Drug Safety and Effectiveness Network Report:

Systematic Review of the Association between Serotonin Affinity of Anti-Depressant Agents and the Occurrence of Fractures, Falls, and Bone Mineral Density Change in Patients With Depression

Authors:

Brian Hutton, Fatemeh Yazdi, Salmaan Kanji, Kiran Rabheru, Ferran Catala-Lopez, Andrea Cipriani, Dean Fergusson, Lise Bjerre, Justin Thielmann, Andrea Tricco, Sharon Straus, David Moher

On behalf of the NETMAN team

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Authorship Contributions:

- Dr. Brian Hutton contributed to development and authorship of the study protocol, performed network meta-analyses, generated summary graphics, and drafted the preliminary draft of the clinical report. He was also involved in decision-making during the review process.
- Fatemeh Yazdi coordinated the research staff and progress of the review, performed data collection of observational studies, and performed data cleaning.
- Dr. Sal Kanji contributed to the development of the study protocol, interpretation of findings, and provided feedback on drafts of the clinical report.
- Dr. Kiran Rabheru contributed to the development of the study protocol, interpretation of findings, and provided feedback on drafts of the clinical report.
- Dr. Ferran Catala Lopez was a visiting trainee who contributed to preparation of data and figures for network meta-analyses, performance of network meta-analyses, and review of the clinical report.
- Justin Thielmann contributed to data collection from eligible observational studies.
- Dr. Andrea Cipriani (Oxford) is the leader of a group who have performed several meta-analyses of anti-depressant agents for the Cochrane Collaboration. He contributed RCT data to inform network meta-analyses for this report.
- Dr. David Moher contributed to the development of the study protocol, interpretation of findings, and provided feedback on drafts of the clinical report. He was also involved in decision-making during the review process.
- Drs. Dean Fergusson, Lise Bjerre, Andrea Tricco, and Sharon Strauss, contributed clinical and methodologic expertise to the protocol development for this work and provided critical review of the drafts of the clinical report.

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GLOSSARY	
Term	**Overview**
Bayesian Analysis	A statistical analysis conducted according to Bayesian statistical principles. It involves incorporation of existing information regarding the likelihood of an event (i.e., "priors") to estimate the likelihood based on additional information (i.e., posteriors").
Confidence interval	The interval in which a population parameter lies, based on a random sample of the population. The most commonly reported confidence interval is the 95% confidence interval.
Credible interval	In Bayesian statistics, an interval in which the actual value of a parameter of interest lies with a defined probability.
Deviance Information Criteria	A measure of model comparison and accuracy. Smaller values indicate a better-fitting model, with a difference greater than 4 or 5 indicating a much better-fitting model.
Meta-Analysis	Statistical synthesis of the results of individual studies that examine the same question to produce a single estimate of effect.
Network Meta-Analysis	An approach to evidence synthesis which allows for the combination of direct evidence (e.g. information from head-to-head trials of competing interventions) and indirect evidence (e.g. information from trials of a treatment against a control group such as placebo) to compare three or more treatments in a unified analysis.
Randomized Controlled Trial	A form of experiment in which participants are randomly allocated to receive one of the interventions under study. RCTs are commonly used to establish the efficacy and safety of medical interventions.
Serotonin Affinity	The ability of an antidepressant to to bind to functional serotonin transporters in osteoblasts, osteoclasts, an osteocytes. This potential mechanism raises the possibility that serotonin transporters may play a role in bone metabolism and that medications that affect these transporter systems may also affect bone metabolism and produce osteoporotic fractures.
Systematic Review	A literature review which is conducted to address a focused research question which searches for, identifies, appraises, and synthesizes studies of relevance to the question. A type of review commonly used for evidence based medicine.

ABBREVIATIONS USED IN THIS REPORT	
Abbreviation	**Full Terminology**
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Trycyclic Antidepressant
Non-SSRI/TCA	Other antidepressants studied which did not belong to the SSRI or TCA classes
DIC	Deviance Information Criteria
NMA	Network Meta-Analysis
BMD	Bone Mineral Density
CrI	Credible Interval

1. EXECUTIVE SUMMARY

1.1 Background

In 2012, 5.4% of Canadians aged 15 years or more had symptoms consistent with a mood disorder, and 4.7% were documented as having a major depressive episode. Pharmacotherapy with antidepressants including selective serotonin reuptake inhibitors (SSRIs), trycyclic antidepressants (TCAs), and other non-SSRI, non-TCA agents represent a long-standing component of treatment to manage patients' symptoms on a daily basis. Major depressive disorder is associated with increased morbidity and mortality and also with higher healthcare costs and more severe functional impairment with a large impact on workforce productivity. Currently in Canada, clinicians select from amongst more than a dozen agents to prescribe to their patients to manage their depression.

Recent systematic reviews of observational studies have suggested the presence of a potential association between use of antidepressant treatments and an increased risk of fractures. While suggestive, the observational studies are susceptible to a high risk of residual confounding and bias. As such, establishing a stronger causal link, and the underlying mechanism of this association currently remains unclear. One existing theory is based on the evidence of a pathway by which the serotonin system impacts bone structure. The Drug Safety and Effectiveness Network was approached to explore if the *serotonin affinity level* (i.e. a pharmacokinetic characteristic of drugs derived from a drug's measured dissociation constant which can be classified as low or moderate or high, and which is a measure of how strongly serotonin receptors in the body uptake the drug) of anti-depressant agents used by patients might explain a long-term association between antidepressant use and an increased risk of fractures .and adverse changes in bone mineral density. This is considered to be one part of a bi-modal relationship between antidepressant use and fractures. A second concern is a short-term effect of antidepressant agents wherein there may exist differential risks between drugs for the occurrence of outcomes which may cause patients to fall more frequently (e.g. dizziness, insomnia, blurred vision, hypotension, fatigue). A rigorous evaluation of the risks of these agents can also play an important role in evaluating the benefit/risk balance, thereby helping to guide treatment choices for patients suffering form depression. Given these knowledge gaps, this systematic review was designed to explore the hypothesized bi-modal association between the serotonin affinity level of different antidepressant agents and the occurrence of fractures, adverse changes in bone mineral density, and the occurrence of fall-related outcomes.

1.2 Research Questions

This systematic review was performed to address a DSEN query by addressing the following research questions:

1. Does the choice of antidepressant agent increase the risk of falls? Is there a differential risk in fall-related events between individual anti-depressant agents? (i.e.vision problems, hypotension, dizziness, insomnia, fatigue, drowsiness?)
2. Does the serotonin affinity level of currently available anti-depressant agents (i.e. SSRIs, TCAs, non-SSRI and TCA agents) impact the risk of fractures?
3. Does the serotonin affinity level of currently available anti-depressant agents (i.e. SSRIs, TCAs, non-SSRI and TCA agents) modify the risk of negative changes in bone mineral density?

1.3 Methods

We collaborated with an Oxford-based research group (authors of a previous network meta-analysis evaluating the efficacy and tolerability of antidepressants) to collect information from a large number of randomized controlled trials reporting on side effects of interest chosen for this review that could place patients at an increased risk of falls: vision problems, dizziness, hypotension, insomnia, fatigue, and drowsiness. A systematic literature search was designed and performed by an information specialist to identify relevant observational studies as outlined in an a priori designed study protocol. Observational studies performed in patients diagnosed with depression were selected for inclusion if they included relevant antidepressant treatments which could also be classified into serotonin affinity classes (low, moderate or high based on dissociation constant value), and if relevant outcomes [fractures, change in bone mineral density, falls] were reported.

Network meta-analyses of randomized controlled trials were used to explore the relative frequencies of fall-related outcomes; agent-level comparisons were the focus, with a secondary focus on drug class. Data from observational studies related to the occurrence of fractures and changes in bone mineral density were summarized and critically appraised with consideration of the serotonin affinity of agents studies. Given the presence of varied outcome reporting and clinical heterogeneity, no meta-analyses of these studies were performed.

