=8), viral infection (N=614, k=3), upper respiratory tract infection (N=917, k=5), pharyngitis (N=293, k=2), pyrexia (N=400, k=2), nasopharyngitis (979, k=5), influenza (N=624, k=3), nasal congestion (N=479, k=2), cough (N=996, k=4), prolonged QT interval (N=466, k=2) and drowsiness (N=811, k=4; N=201, k=4).

Neurology

Interestingly, dizziness was only linked to methylphenidate when the study population had attention deficit disorder (RR 3.5 95% CI 1.2 to 9.3) and not attention deficit hyperactivity disorder (N=683, k=3). Methylphenidate was not associated with psychosis (N=712, k=4), syncope (N=1,246, k=8), confusion (N=548, k=2), irritability (N=1,721, k=11; N=1,721, k=11),

nervousness (N=362, k=2), depression (N=707, k=4), somnolence (N=173, k=2), anxiety (N=596, k=3; N=482, k=7), aggression (N=417, k=2), affective nervous system adverse events (N=390, k=4), tics or movement disorders (N=1,231, k=8).

Gastrointestinal

Decreased appetite occurred more frequently in the methylphenidate group than placebo (RR 3.7 95% CI 2.6 to 5.2; N=675, k=10, RR 3.1 95% CI 1.5 to 3.7). There is no evidence that methylphenidate increased individuals' chances of experiencing diarrhoea (N=857, k=5), dyspepsia (N=159, k=2), nausea (N=1,995, k=11), vomiting (N=1,916, k=11) or gastroenteritis (N=435, k=4).

Constitutional

Decreased weight was associated with methylphenidate (RR 3.9 95% CI 1.4 to 10.5), as were sleeping problems (RR 1.6 95% CI 1.2 to 2.2). Insomnia (N=349, k=3) and fatigue (N=858, k=7) occurred just as frequently in the placebo as the methylphenidate group when participants had attention deficit hyperactivity disorder. However, insomnia was experienced more frequently by the methylphenidate group when the participants comprised of children and adolescents with attention deficit disorder (RR 1.6 95% CI 1.3 to 1.8).

E.2 Main Results of Remaining Medications

E.2.1 Paroxetine

Included reviews

Seven reviews were included.

1. Intervention

The doses of paroxetine administered were between 10 mg/day and 200 mg/day.

2. AMSTAR score

The AMSTAR quality appraisal indicated that six of the included reviews were high quality and that one was medium quality.

3. Outcomes

The outcomes assessed included the following: somnolence, insomnia, suicidality, headache and the corrected QT interval.

4. Adverse events

Constitutional

There was increased frequency of insomnia in the paroxetine group with major depression (N=4,278, OR 2.8 95% CI 2.4 to 3.4) as well as in the paroxetine group with obsessive compulsive disorder (N=648, k=2, RR 1.7 95% CI 1.2 to 2.5) as compared to placebo.

Gastrointestinal

None.

Neurology

The data indicated that paroxetine was significantly linked to somnolence in adults (N=6,181, OR 2.9 95% CI 2.4 to 3.4) and children (N=537, k=2, RR 1.9 95% CI 1.1 to 3.1). Data from two reviews on children and adolescents with major depression indicated that suicidality did not occur more frequently in the paroxetine group than placebo (N=702, k=4; N=663, k=6). However, the review by Barbui et al. on adults with major depression suggests that paroxetine may be associated with suicidal tendencies (N=2,729, k=15, OR 2.6 95% CI 1.2 to 5.6). Additionally, Bridge et al. found no significant difference among children and adolescents with obsessive compulsive disorder in suicidal ideation, suicide attempt or preparatory actions toward imminent suicidal behavior (N=662, k=3, OR3.4 95% CI 0.9 to 12.5).

Other

Headaches did not occur more frequently in the paroxetine group than placebo (N=648, k=2). The data indicates a decrease in the corrected QT interval (measured in milliseconds) in the paroxetine group (N=1,486, k=2, MD -1.0 95% CI -5.8 to -3.7) as compared to placebo.

E.2.2 Fluoxetine

Included reviews
Six reviews were included.

1. Intervention
The dose of fluoxetine given was between 10 mg/day and 200 mg/day. Certain reviews, such as Bridge 2007, did not report a dose regimen that was followed but highlighted that a flexible dosing system was used.

2. AMSTAR score
The AMSTAR scores calculated indicated that four high quality reviews and two medium quality reviews were included.

3. Outcomes
The following outcomes were included in the reviews: insomnia, somnolence, suicidality, headaches, insomnia and suicide attempts.

4. Adverse events
Constitutional
No increased frequency of insomnia was found in the fluoxetine group with obsessive compulsive disorder (N=569, k=2). However, the data suggested that fluoxetine was linked to insomnia in individuals with major depression (N=2,964, OR 1.9 95% CI 1.5 to 2.5).

Gastrointestinal
No increased risk of nausea was detected in the fluoxetine group (N=569, k=2).

Neurology
The data suggested that fluoxetine may cause somnolence in individuals with major depression (N=2,080, OR 2.0 95% CI 1.4 to 2.8). Four separate reviews indicated a lack of association between fluoxetine and suicidality in individuals with major depression (N=536, k=3; N=458, k=2; N=458; N=576, OR 1.4 95% CI 0.7 to 3.1). Additionally, no significant difference was found in suicidality in individuals with obsessive compulsive disorder (N=132, OR 3.1 95% CI

0.1 to 76.1). Also, suicide attempts (N=458) did not occur more frequently in the fluoxetine group, nor did headaches (N=569, k=2).

Other
None.

E.2.3 Citalopram

Included reviews
Five reviews were included.

1. Intervention
The doses of 95% citalopram ranged from 20 mg/day to 60 mg/day. Three reviews failed to mention the doses given.

2. AMSTAR score
The AMSTAR scores of these reviews were wide ranging. The lowest score was 4 (Holtmann 2006) and the highest score was 11 (Hetrick 2012).

3. Outcomes
The following outcomes were reported in the reviews that met the inclusion criteria: somnolence, insomnia, the corrected QT interval and suicidality or suicide-related events. Four reviews reported dichotomous outcomes and one did not.

4. Adverse events
Constitutional
Insomnia occurred more frequently in the citalopram group than placebo (N=3607, OR 2.2 95% CI 1.2 to 3.8).

Gastrointestinal
None.

Neurology
Data from three reviews indicated a lack of association between suicidality in children and adolescents and citalopram (N=418, k=2; N=418, k=2; k=2). Citalopram was significantly linked to somnolence (N=3034, OR 3 95% CI 1.9 to 4.9).

Other
There is evidence to suggest a significant difference in the corrected QT interval for citalopram (N=696, k=5, D=10.6 95% CI 3.9 to 17.2).

E.2.4 Venlafaxine

Included reviews
Five reviews were included.

1. Intervention
Doses of venlafaxine ranged from 75 mg/day to 225 mg/day in one review (Coleman, 2012). Flexible dosing was used in another review (Bridge, 2007). Three reviews failed to report the dosages used.