1.4 Results

1.4.1 Summary of Key Clinical Findings

- A total of 202 randomized controlled trials meeting the eligibility criteria for our review were included. Amongst them, 62 reported on vision problems, 119 reported on insomnia, 98 reported on fatigue, 141 reported on dizziness, 46 reported on hypotension, and 145 reported on drowsiness. The collection of included trials was composed of trials from a series of systematic reviews for antidepressant pharmacotherapies across which studies were selected based on analogous criteria. Overall 194 (96%) trials were conducted in patients with moderate to severe depression, while the remaining studies were conducted in patients with severe depression.
- A total of 5 observational studies meeting the inclusion criteria for our review were located. These studies were heterogeneous in terms of outcomes studied, patient population characteristics, and approaches to statistical analysis.
- Based on network meta-analyses of actively controlled randomized trials, there is evidence to support an increased risk between certain therapies for the outcomes reviewed, many of which are current considerations in current clinical practice. Across most outcomes, all classes of agents showed increased risks of harms compared to placebo. There was a general lack of clinically relevant differences for comparisons between agents in the same class. The reputation of increased risk of TCAs was reflected for several agents in this class for several outcomes including dizziness. Several SSRIs and non-SSRI/TCA agents were associated with an increased risk of insomnia compared to TCAs, though SSRIs were associated with less drowsiness relative to the other classes.

For some outcomes, a high level of uncertainty as reflected by wide credible intervals led to the identification of few differences.

- Based on clinical review of observational studies, there is not sufficient or consistent evidence to confirm a long-term association between the serotonin affinity level of antidepressants and fracture risk or changes in BMD in the body.

1.5 Strengths and Limitations

- Our network meta-analyses to address the short-term association between anti-depressant agents and adverse effects which could contribute to the risk of falls were based on a large number of trials derived from a collaboration with an academic research group who has performed a series of systematic reviews of antidepressant agents, and thus represents a considerable amount of important imformation. However, the notable variation in the number of studies included for analysis for each outcome suggests considerable variability in the transparency of reporting of harms information. When dealing with rare harms outcomes, this can lead to wide uncertainty around summary estimates.
- As noted above, few observational studies meeting the inclusion criteria for our review were identified. Further research incorporating analyses whose primary focus is serotonin affinity are still needed.
- Many observational studies were excluded during screening because reports presented interventions at the antidepressant class level, and serotonin affinity level varies within classes of antidepressants. Thus, clear classifications in these studies with regard to exposure could not be made.
- Evaluation of the long-term association with serotonin affinity is limited by the quality of the included observational studies as a consequence of their residual confounding, as well as variation in the outcomes reported and manner in which exposure groups were defined.

1.6 Conclusions

- Based on findings from network meta-analyses of randomized trials of short duration, many important differences exist between antidepressant agents in terms of the risks of adverse effects which may lead to the occurrence of falls, however it is not known how often such harms may lead to falls. These differences are often associated with differences between drug classes. As was anticipated, no discernable association between the serotonin affinity of antidepressants and the occurrence of these harms was evident.
- Little observational information directly addressing the serotonin affinity level of antidepressants on fractures and bone mineral density was found. As serotonin affinity does not directly correlate to drug class and it was common to encounter studies only evaluating antidepressant users at the class level, the ability to draw interpretations based on serotonin affinity was limited. Findings from observational research did not identify a consistent pattern of findings for fracture risk or bone mineral density change in relation to serotonin affinity. Interpretations are also limited by the complications of confounding by patient age and depression severity. Future primary research studies focusing on affinity could potentially improve knowledge gaps in this area of study.

1. Clinical Background

Selective serotonin reuptake inhibitors (SSRIs) and other antidepressant pharmacotherapies (including trycyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and other agents) are frequently used drugs in Canada and the United States associated with notable increases in consumption in recent years.[1,2] In addition to management of depression, research suggests these agents are also becoming more commonly used for mild mood disorders and other indications including anxiety, migraine headaches, sleep disorders and fibromyalgia.[3-5] These drugs provide important benefits for patients regarding management of various symptoms. However, research over the past twenty years has suggested associations of antidepressant use with fractures and falls (and other side effects, such as dizziness, which may put patients at a risk of falls).[6-10] Fractures and falls represent a major source of costs, significant morbidity and mortality, particularly in the elderly population. Nursing home patients are cited as being as many as three times more likely to suffer falls than those living in the community.[11]

Schwan et al[12] noted the existence of a serotonin system in bone whose exact role is unclear, and several observational studies have suggested that an increased risk of fracture exists with antidepressant drugs. Bliziotes[13] highlights both pre-clinical and epidemiological data suggesting a deleterious regulatory effect of serotonin on bone and an increased risk of bone disease in SSRI-using patients. Warden and Haney[14] reviewed in-vitro and animal studies and concluded there is strong evidence that serotonin and serotonin transporter play a role within the skeleton. Haney and Warden[15] reviewed evidence from clinical studies, and suggest that while an answer is not yet clear, there is accruing evidence that serotonin pathways play an important role within bone. Preliminary literature scoping suggests existence of at least a small number of studies that have attempted to address the hypothesis of increased fracture risk and bone mineral density (BMD) change in association with increased serotonin affinity.[16-18]

There is reason to wonder whether there may be a potential bi-modal effect of antidepressant use on the risk of changes in bone mineral density and fractures due to both a long-term mechanism and a short-term mechanism. This may stem from a long-term increase in risk of fracture as a consequence of serotonin transporters being expressed in bone cells and playing a role in determination of both mass and strength, as well as a short-term increase in the risk of falls which may occur due to onset of symptoms like hypotension, vision problems, insomnia and dizziness. The former may stem from a particular pharmacokinetic characteristic of antidepressant agents, *serotonin affinity*, which varies both within and across traditional classes of antidepressant drugs. In the past such an association has been examined in relation to the occurrence of myocardial infarction.[19] Verdel et al[16] studied the role of antidepressants in fracture risk using a case-control design in depressed patients that looked at both osteoporotic and non-osteoporotic fractures, and found a trend for elevated risk of osteoporotic fracture as antidepressant affinity for serotonin increased from low to high.

To our knowledge, there is no existing review examining the incidence of potential fall-related harms of antidepressant agents or the association between bone mineral density changes, fracture risk and the serotonin affinity level for antidepressant therapies. The extent to which randomized controlled trials (RCTs) have data on the incidence of fractures or bone mineral density changes is unclear given that this is not a primary focus, and their short duration and data collection may

not have included such measures. If so, RCTs may remain helpful to identify side effects placing patients at a greater risk of falls in the short-term, while review of longer term observational research will be important to assess long-term incidence of fractures and changes in bone mineral density.

To address this research gap, we performed a systematic review incorporating data from both randomized and observational studies. We performed network meta-analyses of randomized trial data to address the short-term aspect of modified falls risk as a consequence of side effects of antidepressant agents, and subsequently generated a detailed overview of existing observational literature which has addressed the hypothesized association of the serotonin affinity of antidepressants with risk of fractures, falls and changes in bone mineral density in the population of depressed patients.

2. Research Questions

This review addressed the following safety concerns related to antidepressant use. In patients with depression:

a) Does the choice of antidepressant agent increase the risk of falls? Is there a differential risk in fall-related events between individual anti-depressant agents? (i.e.vision problems, hypotension, dizziness, insomnia, fatigue, drowsiness?)

b) Does the serotonin affinity level of currently available anti-depressant agents (i.e. SSRIs, TCAs, non-SSRI and TCA agents) impact the risk of fractures?

c) Does the serotonin affinity level of currently available anti-depressant agents (i.e. SSRIs, TCAs, non-SSRI and TCA agents) modify the risk of negative changes in bone mineral density?

3. Methods/Design

A protocol for this review was developed a priori by the research team and was peer reviewed by experts in the field. This protocol is available by request from the research team.