2. AMSTAR score
The AMSTAR scores calculated indicate that two of the included reviews were of high quality and three were of medium quality.

3. Outcomes
The following outcomes were assessed in the included reviews: somnolence, insomnia, suicidal behavior, suicidality and nausea. Four reviews reported dichotomous data.

4. **Adverse events**
Constitutional
Insomnia occurred more frequently in the venlafaxine group than placebo (N=8,712, OR 2.1 95% CI 1.8 to 2.6).

Gastrointestinal
Venlafaxine was significantly linked to nausea (N=334, k=2, RR 68.2 95% CI 0.5 to 4,424.1).

Neurology
No significant difference was found in suicidality (including self-harm thoughts, self-harm, suicidal ideation and suicide attempts) in study populations with major depression (N=334, k=2) or anxiety disorders other than obsessive compulsive disorder (OR 3.0 95% CI 0.1 to 75.3).

However, a second review indicated that venlafaxine was associated with suicide-related events (k=2, RR 13.8 95% CI 1.8 to 103.6).

Other
None.

E.2.5 Sertraline

Included reviews
Four reviews were included.

1. Intervention
The sertraline doses administered ranged between 50 mg/day and 200 mg/day in one review.[97] One review offered that it used a flexible dosing regime, otherwise the doses were unclear.

2. AMSTAR score
The AMSTAR scores calculated indicate that three of the reviews are good quality reviews and that one review is a medium quality review.

3. Outcomes
The following outcomes were assessed: somnolence, insomnia, suicidality, nausea, headaches, dyspepsia, sedation, diarrhoea and sexual adverse events. Three of the reviews provided dichotomous data.

4. Adverse events
Constitutional
Insomnia occurred more frequently in the sertraline group than placebo (N=4,418, OR 1.8 95% CI 1.5 to 2.2; N=579, k=3, RR 2.2 95% CI 1.1 to 4.6).

Gastrointestinal
No significant difference was found in dyspepsia (N=412, k=2). Nausea (N=598, k=4, RR 2.6 95% CI 0.9 to 7.6) and diarrhoea (N=579, k=3, RR 2.2 95% CI 1.1 to 4.2) occurred more frequently in the sertraline group than placebo.

Neurology

No significant differences were found in suicidality (N=373, k=2; N=243, OR 0.3 95% CI 0.0 to 8.2) or sedation (N=511, k=3). Somnolence occurred more frequently in the sertraline group than placebo (N=4,037, OR 2.1 95% CI 1.7 to 2.6).

Other
No significant differences were found in headaches (N=431, k=3) or sexual side effects (N=598, k=4).

E.2.6 Bupropion

Included reviews
Two reviews were included.

1. Intervention
The initial dose of bupropion used for one of the reviews was 150mg per day, which was finally raised to 300mg per day if well tolerated. The doses were not clearly reported in the second review.

2. AMSTAR score
The AMSTAR scores of these papers were calculated as 8 and 11.

3. Outcomes
The following outcomes were reported in these reviews: somnolence, insomnia, headaches, nausea and diarrhoea.

4. Adverse events
Constitutional
The review looking at participants with SAD demonstrated that bupropion increases a person's chances of experiencing insomnia (N=1048, k=3, RR 1.5 95% CI 1.1 to 1.9).

Gastrointestinal
In the review that included participants with SAD, diarrhoea did not occur more frequently in the bupropion group than placebo (N=1048, k=3, RR=1.0 95% CI 0.7 to 1.6). The review reports evidence, however, that nausea occurs more frequently in the bupropion group (N=1048, k=3, RR 1.6 95% CI 1.1 to 2.4). Similarly, the review analysing participants with major depression

indicated the increased chance of insomnia in the bupropion group in comparison to placebo (N=5249, OR 2.3 95% CI 1.8 to 2.8).

Neurology
Alberti et al. reported that somnolence occurred more frequently in the bupropion group than placebo (N=4098, OR 0.6 95% CI 0.4 to 0.9).

Other
Headaches occurred more frequently in the bupropion groups than placebo (N=1048, k=3, RR 1.3 RR 1.0 to 1.6).

E.2.7 Desvenlafaxine

Included reviews
Two reviews were included.

1. Intervention
The doses of desvenlafaxine given in one of these reviews was 50 mg/day to 200 mg/day. The other review did not report the dose regimen.

2. AMSTAR score
The AMSTAR scores calculated for the included reviews were 7 and 8.

3. Outcomes
The following outcomes were assessed in the eligible reviews: somnolence, insomnia and nausea. Two of the reviews reported dichotomous outcomes and the third reported prevalence rates for desvenlafaxine and placebo.

4. Adverse events
Constitutional
Moderate evidence was found to indicate that desvenlafaxine increased a person's chances of experiencing insomnia (N=9873, OR 2.9 95% CI 2.5 to 3.4).

Gastrointestinal
None.

Neurology
Strong evidence was found to support that somnolence occurred more frequently in the desvelafaxine group than placebo (N=5612, OR 2.9 95% CI 2.2 to 3.8).

Other
None.

E.2.8 Escitalopram

Included reviews
Two reviews were included.

1. Intervention
The dose of escitalopram given was 10 mg/day to 45 mg/day.

2. AMSTAR score
The AMSTAR scores calculated for the included reviews were 8 and 11.

3. Outcomes
The following outcomes were assessed: somnolence, insomnia and suicidality.

4. Adverse events
Constitutional
Insomnia occurred moderately more frequently in the escitalopram groups than placebo (N=6,891 OR 1.9 95% CI 1.5 to 2.3).

Gastrointestinal
None.

Neurology
Suicidality did not occur more frequently in the escitalopram groups than placebo (N=575, k=2). However, the data suggested that escitalopram was significantly linked to somnolence (N=5,276 OR 2.6 95% CI 1.8 to 3.8).

Other
None.

E.2.9 Duloxetine
Included reviews
One review was included.

1. Intervention
The dose of duloxetine given was not explicitly stated in the review.

2. AMSTAR score
The AMSTAR score calculated for the included review was 8.

3. Outcomes
The following outcomes were assessed in this review: somnolence and insomnia.

4. Adverse events
Constitutional
Moderate evidence indicated that duloxetine increased a person's chance of having insomnia (N=5,924, OR 2.0 95% CI 1.62 to 2.5).

Gastrointestinal
Desvenlafaxine was strongly linked to nausea (k=27, OR 3.0 95% CI 1.4 to 6.4).

Neurology
There is strong evidence that duloxetine is significantly linked to somnolence (N=5,612, OR 2.9 OR 2.2 to 3.8).

Other
None.

E.2.10 Trazodone

Included reviews
One review was included.

1. Intervention
The administered dose of trazodone ranged between 50 mg/day to 200 mg/day.

2. AMSTAR score
The AMSTAR scores calculated indicated that the review by Fink et al. is a high quality systematic review.

3. Outcomes
The following outcomes were reported: sedation, dry mouth and nausea. All outcomes were dichotomous.

4. Adverse events
Constitutional
Dry mouth did not occur more frequently in the trazodone group than placebo (N=146, k=2).

Gastrointestinal
Nausea did not occur more frequently in the trazodone group than placebo (N=119, k=2).

Neurology
Sedation did not occur more frequently in the trazodone group than placebo (N=254, k=2).

Other
None.

E.11 Clomipramine

Included reviews
There were no eligible papers for clomipramine.

E.12 Clozapine

Included reviews
One review was included.

1. Intervention
The doses of clozapine administered in this eligible review ranged from 26 mg/day to 403 mg/day.

2. AMSTAR score
The AMSTAR quality appraisal indicated that this review had a score of 9/11 and was a high quality systematic review.

3. Outcomes
Weight gain was the only outcome of interest assessed by the review.

4. Adverse events
Constitutional
Weight gain occurred more frequently in the clozapine group than placebo (N=915, OR 13.8 95% CI 2.2 to 49.2).

Gastrointestinal
None.

Neurology
None.

Other
None.

E.2.13 Fluphenazine

Included reviews
One review was included.

1. Intervention
The doses of fluphenazine administered in this eligible review ranged from 2.5 mg/day to 20 mg/day.

2. AMSTAR score
The AMSTAR quality appraisal indicated that this review had a score of 11/11, therefore it is a high quality systematic review.

3. Outcomes
The following outcomes were assessed by this review: akathisia, rigidity, tremor and rash.

4. Adverse events
Constitutional
None.

Gastrointestinal
None.

Neurology
The evidence suggests the fluphenazine increases an individual's chances of experiencing akathisia (N=227, k=2, RR 3.4 95% CI 1.2 to 9.6) and tremor (N=227, k=2, RR 3.2 95% CI 1.3 to 8.1).

Other
No significant difference was found in rash (N=227, k=2). The evidence suggests that fluphenazine is significantly linked to rigidity (N=227, k=2, R 3.5 95% CI 1.8 to 7.1).

E.2.14 Buspirone

Included reviews
One review was included.

1. Intervention
The doses of buspirone administered in this eligible review ranged from 5 mg/day to 60 mg/day.

2. AMSTAR score
The AMSTAR quality appraisal indicated that this review had a score of 11/11, therefore it was a high quality systematic review.

3. Outcomes
The following outcomes were assessed by this review: drowsiness, dizziness, dry mouth, nausea, headaches, somnolence and tinnitus.

4. Adverse events
Constitutional
No significant differences were found in dry mouth (N=437, k=3).

Gastrointestinal
The evidence suggests that buspirone is significantly linked to nausea (N=429, k=3, RR 2.2 95% CI 1.1 to 4.1).

Neurology
No significant differences were found in somnolence (N=183, k=2). The data suggests that buspirone is significantly associated with dizziness (N=635, k=3, RR 3.2 95% CI 1.8 to 5.6).

Other
No significant differences were found in drowsiness (N=481, k=2), headaches (N=416, k=2) or tinnitus (N=183, k=2).

E.2.15 Hydroxyzine

Included reviews
One review was included.

1. Intervention
The doses of hydroxyzine administered in the eligible were greater than or equal to 25 mg/day.

2. AMSTAR score
The AMSTAR quality appraisal indicated a score of 11/11 for this review.

3. Outcomes
The following outcomes were assessed by this review: "agitation/anxiety/nervousness/tension," dizziness, dry mouth, insomnia and "sleepiness/drowsiness/somnolence."

4. Adverse events
Constitutional
No significant differences were found in dry mouth (N=203, k=2) or insomnia (N=203, k=2).

Gastrointestinal
None.

Neurology
No significant differences were found in agitation, anxiety, nervousness or tension (N=242, k=2). Neither dizziness (N=242, k=2) nor somnolence (N=584, k=4) occurred more frequently in the hydroxyzine group than placebo.

Other
None.

E.2.16 Alprazolam

Included reviews
There were no eligible papers for alprazolam.

E.2.17 Diazepam

Included reviews
There were no eligible reviews for diazepam.

E.2.18 Lorazepam

Included reviews
There were no eligible reviews for lorazepam.

E.2.19 Carbamazepine

Included reviews
There were no eligible reviews for carbamazepine.

E.2.20 Lithium

Included reviews
Three reviews were included.

1. Intervention
The doses of lithium administered in one of the eligible reviews ranged from 900 mg/day to 1,250 mg/day. The doses of lithium used in the other two reviews were unclear.

2. AMSTAR score
The AMSTAR quality appraisal indicated that the eligible reviews scored between 9/11 to 11/11.

3. Outcomes
The following outcomes were assessed by these reviews: hypothyroidism, somnolence, nausea, diarrhoea, suicide, weight gain and skin disorders.

4. Adverse events
Constitutional
There is evidence that lithium is significantly associated with weight gain (N=1,224, k=5, OR 1.9 95% CI 1.3 to 2.8).

Gastrointestinal
There is evidence that lithium increases an individual's chances of experiencing nausea (N=770, k=5, RR 1.76 95% CI 1.07 to 2.92) and diarrhoea (N=770, k=5, RR 2.4 95% CI 1.4 to 4.1).

Neurology
No significant differences were found in suicide (N=565). There is evidence that lithium is significantly linked to somnolence (N=770, k=5, RR 2.0 95% CI 1.0 to 3.8).

Other
No significant differences were found in skin disorders (N=213, k=2) or hypothyroidism (N=310, k=3; N=213, k=2).

E.2.21 Amphetamine Salts

Included reviews
One review was included.

1. Intervention
The doses of amphetamine salts administered in the eligible reviews ranged from 10 mg/day to 70 mg/day.

2. AMSTAR score
The AMSTAR quality appraisal indicated that the score of the review was 11/11.

3. Outcomes
The following outcomes were assessed by these reviews: decreased appetite, "insomnia/trouble sleeping," abdominal pain and headaches.

4. Adverse events
Constitutional

Amphetamine salts were found to be significantly associated with insomnia or having trouble sleeping (N=1,280, k=5 RR 3.3 95% CI 1.3 to 9.0).

Gastrointestinal
Decreased appetite was more frequently experienced in the amphetamine salts group than placebo (N=1,124, k=5 RR 6.4 95% CI 1.6 to 26.5).

Neurology
None.

Other
There was no association extracted between amphetamine salts and the occurrence of headaches. However, amphetamine salts were significantly linked to abdominal pain.