3.1 Overview of Approach to Answering the Research Questions

In this review, we have addressed question (a) by performing network meta-analyses of a large number of RCTs of antidepressant agents. Questions (b) and (c) were addressed using information from eligible observational studies. **Figure 1** outlines our approach to address the bi-modal association of interest in this systematic review. It was planned that two sets of evidence syntheses correlated with study design would be pursued as follows:

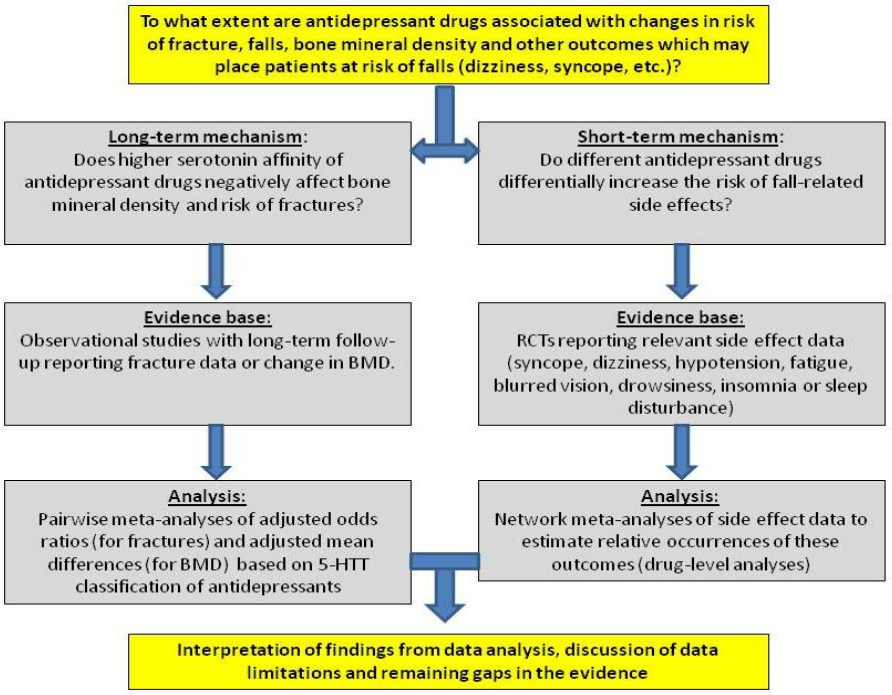
- ***Short-term mechanism (i.e. findings related to increases in risk of fall)***. Examination of previous systematic reviews and RCTs of antidepressants show that reporting of several adverse events which are potential predictors of falls (dizziness, hypotension, fatigue,

vision problems, insomnia, drowsiness) is common. Use of data to study potential differences in the risk of such side effects, and thus also potential shifts in the short-term risk of falls, can help to address the hypothesis that antidepressants may negatively impact patients' awareness; reduced awareness may be associated with both a greater number of falls and fractures. Pharmacologically, our clinical experts suggested there is no rationale to suggest an impact of serotonin affinity on the occurrence of these outcomes, as the titration of therapy takes weeks or months while it is widely believed that serotonin induced bone homeostasis requires considerably longer time to manifest. Instead, the increased risk of falls (and fragility fractures in the elderly) for some antidepressants is related to their their anticholinergic and antihistaminergic side effects such as sedation, orthosthatic hypotension and/or confusion.[20,21] However, to consider the possibility of such an association, in addition to performing our meta-analyses at the agent level, we have presented findings by both drug class (SSRIs, TCAs, non-SSRI/TCAs) and serotonin affinity level (low, moderate, or high as outlined later).

- ***Long-term mechanism (i.e. findings related to changes in BMD and fracture risk)***. RCTs of antidepressant therapies are generally of short duration (i.e. 6-12 weeks). Given the likely need for longer exposure to impact BMD to an identifiable extent, consideration of observational studies of depressed patients with longer-term follow-up to address this hypothesized mechanism of serotonin on bone was considered appropriate to assess for changes in bone mineral density and fractures. The impact of serotonin affinity was considered of particular importance in this hypothesized mechanism.

Sections 3.2 describes our approaches to identify literature relevant to the two mechanisms of interest for this review.

FIGURE 1: Overview of Analytic Strategy, Long-term and Short-term Associations



3.2 Identification of Relevant Literature

3.2.1 Identification of Randomized Controlled Trials for Network Meta-Analyses

To address the short-term mechanism, a primary search for RCTs was not performed as we collaborated with the authors of a 2009 network meta-analysis studying the effectiveness and tolerability of twelve antidepressants published in the Lancet[22]. These researchers are involved in the performance of Cochrane reviews assessing the benefits of pharmacotherapies for depression. They have been expanding their 2009 work to systematically review additional active antidepressant agents and incorporate placebo-controlled trials based on a priori developed Cochrane systematic review protocols which were designed to include consistent methodology across reviews for each antidepressant agent. In addition to their focus on effectiveness and tolerability, the research team collected detailed adverse events information relevant to the objectives of this systematic review, namely the gathering of data on the occurrence of six side effects of relevance to this work: vision problems (mainly defined to be blurred vision), hypotension, dizziness, insomnia, fatigue, and drowsiness. Our collaboration with this group led to access of detailed adverse event data for a total of 26 antidepressants from a total of 202 randomized trials, with the number of trials and agents with available data varying across outcomes due to reporting limitations. Their data is a collection of data from systematic reviews they performed which compared duloxetine, escitalopram, sertraline, fluoxetine, fluvoxamine, mirtazapine, milnacipran, reboxetine, paroxetine and venlafaxine against other active agents for depression. As part of the inclusion criteria for these reviews, two-armed studies involving placebo as one of the groups were not retained, however their team continues to add this data presently. Placebo groups from three armed studies were retained for full data collection.

3.2.1 Literature Search for Observational Studies to Address Long-term Mechanism

Peer reviewed literature searches[23] of Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (1946 to Aug 16 2012), Embase Classic+Embase (1947 to 2012 August 17), PsycINFO (1806 to August Week 2 2012), Cochrane Database of Systematic Reviews (Aug 17 2012) and Cochrane Central (August 17 2012) were performed by an information specialist to identify observational studies relevant to addressing the long-term mechanism outlined above. Prior to implementation of the search, the draft strategy was peer reviewed by a second information specialist according to PRESS criteria.[23] The Medline search strategy used has been provided in **Appendix 1**. Recent systematic reviews studying the association between antidepressant use and fracture risk[24-26] have also been described in our review of the observational evidence.

3.3 Study Selection Process and Criteria

Table 1 summarizes the inclusion criteria used for this review. RCTs of antidepressant agents gained from our collaboration were identified using a consistent set of inclusion criteria across reviews. For primary literature searching and screening for observational research, review of citations based on title, keywords and abstract (Level 1 screening) and full text articles (Level 2 screening) was carried out independently by two reviewers (FY, JT). Level 1 citations deemed

potentially relevant or lacking sufficient information to make a decision were carried forward to Level 2. Study selection was conducted using Distiller Systematic Review Software (DSR). Where consensus was not achieved following discussion, a third independent party (BH) was consulted to settle disagreements. The process of literature selection from the latter is reported using a flow diagram as recommended by the PRISMA statement.[27]

Table 1: Summary of Study Selection Criteria for Observational Studies		
Selection Criteria	**Short-term Mechanism**	**Long-term Mechanism**
Population	Adults with major depression according to standardised criteria (e.g. DSM). Concurrent diagnoses of another psychiatric disorder were not considered as exclusion criteria. Studies involving patients with concurrent primary diagnoses of Axis I/ II disorders or other serious medical illness were excluded.	Adults diagnosed with depression of any severity. Studies consisting of mixed populations were only included if depressed patients represent the predominant population or if subgroup data are available.
Intervention and Comparators	• SSRIs, TCAs, and non-SSRI/TCA agents were eligible, as were placebo and no treatment to maximize indirect information for network meta-analyses. • RCTs were only eligible if evaluating approved doses of antidepressants.	
Outcomes	Vision problems, hypotension, dizziness, insomnia, fatigue, drowsiness	Fractures; bone mineral density change (one or more body sites); falls.
Study Designs	RCTs	Observational studies including control groups; cross-sectional studies were excluded.

As the traditional drug classes (i.e. SSRIs, TCAs, non-SSRI/TCAs) contain agents of different serotonin affinity levels (for an overview of serotonin affinity see Section 3.5), studies classifying drug exposure only as, for example, 'TCA users/non-users', were not included unless it was feasible to get a strong sense of the drugs within each class that were used. Where studies included a list of agents for TCAs and nonSSRI/TCAs included, even if they could not all be fully distinguished as low or medium, the study was retained if it could be determined that no high affinity agents were included. This would still allow for a contrast of high versus low/medium affinity (i.e. SSRIs vs the others).