Appendix F - Variation in Results

	Diagnosis 1	Diagnosis 2	Diagnosis 3	Diagnosis 4	Diagnosis 5	Diagnosis 6	Diagnosis 7	Diagnosis 8	Diagnosis 9	Diagnosis 10	Diagnosis 11
FLUOXETINE											
Insomnia	Depression	Obsessive compulsive disorder	*	*	*	*	*	*	*	*	*
Age:	Adults	Adults	*	*	*	*	*	*	*	*	*
OR or RR*:	1.9 (1.5, 2.5)	* 1.2 (0.8, 1.7)	*	*	*	*	*	*	*	*	*
PAROXETINE											
Suicidality	Depression	Depression	Obsessive compulsive disorder	*	*	*	*	*	*	*	*
Age:	Adults	C&A	C&A	*	*	*	*	*	*	*	*
OR or RR*:	2.6 (1.2, 5.5)	* 1.6 (0.5, 5.3)	* 3.4 (0.9, 12.5)	*	*	*	*	*	*	*	*
ARIPIPRAZOLE											
Akathisia	Bipolar or schizoaffective disorder	Bipolar depression	Schizophrenia	Bipolar mania	Bipolar I,II, Acutely Manic or Mixed States	Schizophrenia	*	*	*	*	*
Age:	All ages	Adults	Unclear	Unclear	All ages	Adults	*	*	*	*	*
OR or RR*:	* 3.2 (2.3, 4.4)	* 5.6 (3.4, 9.3)	1.7 (0.9, 3.0)	4.8 (2.3, 10.1)	* 3.7 (2.5, 5.4)	* 1.6 (1.1, 2.3)	*	*	*	*	*
Extrapyramidal symptoms	Bipolar or schizoaffective disorder	ASD or PDD	Other	PDD or ID	Bipolar depression	Schizophrenia	Schizophrenia spectrum	Dementia	Bipolar I, II, Acutely Manic or Mixed States	Schizophrenia	Acute mania
Age:	All ages	C&A	C&A	Children	Adults	Unclear	Adults	Unclear	All ages	Adults	Adults
OR or RR*:	* 2.2 (1.5, 3.4)	* 1.9 (0.9-3.7)	3.8 (2.2, 6.2)	2.4 (0.9, 5.2)	* 3.2 (2.3, 4.5)	1.1 (0.6, 2.0)	1.0 (0.8, 1.2)	1.3 (0.7, 2.6)	* 2.4 (1.9, 3.2)	* 1.6 (0.6, 4.2)	1.4 (1.0 1.9)
Anticholinergic use	Bipolar or schizoaffective disorder	Schizophrenia spectrum disorders	*	*	*	*	*	*	*	*	*
Age:	In all ages	Adults	*	*	*	*	*	*	*	*	*
OR or RR*:	* 3.3 (1.8, 5.9)	1.1 (0.8, 1.4)	*	*	*	*	*	*	*	*	*
Tremor	Bipolar or schizoaffective disorder	ASD or PDD	*	*	*	*	*	*	*	*	*
Age:	All ages	C&A	*	*	*	*	*	*	*	*	*

OR or RR*:	* 1.5 (0.9, 2.3)	* 10.3 (1.4, 76.6)	*	*	*	*	*	*	*	*	*
Sedation	ASD or PDD	Bipolar depression	Schizophrenia spectrum	Dementia	ASD or ID	Bipolar I, II, Acutely manic or Mixed States	*	*	*	*	*
Age:	C&A	Adults	Adults	Unclear	C&A	Adults	*	*	*	*	*
OR or RR*:	* 4.3 (1.6, 11.6)	* 2.4 (1.1, 5.5)	* 1.4 (0.8, 2.3)	2.6 (1.6, 4.6)	* 0.8 (0.7, 0.9)	* 2.6 (1.7, 3.9)	*	*	*	*	*
Somnolence	Bipolar or schizoaffective disorder	Other	PDD or ID	Bipolar depression	Dementia	*	*	*	*	*	*
Age:	All ages	C&A	Children	Adults	Older adults	*	*	*	*	*	*
OR or RR*:	* 1.9 (0.9, 3.7)	6.1 (2.8, 12.2)	25.8 (1.3, 112.3)	* 1.8 (0.9, 3.4)	3.5 (1.6, 7.5)	*	*	*	*	*	*
RISPERIDONE											
Abnormal gait	Alzheimer's disease	Dementia	*	*	*	*	*	*	*	*	*
Age:	Older adults	Older adults	*	*	*	*	*	*	*	*	*
OR or RR*:	5.3 (2.2, 12.6)	1.2 (0.7, 2.0)	*	*	*	*	*	*	*	*	*
Weight gain	Schizophrenia or bipolar	PDD or ID	ASD or ID	ASD or ID	Mania	*	*	*	*	*	*
Age:	C&A	C&A	C&A	C&A	Adults	*	*	*	*	*	*
OR or RR*:	6.0 (3.0, 11.4)	7.8 (1.9, 25.2)	* 0.9 (0.85, 0.96)	4.4 (2.8, 6.9)	1.7 (0.7, 4.1)	*	*	*	*	*	*
Somnolence	Alzheimer's disease	Schizophrenia or bipolar	PDD or ID	Dementia or Alzheimer's	Schizophrenia	Dementia	*	*	*	*	*
Age:	Older adults	C&A	C&A	Older adults	Adults	Older adults	*	*	*	*	*
OR or RR*:	2.4 (1.8, 3.2)	7.3 (4.6, 11.2)	9.6 (3.5, 22.8)	1.4 (0.9, 2.1)	1.3 (0.7, 2.5)	3.6 (2.7, 4.7)	*	*	*	*	*
Anticholinergic use	Schizophrenia	Bipolar disorder	Schizophrenia		*	*	*	*	*	*	*
Age:	Unclear	Unclear	Adults		*	*	*	*	*	*	*
OR or RR*:	1.1 (0.6, 2.4)	4.4 (2.7, 7.3)	1.4 (0.8, 2.2)		*	*	*	*	*	*	*
Extrapyramidal symptoms	Alzheimer's disease	Schizophrenia or bipolar	PDD or ID	Dementia or Alzheimer's	Schizophrenia	Bipolar disorder	Schizophrenia	Dementia	Other	Dementia	*
Age:	Older adults	C&A	C&A	Older adults	Unclear	Unclear	Adults	Unclear	C&A	Older adults	*
OR or RR*:	1.8 (1.0, 3.2)	3.7 (2.2, 6.0)	3.7 (1.7, 7.2)	1.9 (1.2, 3.0)	1.1 (0.5, 2.6)	4.2 (2.6, 7.1)	1.3 (0.9,1.7)	3.0 (2.0, 4.7)	3.4 (2.0, 5.5)	1.8 (1.4, 2.4)	*
OLANZAPINE											

Extrapyramidal symptoms	Schizophrenia or bipolar	Other	Schizophrenia	Acute mania							
Age:	C&A	Adults	Adults	Adults							
OR or RR*:	6.4 (2.4, 13.8)	*1.1 (0.5, 2.7)	1.0 (0.6, 1.1)	0.7 (0.5, 1.1)							
Anticholinergic use	Agitated with suspected mental illness	Schizophrenia	Other	Schizophrenia							
Age:	Adults and older adults	Adults and older adults	Adults	Adults							
OR or RR*:	*1.3 (0.5, 3.3)	*0.9 (0.3, 2.8)	*0.5 (0.3, 0.8)	*1.2 (0.5, 2.9)							
QUETIAPINE											
Extrapyramidal symptoms	Schizophrenia or bipolar	Bipolar depression	Generalised anxiety	Schizophrenia	Major depression	Schizophrenia	Dementia	Alzheimer's disease	Acute bipolar depression	*	*
Age:	C&A	Adults	Adults	All ages	All ages	Adults	Unclear	Older adults	All ages	*	*
OR or RR*:	2.5 (0.9, 6.1)	* 1.4 (0.9, 2.2)	1.8 (1.1, 2.9)	* 1.0 (0.7, 1.3)	1.8 (0.9, 3.6)	0.9 (0.6, 1.3)	1.2 (0.5, 3.1)	0.9 (0.4, 2.0)	* 2.8 (2.1, 3.6)	*	*
Urinary tract symptoms	Dementia	Alzheimer's disease	Dementia	*	*	*	*	*	*	*	*
Age:	Unclear	Older adults	Older adults	*	*	*	*	*	*	*	*
OR or RR*:	2.4 (1.2, 5.2)	1.7 (0.6, 5.3)	1.9 (0.9, 3.8)	*	*	*	*	*	*	*	*
Constipation	Schizophrenia spectrum	Acute bipolar depression	*	*	*	*	*	*	*	*	*
Age:	Adults	All ages	*	*	*	*	*	*	*	*	*
OR or RR*:	* 1.9 (0.9, 3.8)	* 2.1 (1.5, 2.8)	*	*	*	*	*	*	*	*	*
VALPROATE											
Sedation	Dementia	Bipolar disorder	ASD or ID	Schizophrenia spectrum	*	*	*	*	*	*	*
Age:	Adults and older adults	Adults and older adults	C&A	Adults	*	*	*	*	*	*	*
OR or RR*:	2.5 (1.4, 4.5)	* 1.6 (0.8, 3.1)	* 1.2 (0.9, 1.6)	* 1.5 (1.0, 2.2)	*	*	*	*	*	*	*
Dizziness	Bipolar disorder	Bipolar disorder	*	*	*	*	*	*	*	*	*
Age:	Adults and older adults	Adults	*	*	*	*	*	*	*	*	*
OR or RR*:	* 3.2 (1.1, 8.9)	* 0.8 (0.2, 3.8)	*	*	*	*	*	*	*	*	*
LISDEXAMFETAMINE											

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Headache	Binge eating disorder	ADHD	*	*	*	*	*	*	*	*	*
Age:	Adults	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 1.6 (1.1, 2.2)	* 1.1 (0.7, 1.6)	*	*	*	*	*	*	*	*	*
Nausea	Binge eating disorder	ADHD	*	*	*	*	*	*	*	*	*
Age:	Adults	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 1.6 (1.0, 2.6)	* 1.5 (0.6, 3.6)	*	*	*	*	*	*	*	*	*
METHYLPHENIDATE											
Stomach ache	ADD	ADHD	*	*	*	*	*	*	*	*	*
Age:	C&A	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 1.6 (0.9, 2.4)	*1.3 (1.0, 1.7)	*	*	*	*	*	*	*	*	*
Dizziness	ADD	ADHD	*	*	*	*	*	*	*	*	*
Age:	C&A	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 3.5 (1.2, 9.3)	* 2.5 (0.7, 9.0)	*	*	*	*	*	*	*	*	*
Insomnia	ADD	ADHD	*	*	*	*	*	*	*	*	*
Age:	C&A	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 3.1 (2.5, 3.7)	* 1.3 (0.4, 4.9)	*	*	*	*	*	*	*	*	*
Headache	ADD	ADHD	*	*	*	*	*	*	*	*	*
Age:	C&A	C&A	*	*	*	*	*	*	*	*	*
OR or RR*:	* 1.5 (1.0, 2.1)	* 1.2 (0.9, 1.6)	*	*	*	*	*	*	*	*	*

Appendix G – Excluded Papers

These papers either analysed classes of medications instead of individual medications, analysed efficacy outcomes instead of tolerability profiles or were otherwise not relevant for the purpose of this umbrella review. **N=520**	
Author	**Year**
Acharya, N. et al.	2006
Adida, M. et al.	2014
Agnes, M. et al.	2007
Aguiar-Ibanez, R. et al.	2009
Alabed, S. et al.	2011
Alawami, M. et al.	2014
Alvarez, Y. et al.	2013
Amato, L. et al.	2011
Amato, L. et al.	2007
Amato, L. et al.	2010
Ananthavarathan, P.	2014
Andrisano, C. et al.	2013
Anglin, R. et al.	2014
Anonymous	1980
Anonymous	2005
Aponte, J. et al.	2008
Arango, C. et al.	2012
Armenteros, J. et al.	2006
Arnold, L. et al.	2000
Arroll, B. et al.	2009
Asmal, L. et al.	2013
Atti, A. et al.	2014

Aurora, R. et al.	2012
Bacaltchuk, J. et al.	2003
Bagnall, a. et al.	2003
Bagot, K. et al.	2014
Bains, J. et al.	2002
Baldwin, D. et al.	2011
Ballard, C. et al.	2006
Banaschewski, T. et al.	2008
Banzi, R. et al.	2015
Barbui, C. et al.	2011
Barbui, C. et al.	2004
Barnard, A. et al.	2002
Basan, A. et al.	2004
Bauer, M. et al.	2012
Beck, a. et al.	2005
Bellantuono, C. et al.	2006
Bellino, S. et al.	2014
Berner, M. et al.	2007
Bersudsky, Y. et al.	2009
Beumont, P. et al.	2004
Beynon, S. et al.	2009
Bhoopathi Paranthaman, S. et al.	2006
Binks, C. et al.	2006
Bishara, D. et al.	2013
Blume, S. et al.	2010
Bodalia, P. et al.	2010
Bola, J. et al.	2011
Bond, D. et al.	2010

Bond, D. et al.	2008
Bouchard, L. et al.	2015
Bowden, C.	2003
Brams, M. et al.	2010
Brecht, S. et al.	2008
Bresee, L.	2011
Bridle, C. et al.	2004
Briken, P. et al.	2002
Briken, P. et al.	2002
Bril, V. et al.	2011
Broadstock, M. et al.	2007
Brunnauer, A. et al.	2013
Bruno, E. et al.	2015
Brunoni, A. et al.	2011
Budman, C.	2014
Bushe, C. et al.	2007
Bushe, C. et al.	2004
Bushe, C. et al.	2007
Bushe, C. et al.	2013
Byrne, A. et al.	2009
Caldwell Patrina, H. et al.	2016
Campbell, N. et al.	2009
Candy, B. et al.	2008
Carson, S. et al.	2006
Carucci, S. et al.	2013
Carvalho, A. et al.	2015
Castells, X. et al.	2010
Castells, X. et al.	2013