The validity of network meta-analyses is contingent upon meeting the assumptions of *homogeneity* (i.e. studies within each pairwise comparison in a treatment network are alike), *similarity* (i.e. studies across pairwise comparisons in a treatment network are alike), and *consistency* (i.e. findings from direct and indirect evidence are relatively similar).[28] We assessed the consistency assumption according to recommended statistical methods outlined in our description of statistical methods below. The assumptions of homogeneity and similarity require the inspection of clinical and methodologic aspects of the study designs and patient populations across included RCTs. The systematic reviews from which our RCTs were identified were conducted using homogenous protocols and our collaborators have provided assurance these studies are highly amenable to meta-analysis. As our collaborators are still generating the lengthy information tables describing the patient populations, study methods and associated risk of bias scores, we will modify this report to include this information DSEN once it is made available to us. As such, more detailed overviews of patient population characteristics and study methods/risk of bias have not been reported at this time.

3.4 Data Extraction and Risk of Bias Assessment

Randomized Studies

Primary data collection of randomized studies was performed independently by two reviewers from our collaborating group from Oxford. Risk of Bias evaluation of included RCTs is based upon the Cochrane Risk of Bias Scale.[29] Summary tables of study characteristics and risk of bias findings are still being completed by the collaborating group and will be provided to DSEN once complete. This report will be updated with both an appendix of this information as well as relevant updates to the main text of the report when related sensitivity analyses are performed.

Observational Studies

Primary data collection of included observational studies was performed independently by two reviewers (FY, JT) using a standardized, pilot tested electronic data collection form. Distiller SR software was used to compare collected data for accuracy and agreement, with disagreements being settled by discussion. For assessing risk of bias, observational studies were assessed using the Downs and Black scale,[30] a tool which can be used to assess the quality of non-randomized studies. A limiting factor of observational work in the study of antidepressant use and fractures has been disentangling the associations between age, depression level, bone mineral density, medication use, the rate of falls, and the impact of potential depression-inducing comorbidities on fracture incidence.[12] Residual confounding was thus felt to reflect a critical obstacle in this review.[13,24,31] In addition to study design information and outcomes data, collection of other data to evaluate the potential effect of drugs on fracture risk and changes in bone mineral density was planned. This included the following: duration, patterns and compliance of antidepressant use; patient co-morbidities; co-medications (e.g. blood pressure lowering agents, antiarrhythmic agents, NSAIDs, anti-epileptic agents, mood stabilizers, osteoporosis agents, thyroid medications, etc), and other such information. Gathering this information allowed assessment of comparability of populations across studies, the conduct of subgroup analyses, and assessment of the degree of residual confounding of adjusted measures of association.

3.5 Serotonin Affinity of Antidepressant Agents

To address hypotheses based on serotonin affinity, drugs were categorized based on their degree of serotonin affinity in analyses studying the occurrence of fractures and bone mineral density in long-term studies. **Table 2** presents the classifications based on drugs' dissociation constants which are based on the Psychoactive Drug Screening Program and which were used in a previous research study.[16]

Table 2: Categorizations of Antidepressants by Serotonin Affinity

Agent, Classified by Traditional Drug Class	Classification based on affinity for 5-HTT		
	High (K_i<10nM)	Medium (K_i 10-1000nM)	Low (K_i>1000nM)
SSRIs			
Citalopram	X		
Escitalopram	X		
Fluoxetine	X		
Fluvoxamine	X		
Paroxetine	X		
Sertraline	X		
TCAs			
Amitriptyline		X	
Clomipramine	X		
Desipramine		X	
Dibenzepin			X
Dosulepin	X		
Doxepin		X	
Imipramine	X		
Nortriptyline		X	
Reboxetine		X	
Trimipramine		X	
Non-SSRI/TCAs			
Amoxapine		X	
Bupropion			X
Desvenlafaxine		X	
Duloxetine	X		
Maprotiline			X
Milnacipran	X		
Mianserin			X
Mirtazapine			X
Nefazodone		X	
Tranylcypromine			X
Trazodone		X	
Venlafaxine		X	

K_i=affinity constant; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

3.6 Data Analysis

3.6.1 Sequential Approach to Summary of the Evidence

Findings from observational studies related to the above described long-term mechanism of interest are summarized separately from findings from review of randomized trial data related to the corresponding short-term mechanism of interest. In both cases, we begin with a narrative overview of the amount of literature available as well as of the included studies focused on discussion of the degree of clinical and methodologic homogeneity present. This includes overview of findings from risk of bias assessments, as well as other important differences between studies in terms of patient characteristics, study design, statistical analysis, and so forth.

To address the short-term mechanism of interest based on RCTs, network meta-analyses were carried out for each clinical outcome placing patients at an increased risk of falls: vision problems, hypotension, dizziness, insomnia, fatigue, and drowsiness. Network meta-analysis is an approach to evidence synthesis which allows for the combination of *direct* and *indirect* evidence to compare three or more treatments in a unified analysis.[32,33] Indirect comparisons between treatments A and B based on a common comparator C where no trials of A versus B exist (i.e. no direct evidence), but trials of A versus C and B versus C exist (i.e. indirect evidence) were originally proposed by Bucher et al,[34] and Lumley[32] and Lu and Ades[33] subsequently developed extensions of this methodology. In addition to estimating all pairwise comparisons between treatments in a network, this technique can also be used to estimate probabilities of treatment of superiority to rank the treatments. Prior to performing network meta-analyses, we first considered pairwise random effects meta-analyses of all data performed from a frequentist approach using Comprehensive Meta-Analyst version 2.2 (Biostat Inc, New Jersey, USA; www.meta-analysis.com) in order to explore for heterogeneity within different pairwise comparisons. The following section provides a more detailed description of our approach to fitting network meta-analysis models.

With regard to the long-term mechanism, findings from observational literature are summarized narratively, and tables and figures are used to present study-level estimates of interest to visualize the degree of consistency of findings between studies for each outcome measure of interest. For reasons of heterogeneity in terms of both study characteristics and outcomes, no formal meta-analyses of observational studies were performed.

3.6.2 Statistical Methods for Network Meta-Analysis

We performed Bayesian network meta-analyses as outlined by Dias et al using a common heterogeneity parameter to synthesize information for each outcome under study.[35] Both fixed and random effects models were fit based on burn-in iterations of 30,000 or more, and parameter estimates were based on additional samples of 30,000 or more. Placebo was chosen as a reference group for all meta-analyses. Model fit assessment was performed by comparing the total number of unconstrained data points (i.e. the total # of treatment arms across studies included in each analysis) to the total residual deviance for each analysis, while comparisons between fixed and random effects models were based on deviance information criteria (DIC); a

difference of 5 points or more was considered an important difference between models, where a smaller value suggests improved model fit. We based our interpretations on random effects models unless an important difference in model fit was found. All pairwise comparisons between competing interventions were expressed as odds ratios (OR) with corresponding 95% credible intervals (CrI). *Consistency* of findings between direct and indirect information is important to assess in network meta-analyses to ensure validity of combining these sources of information to inform treatment comparisons; consistency of results from direct and indirect information in the networks under study was evaluated using established techniques[36] by comparison of DIC from an inconsistency NMA model with the DIC from the corresponding consistency NMA model, as well as by comparison of residuals generated from these two models using a scatterplot to assess for differences. As recommended elsewhere,[35] trials with zero events in a treatment arms were modified by adding 0.5 events to the numerator of each trial arm and 1 subject to the denominator of each trial arm. In addition to estimation of odds ratios, we also estimated average treatment rankings, probabilities of superiority for each treatment, and Surface Under the Cumulative Ranking (SUCRA) probabilities[37] to explore the risks of each treatment. All network meta-analyses were performed using Winbugs software version 1.4.3 (MRC Biostatistics Unit). Vague prior distributions were assigned for parameters throughout the models for meta-analysis to enable the data to drive findings, and we assessed convergence of all models by fitting multiple chains and exploring Gelman Rubin trace plots. Network diagrams summarizing the geometry of evidence available for each clinical outcome were generated using Stata 13.0 software.[38]

As a sensitivity analysis to address potential heterogeneity in the control group risk of side effects across studies, we also fit network meta-regrssion meta-analyses adjusting for control group risk.[39] Comparison of the fit of these models against our primary analyses was also performed using DIC criteria. We have noted any important differences in our findings.