Castells, X. et al.	2011
Cerullo, M. et al.	2013
Chakos, M. et al.	2001
Chakos, M. et al.	2001
Charison, F. et al.	2009
Chassang, S. et al.	2015
Cheine, M. et al.	1999
Chiesa, A. et al.	2012
Choi, Y.	2009
Chow, T. et al.	2007
Chue, P. et al.	2012
Ciprani, A. et al.	2013
Ciprani, A. et al.	2010
Citrome, L.	2007
Claudino Angelica, M. et al.	2006
Clinch, C. et al.	2006
Coghill, D. et al.	2014
Cong, W. et al.	2012
Conti, C. et al.	2008
Cooper, C. et al.	2011
Cooper, K. et al.	2015
Cornacchio, A. et al.	2011
Correll, C.	2012
Correll, C. et al.	2007
Cosgrove, L. et al.	2011
Courtney, D.	2004
Cox Georgina, R. et al.	2012
Cruz, N. et al.	2010

Cunill, R. et al.	2013
Curran, C. et al.	2004
Curran, S. et al.	2009
Damsa, C. et al.	2004
Dassanayake, T. et al.	2011
David, A. et al.	2005
Davis, J. et al.	1999
De Hert, M. et al.	2015
De Menezes, G. et al.	2011
De Oliveira, I. et al.	1996
Deb, S. et al.	2007
Declercq, T. et al.	2013
Del Casale, A. et al.	2012
Derry, S. et al.	2007
Deshauer, D. et al.	2008
Deshpande, A. et al.	2012
Devasahayam, A. et al.	2011
Dimitrova, M. et al.	2012
Dodd, S. et al.	2015
Dold, M. et al.	2015
Dold, M. et al.	2012
Domecq, J. et al.	2015
Donovan, M. et al.	2010
Dove, D. et al.	2012
Drieling, T. et al.	2007
Drieling, T. et al.	2007
Drijgers, R. et al.	2009
Duggan, C. et al.	2008

Eckert, L. et al.	2006
Edwards, J. et al.	1999
Edwards, S. et al.	2009
Einarson, T.	1980
Einarson, T. et al.	1998
El-Sayeh, H. et al.	2006
El-Sayeh, H. et al.	2006
Elnazer, H. et al.	2015
Endeshaw, Y.	2001
Englisch, S. et al.	2013
Eom, C. et al.	2012
Epstein, T. et al.	2014
Farre, M. et al.	2012
Fava, G. et al.	2015
Fergusson, D. et al.	2005
Fiedorowicz, J. et al.	2012
Fineberg, N. et al.	2007
Fischer, C. et al.	2006
Fleischhacker, W.	2009
Foley, D. et al.	2011
Forlenza, O. et al.	2008
Forneris, C. et al.	2013
Fountoulakis, K. et al.	2009
Fountoulakis, K. et al.	2013
Fountoulakis, K. et al.	2004
Fountoulakis, K. et al.	2009
Fountoulakis, K. et al.	2008
Franco, K. et al.	2006

Fridman, M. et al.	2015
Friedman, J. et al.	2014
Frogley, C. et al.	2012
Furukawa, T. et al.	2003
Gajwani, P. et al.	2006
Gardette, V. et al.	2014
Gartlehner, G. et al.	2009
Geddes, J. et al.	2003
Gentile, S.	2009
Gentile, S.	2009
Gentile, S.	2010
Gentile, S.	2011
Gentile, S.	2013
Ghanizadeh, A.	2013
Ghanizadeh, A. et al.	2013
Ghanizadeh, A. et al.	2015
Gibbons, R. et al.	2008
Gibson Roger, C. et al.	2008
Gijsman, H. et al.	2004
Gilbert, D. et al.	1999
Gillies, D. et al.	2013
Gjessing Jensen, K. et al.	2015
Glazener, C. et al.	2003
Glick, I. et al.	2011
Glue, P. et al.	2010
Godfrey, J.	2009
Goedhard, L. et al.	2006
Gonzalez De Dios, J. et al.	2006

Gonzalez-Pinto, A. et al.	2015
Goodwin, G. et al.	2003
Gorman, D. et al.	2015
Gould, R. et al.	2014
Grande, I. et al.	2014
Greenberg, R. et al.	1994
Grilli-Tissot, M. et al.	2014
Grunze, H. et al.	2013
Guina, J. et al.	2015
Gul, M. et al.	2008
Gunjal, S. et al.	2015
Gunnell, D. et al.	2006
Gutkovich, Z. et al.	2008
Guzzetta, F. et al.	2007
Haack, S. et al.	2009
Hampel, H. et al.	2015
Han, C. et al.	2014
Hansen, R. et al.	2013
Hansen, R. et al.	2005
Hansen, R. et al.	2009
Hanssen, H.	2012
Hasan, A. et al.	2013
Hawton, K. et al.	2015
Hazell, P. et al.	2013
Hedges, D. et al.	2007
Heiligenstein, J. et al.	1993
Heilmann, K. et al.	2015
Henkel, V. et al.	2006

Hennissen, L. et al.	2015
Herrmann, N. et al.	2007
Hetrick, s. et al.	2012
Hirota, T. et al.	2014
Hirsch, L. et al.	2012
Ho, J. et al.	2011
Holbrook, A. et al.	1999
Holbrook, A. et al.	2001
Hosalli, P. et al.	2003
Hoskins, M. et al.	2015
Hu, X. et al.	2011
Huang, X. et al.	2009
Hubbard, J. et al.	1991
Hulshuof, T. et al.	2014
Hunter, R. et al.	2013
Hurwitz, R. et al.	2010
Iersel, M. et al.	2005
Ilieva, I. et al.	2015
Imai, H. et al.	2014
Inada, T. et al.	2003
Ingenhoven, T. et al.	2010
Ingenhoven, T. et al.	2011
Ipser, J. et al.	2007
Ipser, J. et al.	2009
Ipser, J. et al.	2009
Irani, T. et al.	2013
Irving, C. et al.	2009
Jackson, J. et al.	2013

Jackson, J. et al.	2014
Jain, S. et al.	2014
Jakubovski, E. et al.	2015
Jarema, M.	1996
Jensen, P. et al.	2007
Jesner, O. et al.	2007
Joffe, R. et al.	1996
Jonas, J. et al.	1996
Jones, R. et al.	2006
Jones, R. et al.	2011
Joy, C. et al.	2006
Julious, S.	2013
Kaizar, E. et al.	2006
Kantrowitz, J. et al.	2008
Kapczinski, F. et al.	2003
Karson, C. et al.	2016
Katz, I. et al.	2007
Katzman, M. et al.	2007
Kavale, K.	1982
Keefe, R. et al.	1999
Kelly, C. et al.	2010
Kennedy, E. et al.	2007
Khan, B. et al.	2012
Kidwell, K. et al.	2015
Kimko, H. et al.	2012
King, S. et al.	2006
Kirsch, I. et al.	2008
Kirsch, I. et al.	1999