3.6.3 Reporting of Findings from Analysis

Graphical and numeric presentations of findings are provided to convey the findings of our work. For network meta-analyses, we have included the following:

- ***Treatment network diagrams*** which show the geometry of available evidence for all possible treatment comparisons in terms of the included treatments with available data, the numbers of studies supporting each comparison of treatments, and the included numbers of subjects.
- ***Forest plots*** which provide summary point estimates and corresponding 95% credible intervals for all pairwise comparisons against our reference group, placebo, estimated using network meta-analysis. In this review, odds ratios greater than 1 for comparisons against placebo suggest an increased risk of harms. In these plots we have grouped agents by drug class and have used color to identify agents of different serotonin affinity levels to explore for any associations with side effect risk.
- ***League tables*** (sometimes also called staircase diagrams) which summarize all possible comparisons between treatments in the network. In these figures we have colored agents according to drug class (green=SSRIs, orange=TCAs, purple=non-SSRI/TCA) and used a

combination of yellow coloring and bolded font to highlight statistically significant differences.

- ***SUCRA values and median treatment rankings*** which provide an additional summary measure of treatment risk which can be considered as a secondary quantity to support pairwise comparisons presented in the above forest plots and league tables. In this review, SUCRA values (range 0-100%) nearer 100% and treatment rankings nearer 1 suggest a lower risk of harms. We note that these quantities should not be considered in isolation to draw findings based on ongoing methods research which has addressed some concerns with such an approach.[40]
- In addition to providing the above information through tables and figures, we have also provided associated brief text summaries to guide interpretation regarding the differences that were identified.

For network meta-analyses, we have reported findings only for antidepressants available for the treatment of depression in Canada as identified from inspection of the Ontario Drug Benefit Plan Formulary Listing and the British Columbia Drug Benefit Plan Formulary Listing. Thus, while our network meta-analyses have included additional treatments where data was available (these agents included amineptine, dothiepine, hypericum, mianserin, milnacipran, nefazodone, pramipexole, reboxetine, and tianeptine) and full results will be included in peer reviewed manuscripts, in this systematic review we report only on the following agents:

- **SSRIs**: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.
- **TCAs**: amitriptyline, clomipramine, desipramine, doxepin, imipramine, nortriptyline
- **Non-SSRI/TCAs**: desvenlafaxine, duloxetine, mirtazapine, moclobemide, maprotiline, venlafaxine.
- Reviews for bupropion and trazodone were not available from our collaborating group.

Findings from observational research are described primarily in text format with accompanying tables and figures to summarize key messages.

4. Results

We present first our findings addressing the short-term mechanism of interest, namely our results from meta-analyses comparing the occurrence of vision problems, hypotension, dizziness, insomnia, fatigue, and drowsiness. Findings from our review of observational literature and variations in the occurrence of falls, fractures and changes in bone mineral density are presented afterward beginning in Section 4.2.

4.1 Overview of Findings: Risks of Fall-Related Side Effects from Randomized Controlled Trials

4.1.1 Availability of Randomized Evidence

A total of 202 RCTs were included in the analyses, with the number of studies and patients varying according to the outcome of interest (see **Table 3**). As our database of RCTs was formed based on existing published systematic reviews for a large number of treatments, we have not

reported a summary flow diagram for study selection. Included trials were published across a broad time frame, with totals of 7 (3.4%), 22 (10.9%), 36 (17.8%), 52 (25.7%), 38 (18.8%), and 33 (16.3%) studies published before 1985, between 1985-89, between 1990-94, between 1995-99, between 2000-2004 and between 2005-2011, respectively (14 studies (6.9%) were unpublished). A total of 194 (96.0%) studies enrolled participants with moderate to severe depression, while the remaining 8 (4.0%) were in participants with severe depression. The median sample size was 120 subjects (range 23-684), and industry funding of at least one study arm was present in 172/202=85.1% of included trials. As noted above, the number of included studies with available data varied across outcomes from 46 to 145, demonstrating considerable non-uniform reporting of harms and a potential corresponding bias. **Table 3** also demonstrates that the number of agents included in our treatment networks varied as a consequence of this reporting disparity.

Table 3: Summary of Numbers of Events and Patients Across Outcomes for Meta-Analyses

Class	Vision Problems		Dizziness		Hypotension		Insomnia		Fatigue		Drowsiness	
Agent	**n**	**N**	**n**	**N**	**N**	**N**	**n**	**N**	**n**	**N`**	**n**	**N**
Placebo	37	1362	179	3314	18	689	224	3637	154	2953	272	4079
SSRIs												
Citalopram	8	353	47	1133	18	517	101	1458	70	1331	85	1490
Escitalopram	9	418	134	2152	3	316	246	2695	164	2360	205	2798
Fluoxetine	75	1159	272	2892	35	779	325	2817	126	1487	271	3060
Fluvoxamine	28	349	109	1274	30	572	151	874	68	674	267	1362
Paroxetine	39	665	280	3037	12	482	264	1971	240	2299	342	2787
Sertraline	75	1126	284	2492	15	217	435	2657	259	2016	241	2786
TCAs												
Amineptine	NA	NA	2	20	NA	NA	19	20	0	21	1	20
Amitriptyline	174	1264	298	1796	81	788	45	878	123	1298	428	1753
Clomipramine	9	57	90	784	44	152	23	251	35	222	27	148
Desipramine	15	89	29	119	4	31	12	89	14	89	14	89
Dothiepine	7	174	8	195	NA	NA	1	81	NA	NA	20	226
Doxepin	NA	NA	6	72	NA	NA	NA	NA	NA	NA	19	72
Imipramine	41	284	318	1314	39	453	105	1081	5	516	258	1174
Nortriptyline	29	62	37	166	9	24	2	24	NA	NA	30	166
Reboxetine	3	84	18	240	24	235	27	260	12	84	13	105
Tianeptine	1	102	NA	NA	NA	NA	NA	NA	NA	NA	5	102
Non-SSRI / TCAs												
Desvenlafaxine	13	298	NA	NA	NA	NA	37	298	27	298	23	157
Duloxetine	52	1295	249	2189	2	175	258	2108	183	2347	207	2209
Hypericum	6	45	13	113	NA	NA	30	90	19	45	8	45
Maprotiline	NA	NA	12	21	NA	NA	NA	NA	NA	NA	NA	NA
Mianserin	NA	NA	5	28	0	96	1	95	NA	NA	22	95
Milnacipran	24	183	71	598	62	583	46	882	5	85	30	629
Mirtazapine	67	832	219	1968	17	540	64	909	219	1820	416	1975
Moclobemide	5	94	12	118	NA	NA	45	193	9	149	13	162
Nefazodone	9	78	47	179	NA	NA	27	179	36	179	37	179
Pramipexole	NA	NA	20	104	NA	NA	14	104	11	104	22	104
Venlafaxine	45	641	256	1774	10	158	215	1808	159	1562	132	1606
Total # RCTs	62 RCTs		141 RCTs		46 RCTs		119 RCTs		98 RCTs		145 RCTs	
Total patients	775	11,111	3,048	28,373	423	6,807	2,721	25,459	1,992	21,939	3,412	29,378

Table 3. Summary of the numbers of events and patients included for analyses of each outcome of interest. Numbers are aggregated across included studies. Totals for agents of interest based on funding status in Canada as well as other agents included in the treatment network are provided. 'NA' is indicated in cases where there were no studies with the associated treatment reporting data for that particular outcome measure.