Kishi, T. et al.	2012
Kishi, T. et al.	2013
Kishi, T. et al.	2015
Kishi, T. et al.	2014
Kishi, T. et al.	2013
Kleinstauber, M. et al.	2014
Klemp, M. et al.	2011
Knights, M. et al.	2014
Koesters, M. et al.	2011
Kok, R. et al.	2011
KoKoAung, E. et al.	2012
Kolla, B. et al.	2011
Komossa, K. et al.	2010
Koning, J. et al.	2010
Kraus, J. et al.	2010
Krishnadas, R. et al.	2010
Krishnaswamy, N. et al.	2013
Kucukaycan, M. et al.	2012
Kumar, S. et al.	2013
Kumar, S. et al.	2011
Kusel, J. et al.	2012
Kwong, K. et al.	1999
Lam, R. et al.	2004
Lanctot, K. et al.	1998
Lanctot, K. et al.	2000
Laoutidis, Z. et al.	2015
Lee, P. et al.	2004
Leslie, W. et al.	2007

Leucht, C. et al.	2012
Leucht, S.	2010
Leucht, S. et al.	2003
Leucht, S. et al.	2014
Leucht, S. et al.	2015
Leucht, S. et al.	2002
Leucht, S. et al.	2012
Levkovitz, Y. et al.	2011
Li, J. et al.	2013
Li, X. et al.	2015
Liao, Y. et al.	2015
Lieb, K. et al.	2010
Lima, A. et al.	2002
Lima, M. et al.	2003
Linde, M. et al.	2013
Ling, Y.	2015
Liu, H. et al.	2011
Liu, X. et al.	2014
Lonergan, E. et al.	2007
Lonergan, E. et al.	2007
Lonergan, E. et al.	2002
Lonergan, E. et al.	2009
Loy, J. et al.	2012
Macedo, C. et al.	2014
MacQueen, G. et al.	2012
Macritchie, K. et al.	2001
Mamo, D.	2007
Mandelli, L. et al.	2008

Maneeton, B. et al.	2015
Maneeton, N. et al.	2011
Maneeton, N. et al.	2013
Maneeton, N. et al.	2016
Mariappan, P. et al.	2007
Marini, S. et al.	2014
Marshall, K. et al.	2014
Martin, J. et al.	2007
Martinon-Torres, G et al.	2004
Martinotti, G. et al.	2013
Mason, M. et al.	2013
Matsunaga, S. et al.	2015
Mattos, P.	2014
Matza, L. et al.	2005
Mayers, A. et al.	2005
Mayo-Smith, M.	1997
Mazzucco, S. et al.	2008
McCleery, J. et al.	2014
McMahon, C. et al.	2011
Melnik, T. et al.	2010
Meszaros, A. et al.	2007
Minozzi, S. et al.	2010
Minozzi, S. et al.	2015
Mircoli, G. et al.	2010
Mircoli, G. et al.	2010
Mitchell, A. et al.	2013
Mochcovitch, M. et al.	2010
Mohler, J. et al.	2015

Moro, M. et al.	2014
Muralidharan, K. et al.	2013
Murphy, B. et al.	2006
Nanau, R. et al.	2013
Narayana, U. et al.	2015
Nefzi, R. et al.	2015
Nelson, J. et al.	2008
Nelson, J. et al.	2009
Noh, E.	2014
Nolte, S. et al.	2004
Norris, S. et al.	2005
Ntais, C. et al.	2005
O'Connor, E. et al.	2009
Oelke, M. et al.	2006
Offidani, E. et al.	2013
Offringa, M. et al.	2013
Orlova, N. et al.	2013
Otasowie, J. et al.	2014
Pacchiarotti, I. et al.	2015
Pae, C. et al.	2008
Paloscia, C. et al.	2007
Pani Pier, P. et al.	2014
Pani, P. et al.	2011
Papanikolaou, K. et al.	2006
Papp, S. et al.	2012
Parkinson, B. et al.	2009
Patel, T. et al.	2013
Pelland, C. et al.	2009

Pellock, J. et al.	2014
Pereira, V. et al.	2014
Perez-Mana, C. et al.	2013
Perez-Mana, C. et al.	2011
Peterson, K. et al.	2008
Pfennig, A. et al.	2013
Pierce, A. et al.	2009
Pinheiro, D.	2008
Pollack, M. et al.	1992
Polycarpou, A. et al.	2005
Pompili, M.	2011
Poolsup, N. et al.	2000
Posner, E. et al.	2005
Prasad, M. et al.	2014
Priest, R.	1980
Pringsheim, T. et al.	2012
Pringsheim, T. et al.	2015
Pringsheim, T. et al.	2011
Quraishi Seema, N. et al.	1999
Rajji, T. et al.	2008
Ramasubbu, R.	2004
Ramsay, R. et al.	1997
Rana, F. et al.	2013
Reddy, S. et al.	2010
Reichow, B. et al.	2013
Reinares, M. et al.	2013
Rej, S. et al.	2012
Rendell, J. et al.	2006

Roge, R. et al.	2012
Rothbart, R. et al.	2013
Ruffmann, C. et al.	2006
Ruxton, K. et al.	2015
Sacchetti, E. et al.	2010
Samalin, L. et al.	2014
Samuel, M. et al.	2011
Samuelsson, E. et al.	2015
Saperia, J. et al.	2006
Sapunar, Z. et al.	2009
Sarkar, S. et al.	2013
Satterthwaite, T. et al.	2008
Schaffer, A. et al.	2015
Schmitt, R. et al.	2005
Schneider, C. et al.	2014
Schueler, Y. et al.	2011
Schulz, S. et al.	2003
Seida, J. et al.	2012
Seitz, D. et al.	2011
Seitz, D. et al.	2013
Serretti, A. et al.	2009
Serretti, A. et al.	2010
Severus, E. et al.	2014
Shamliyan, T. et al.	2008
Shin, D. et al.	2014
Shinfuku, M. et al.	2014
Shulman, M. et al.	2013
Sidor, M. et al.	2011

Silva De Lima, M. et al.	2002
Silva, R. et al.	1996
Sim, F. et al.	2015
Sinclair, L. et al.	2009
Sink, K. et al.	2005
Smith, L. et al.	2007
Smith, L. et al.	2007
Sobow, T.	2007
Sochocky, N. et al.	2013
Sohler, N. et al.	2015
Soomro, G. et al.	2015
Srisurapanont, M. et al.	2001
Steenen, S. et al.	2012
Stein Dan, J. et al.	2006
Stein Dan, J. et al.	2000
Strawn, J. et al.	2015
Stuhec, M. et al.	2015
Swenson, J. et al.	2006
Tamayo, J. et al.	2010
Tapp, A. et al.	2008
Tarricone, I. et al.	2010
Taylor, D. et al.	2000
Taylor, M. et al.	2012
Taylor, M. et al.	2006
Taylor, W. et al.	2004
Tedeschini, E. et al.	2011
Tek, C. et al.	2015
Thaler, K. et al.	2011