4.1.2 Results from Pairwise Meta-Analyses

Prior to pursuing network meta-analyses, we performed pairwise meta-analyses for all treatment comparisons in our network to explore for statistical heterogeneity. We have included these results in **Appendix 2**. We do not comment on their findings in our main text other than to note that we did not detect important statistical heterogeneity where a meta-analysis of multiple studies was possible (considered to be an I^2 value of more than 50%)

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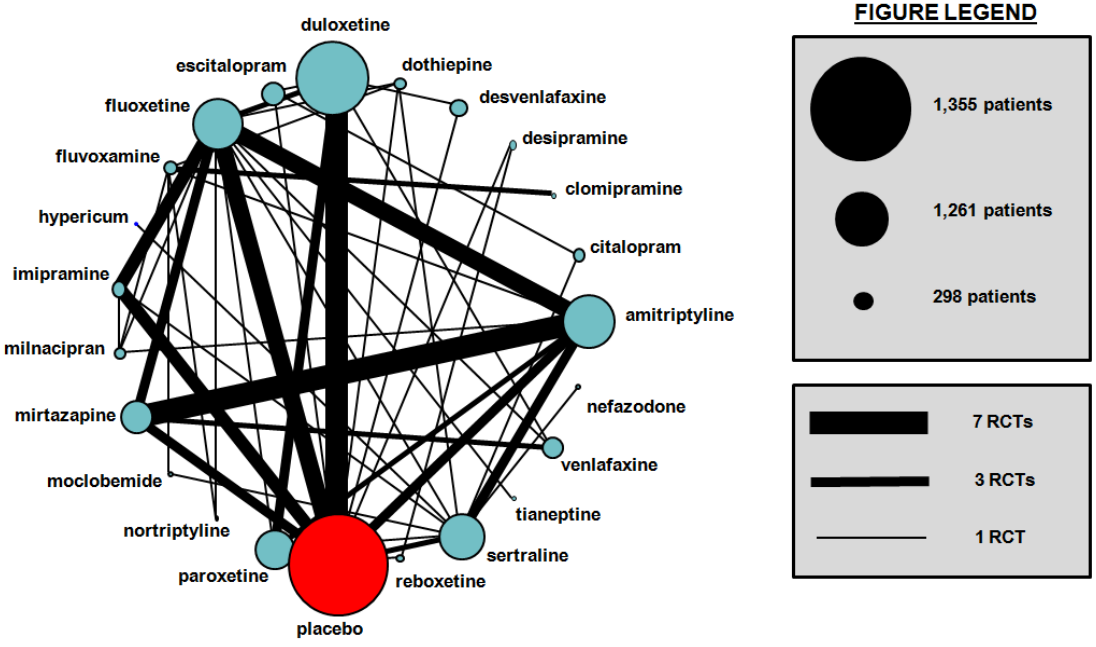
4.1.3 Results from Network Meta-Analysis

4.1.3.1 Findings, Vision Problems

Figure 2 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs.[41-97] A total of 19 interventions were associated with RCTs that reported data on vision problems, with the numbers of trials and randomized patients per treatment ranging from 1 – 22 (median 3, IQR 2-10) and 45 – 1,362 (median 353, IQR 134-979), respectively. Comparisons between amitriptyline and mirtazapine, placebo and duloxetine, fluoxetine and amitriptyline, and fluoxetine and placebo were most prevalent. Many comparisons of treatments were informed by single trials, and many comparisons have not been evaluated in head-to-head RCTs.

Figure 2 - Network Diagram, Vision Problems:
Including Data from 62 studies, 11,111 participants (775 events)

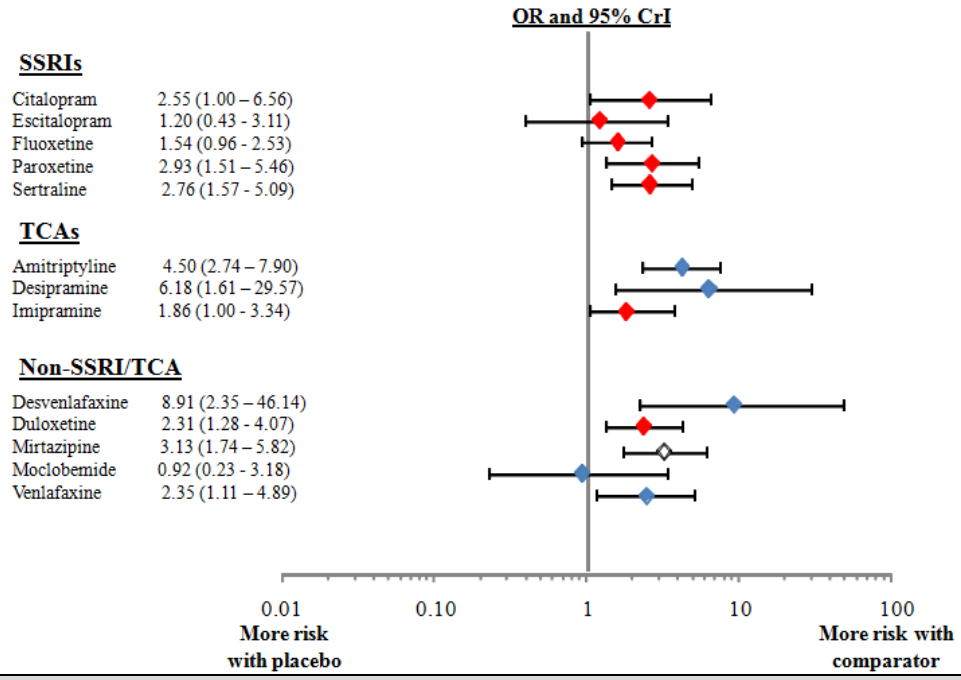


Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Both fixed and random effects models were reasonable fits to the data (residual deviances of 157.5 and 137.3 compared to 140 unconstrained data points); random effects was chosen as the primary model (DIC 653.4, compared to 648.6 for fixed effects). **Figure 3** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while the league table in **Figure 4** summarizes all possible pairwise comparisons between included regimens. Our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be noted from **Figure 3**:
    - Amongst SSRIs, three of five agents (citalopram, paroxetine, sertraline) represented in the treatment network showed a significant increase in the number of participants experiencing vision problems (range of ORs 2.55-2.93). Vision problems for those taking fluoxetine appears possibly associated with an increased risk (OR 1.54, 95% CrI 0.96-2.53). Escitalopram was not associated with an estimate suggesting significantly increased risk.
    - Amongst TCAs, all three agents showed a significant increase in the number of patients experiencing vision problems (range of ORs 1.98-5.74). There was considerable uncertainty associated with the comparison for desipramine.
    - Amongst non-SSRIs/TCAs, four of five agents (desvenlafaxine, duloxetine, mirtazapine, venlafaxine) were associated with an increased risk (range of ORs 2.31-8.91). Moclobemide showed no evidence of increased risk.
    - Based on the pattern of estimates seen when considering the agents by serotonin affinity grouping (red=high, blue=moderate, white=low), we did not observe a relationship between affinity level and the occurrence of vision problems.

Figure 3: Forest Plot of Comparisons versus Placebo, Vision Problems – Summary Odds Ratios and Credible Intervals



Summary estimates from network meta-analysis comparing the frequency of blurred vision. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

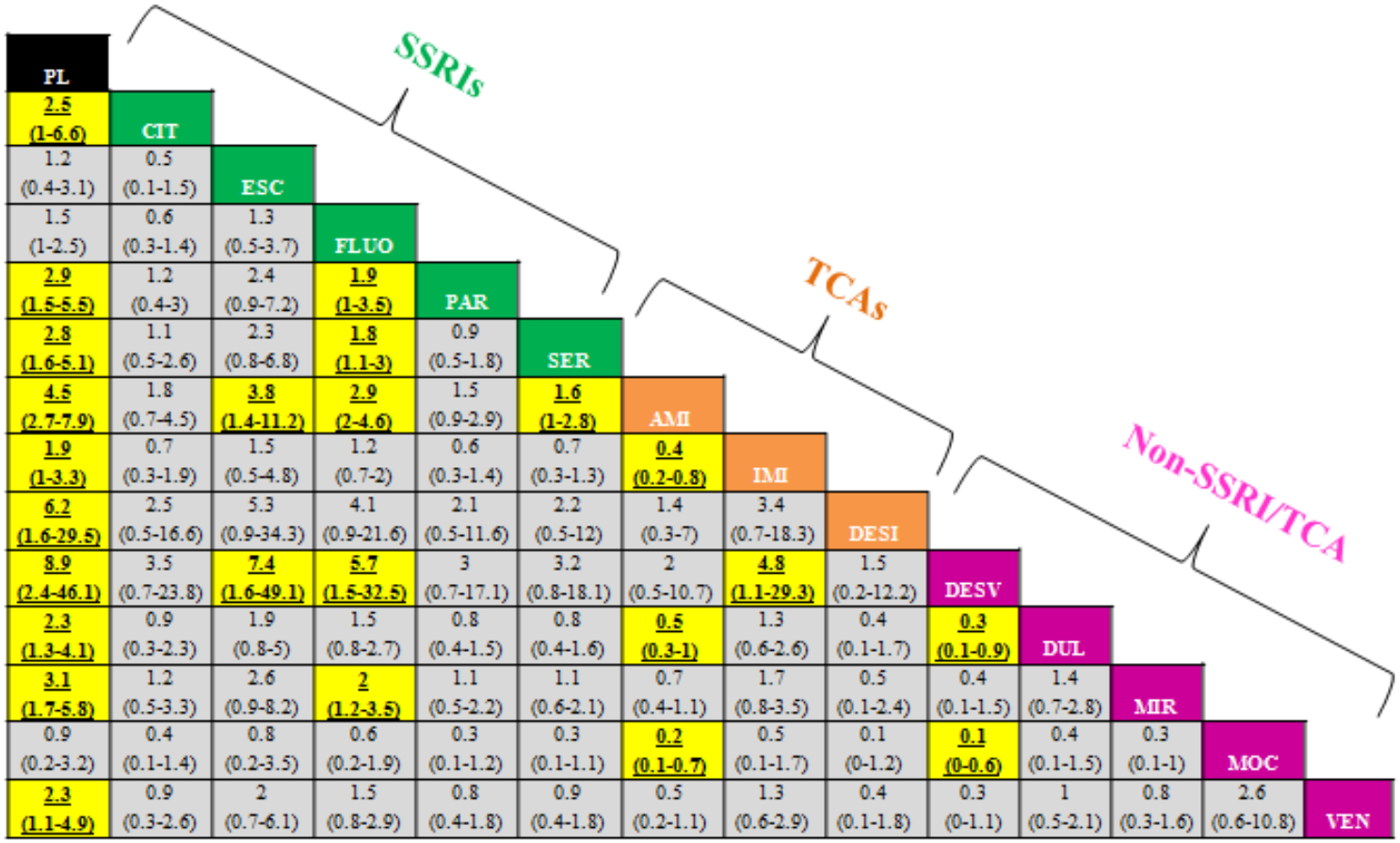
- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class generated from network meta-analysis, **Figure 4** shows the following:

    - Amongst SSRIs, comparisons involving these agents generally showed either an inconclusive result (i.e. a 95% credible interval crossing 1.0, indicating a possible null difference) or that SSRIs were associated with a lower risk of vision problems compared with TCAs or non-SSRI/TCA agents. Comparisons involving escitalopram, paroxetine, sertraline, and citalopram were associated with wide credible intervals and thus were mostly inconclusive, while fluoxetine showed a lower risk of vision problems relative to desvenlafaxine, mirtazapine, and amitriptyline. Regarding comparisons within SSRIs, fluoxetine was associated with fewer vision problems when compared to paroxetine and sertraline.

    - Amongst TCAs, pairwise comparisons involving amitriptyline consistently showed an increased risk of vision problems, including when compared against imipramine (range of ORs suggesting increased risk 1.67-5.0). Imipramine was associated with fewer vision problems than desvenlafaxine, while all comparisons involving desipramine were inconclusive.

    - Amongst non-SSRI/TCA agents, a mix of significant increases and decreases in risk was observed. Desvenlafaxine showed an increase in the risk of vision problems (versus the SSRIs escitalopram and citalopram, as well as versus the TCA imipramine), as did mirtazapine (versus fluoxetine). Fewer reports of patients with vision problems were associated with duloxetine compared to amitriptyline, with moclobemide compared to both desvenlafaxine and amitriptyline, and venlafaxine compared to amitriptyline. Regarding comparisons between the different non-SSRI/TCA agents, desvenlafaxine was associated with a greater risk than duloxetine and moclobemide.

Figure 4: League Table Summary of Pairwise Comparisons, Vision Problems



PL	CIT	ESC	FLUO	PAR	SER	AMI	IMI	DESI	DESV	DUL	MIR	MOC	VEN
2.5 (1-6.6)													
1.2 (0.4-3.1)	0.5 (0.1-1.5)												
1.5 (1-2.5)	0.6 (0.3-1.4)	1.3 (0.5-3.7)											
2.9 (1.5-5.5)	1.2 (0.4-3)	2.4 (0.9-7.2)	**1.9 (1-3.5)**										
2.8 (1.6-5.1)	1.1 (0.5-2.6)	2.3 (0.8-6.8)	**1.8 (1.1-3)**	0.9 (0.5-1.8)									
4.5 (2.7-7.9)	1.8 (0.7-4.5)	**3.8 (1.4-11.2)**	**2.9 (2-4.6)**	1.5 (0.9-2.9)	**1.6 (1-2.8)**								
1.9 (1-3.3)	0.7 (0.3-1.9)	1.5 (0.5-4.8)	1.2 (0.7-2)	0.6 (0.3-1.4)	0.7 (0.3-1.3)	**0.4 (0.2-0.8)**							
6.2 (1.6-29.5)	2.5 (0.5-16.6)	5.3 (0.9-34.3)	4.1 (0.9-21.6)	2.1 (0.5-11.6)	2.2 (0.5-12)	1.4 (0.3-7)	3.4 (0.7-18.3)						
8.9 (2.4-46.1)	3.5 (0.7-23.8)	**7.4 (1.6-49.1)**	**5.7 (1.5-32.5)**	3 (0.7-17.1)	3.2 (0.8-18.1)	2 (0.5-10.7)	**4.8 (1.1-29.3)**	1.5 (0.2-12.2)					
2.3 (1.3-4.1)	0.9 (0.3-2.3)	1.9 (0.8-5)	1.5 (0.8-2.7)	0.8 (0.4-1.5)	0.8 (0.4-1.6)	**0.5 (0.3-1)**	1.3 (0.6-2.6)	0.4 (0.1-1.7)	**0.3 (0.1-0.9)**				
3.1 (1.7-5.8)	1.2 (0.5-3.3)	2.6 (0.9-8.2)	**2 (1.2-3.5)**	1.1 (0.5-2.2)	1.1 (0.6-2.1)	0.7 (0.4-1.1)	1.7 (0.8-3.5)	0.5 (0.1-2.4)	0.4 (0.1-1.5)	1.4 (0.7-2.8)			
0.9 (0.2-3.2)	0.4 (0.1-1.4)	0.8 (0.2-3.5)	0.6 (0.2-1.9)	0.3 (0.1-1.2)	0.3 (0.1-1.1)	**0.2 (0.1-0.7)**	0.5 (0.1-1.7)	0.1 (0-1.2)	**0.1 (0-0.6)**	0.4 (0.1-1.5)	0.3 (0.1-1)		
2.3 (1.1-4.9)	0.9 (0.3-2.6)	2 (0.7-6.1)	1.5 (0.8-2.9)	0.8 (0.4-1.8)	0.9 (0.4-1.8)	0.5 (0.2-1.1)	1.3 (0.6-2.9)	0.4 (0.1-1.8)	0.3 (0-1.1)	1 (0.5-2.1)	0.8 (0.3-1.6)	2.6 (0.6-10.8)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of vision problems with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and median treatment rankings***. **Table 4** presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons, suggesting the lowest risk of vision issues with placebo. SUCRA values and median treatment rankings of SSRIs were qualitatively better compared to those for both TCAs and non-SSRIs/TCAs. Moclobemide, escitalopram, and fluoxetine appeared to be associated with the next lowest risk of vision problems after placebo amongst the treatments of interest.