Thase, M.	1998
Thornley, B. et al.	2003
Thornton, A. et al.	2006
Tiffin, P. et al.	2013
Tondo, L. et al.	2010
Tonin, F. et al.	2015
Trindade, E. et al.	1998
Trinka, E. et al.	2014
Tsapakis, E. et al.	2008
Turner, B. et al.	2014
Ulrichsen, J. et al.	2006
Usala, T. et al.	2008
Van Gaalen, J. et al.	2014
Van Harten, P. et al.	2012
Van Iersel, M. et al.	2005
Van Liempt, S. et al.	2006
Van Lieshout, R. et al.	2010
Van Marwijk, H. et al.	2012
Vasa, R. et al.	2014
Verbeeck, W. et al.	2009
Victoroff, J. et al.	2014
Vieta, E. et al.	2010
Volz, A. et al.	2009
Von Knorring, L. et al.	2005
Von Wolff, A. et al.	2013
Vossen, H. et al.	2009
Waldon, K. et al.	2013
Weinmann, S. et al.	2009

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Weyandt, L. et al.	2014
Wijkstra, J. et al.	2015
Wilens, T	2003
Wilens, T. et al.	1998
Wilens, T. et al.	1995
Williams, K. et al.	2013
Wilson, K. et al.	2001
Wolff, A. et al.	2012
Wu, P. et al.	2006
Xu, J. et al.	2011
Xue, H. et al.	2014
Yang, C. et al.	2015
Young, A. et al.	2009
Young, S. et al.	2015
Zappia, M. et al.	2013
Zeller, S. et al.	2010
Zerjav, S. et al.	2009
Zhang, Y. et al.	2014
Zheng, W. et al.	2016
Zhornitsky, S. et al.	2011
Zuddas, A. et al.	2011
Zuidema, S. et al.	2006

These papers either included more than 20% cross-over studies, analysed the medications of interest with active comparators, presented meta-analyses that were based on selective and non-systematic reviews or were otherwise not relevant for the purpose of this umbrella review.

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Author	Year
Acuna, C.	2008
Allgulander. C. et al.	2008
Allison, D. et al.	1999
Anonymous	2000
Ardizzone, I. et al.	2011
Arroll, B. et al.	2005
Arts, B. et al.	1998
Aursenes, I. et al.	2008
Aursenes, I. et al.	2005
Bak, M. et al.	2014
Baker, R. et al.	2010
Baldessarini, R.	2012
Baldessarini, R. et al.	2008
Baldessarini, R. et al.	2006
Bandelow, B. et al.	2015
Barbui, C. et al.	1996
Barker, M. et al.	2004
Bauer, M. et al.	2010
Bauer, M. et al.	2014
Bauer, M. et al.	1999
Bauer, M. et al.	2015
Bauer, M. et al.	2009
Beasley, C. et al.	1992
Beasley, C. et al.	2000
Beasley Jr, C. et al.	2007
Beasley Jr, C. et al.	2000
Bech, P. et al.	1992

Bech, P. et al.	2000
Bech, P. et al.	1993
Berlim, M. et al.	2013
Berti, C. et al.	1995
Bloch, M. et al.	2010
Bollini, P. et al.	1994
Bollini, P. et al.	1999
Brakoulias, V. et al.	2015
Burrows, G. et al.	1994
Busto, U. et al.	1998
Buttner, M. et al.	2004
Cao, Z. et al.	2013
Carpenter, D. et al.	2011
Chen, Y. et al.	2007
Chiesa, A. et al.	2010
Chiesa, A. et al.	2009
Chung, A. et al.	2011
Clayton, A. et al.	2015
Cohen, D. et al.	2011
Cohen, S. et al.	2015
Connor, D. et al.	2003
Connor, D. et al.	2002
Coughlin, C. et al.	2015
Crenshaw, T.	1997
Cruz, N. et al.	2011
Curtin, F. et al.	2004
Darba, J. et al.	2011
Davis, J. et al.	2001

Davis, J. et al.	2002
Davis, M. et al.	2014
De Vries, Y. et al.	2015
Dold, M. et al.	2011
Dubicka, B. et al.	2006
Eisborg, L.	1991
Entsuah, A. et al.	2001
Entsuah, A. et al.	1995
Eom, C. et al.	2012
Fabre, L. et al.	2012
Fang, F. et al.	2010
Faraone, S. et al.	2003
Fernandes, B. et al.	2015
Feuerstein, T.	1997
Fountoulakis, K. et al.	2013
Fountoulakis, K. et al.	2011
Frisina, P.	2006
Frye, M.	2012
Furukawa, T. et al.	2015
Fusar-Poli, P.	2013
Gabay, A. et al.	2015
Gammans, R. et al.	1992
Garrett, D. et al.	2012
Gartlehner, G. et al.	2013
Girardi, P. et al.	2006
Giupponi, G. et al.	2008
Goldberg, D.	2006
Greis, J. et al.	1995

Grilli Tissot, M. et al.	2003
Gurrera, R. et al.	2007
Haas, S. et al.	2006
Hallfors, D. et al.	1993
Hammad, T. et al.	2006
Han, L. et al.	2015
Hennen, K. et al.	2005
Kane, J.	2013
Lee, H. et al.	2012
Leucht, S. et al.	1999
Ma, H. et al.	2014
Maneeton, N. et al.	2000
Mercer, D. et al.	2009
Messer, T. et al.	2012
Mick, E. et al.	2013
Mittmann, N. et al.	1997
Moteshafi, H. et al.	2012
Moteshafi, H. et al.	2012
Moteshafi, H. et al.	2012
Nashed, M. et al.	2011
Newman, T. et al.	2006
Nowell, P. et al.	1997
Pang, C. et al.	2005
Phillips, A.	2004
Preda, A.	2012
Privitera, M.	1999
Rabenda, V. et al.	2013
Soldatos, C. et al.	1999

Song, F. et al.	1993
Souza, F. et al.	1991
Spielmans, G.	2008
Srisurapanont, M. et al.	1999
Stone, M. et al.	2009
Takkouche, B. et al.	2007
Tamminga, H. et al.	2014
Wang, C. et al.	2012
Willems, A. et al.	2014
Xing, C. et al.	2014
Yang, H. et al.	2013
Yury, C. et al.	2007
Zhang, R. et al.	2011

These papers either analysed observational studies or were otherwise not relevant for the purpose of this umbrella review.

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Author	**Year**
Billioti De Gage, S. et al.	2015
Blicharz-Wladysiuk, M. et al.	2006
Gurumurthy, P. et al.	2013
Hackam, D. et al.	2012
Hartikainen, S. et al.	2007
Ho, S. et al.	2016
Rossi, G. et al.	2012
Swetha Samji, N. et al.	2013
Undela, K. et al.	2015

Vancampfort, D. et al.	2015
Vyas, M. et al.	2015
Wilens, T. et al.	2003
Wingo, A. et al.	2009
Wu, Q. et al.	2012
Wu, Q. et al.	2013
Yuan, Y. et al.	2006