Table 4:
Summary of SUCRA and median ranks, vision problems

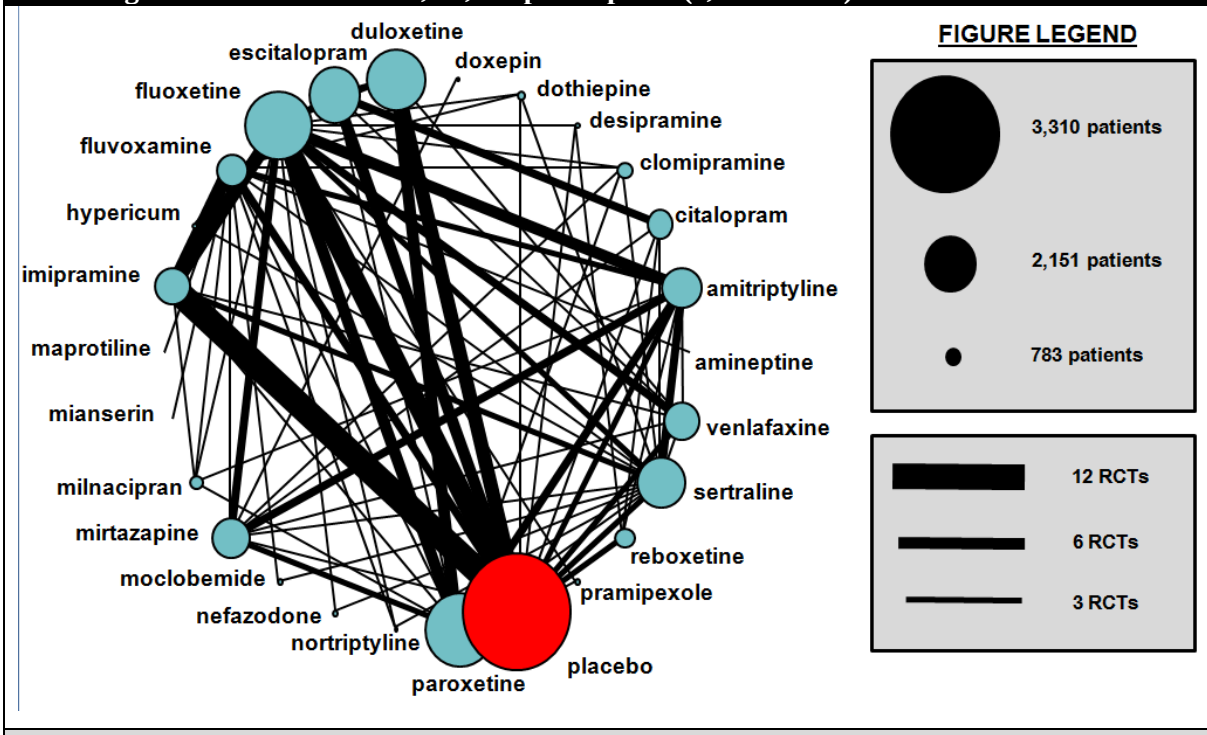
Treatment	SUCRA (%)	Median rank (95% CrI)
Placebo	88.0%	3 (1-6)
SSRIs		
Escitalopram	79.1%	4 (1-12)
Fluoxetine	72.1%	6 (3-9)
Citalopram	45.7%	11 (4-18)
Sertraline	40.6%	12 (7-16)
Paroxetine	37.7%	12 (7-17)
TCAs		
Imipramine	62.2%	8 (4-13)
Desipramine	16.2%	18 (6-19)
Amitriptyline	16.1%	16 (13-18)
Non-SSRI/TCA		
Moclobemide	84.8%	3 (1-12)
Duloxetine	50.7%	10 (5-15)
Venlafaxine	49.7%	10 (4-16)
Mirtazapine	34.4%	13 (8-17)
Desvenlafaxine	7.8%	19 (10-19)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of vision problems.

4.1.3.2 Findings, Dizziness

Figure 5 presents a network diagram summarizing pairwise comparisons that were performed within our set of included RCTs.[41,42,44-47,49,53-56,58,59,61-71,73-75,78,80-83,85-88,90-94,96-185] A total of 26 interventions were associated with RCTs that reported data on dizziness, with the numbers of trials and randomized patients per treatment ranging from 1–45 (median 6, IQR 2-22) and 20–3,314 (median 691, IQR 118-1,925), respectively. Comparisons between imipramine with placebo and fluoxetine with placebo were most prevalent. Several comparisons between treatments were again informed by single small trials, and a number of comparisons were not informed by existing RCTs.

Figure 5 - Network Diagram, Dizziness:
Including Data from 141 studies, 28,373 participants (3,048 events)



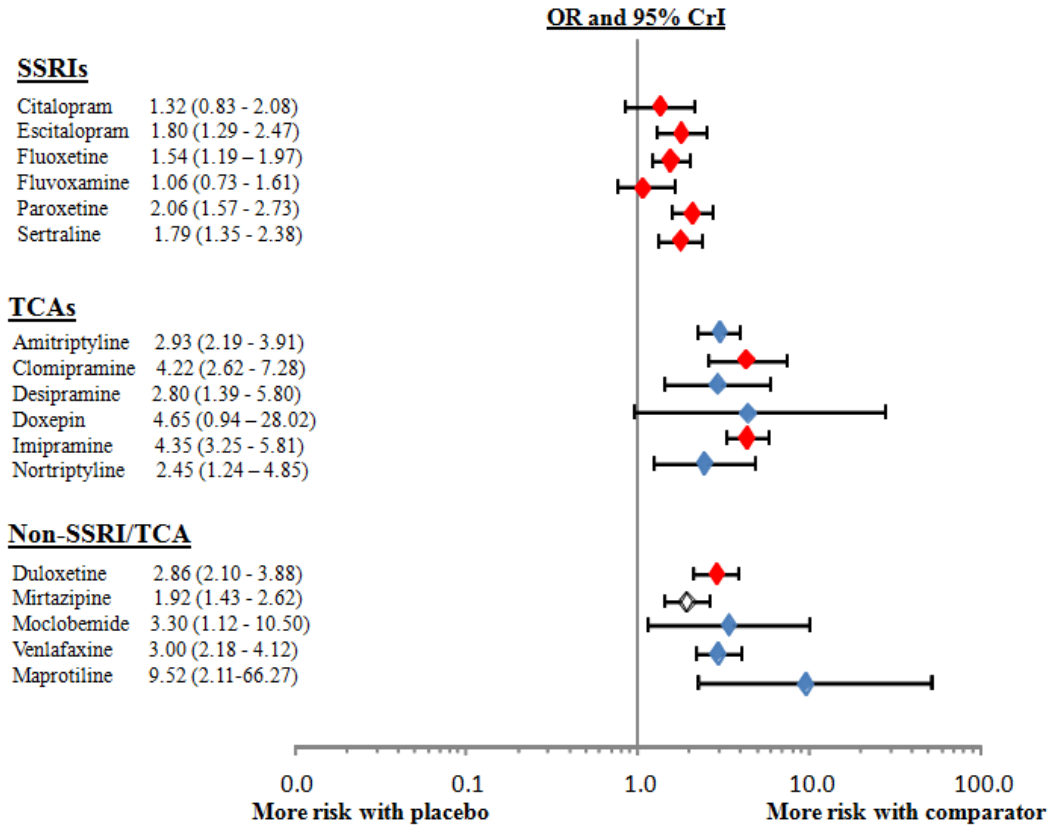
Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Both fixed and random effects models were reasonable fits to the data (residual deviances of 356.7 and 315.2 compared to 328 unconstrained data points; random effects was chosen as the primary model (DIC 1623.3, compared to 1621.2 for fixed effects). **Figure 6** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while **Figure 7** summarizes all pairwise comparisons between interventions. Our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be observed from **Figure 6**.

    - Regarding SSRIs, all agents except fluvoxamine (OR 1.06, 95% CrI 0.73-1.61) were associated with a greater risk of dizziness (range of ORs 1.32-2.06).
    - Regarding TCAs, all agents but doxepin (OR 4.65, 95% CrI 0.94-28.02) were associated with an increased risk (range of ORs 2.45-4.35). Doxepin was included in just one small RCT.
    - Regarding non-SSRI/TCAs, all agents were associated with an increased risk (range of ORs 1.92-9.52).
    - Based on the pattern of summary estimates seen when considering the agents by serotonin affinity grouping (red=high, blue=moderate, white=low), there doesn't appear to be clear evidence of a relationship between serotonin affinity level and the occurrence of dizziness.

Figure 6: Forest Plot of Comparisons versus Placebo, Dizziness – Summary Odds Ratios and Credible Intervals



Summary estimates from network meta-analysis comparing the frequency of dizziness. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

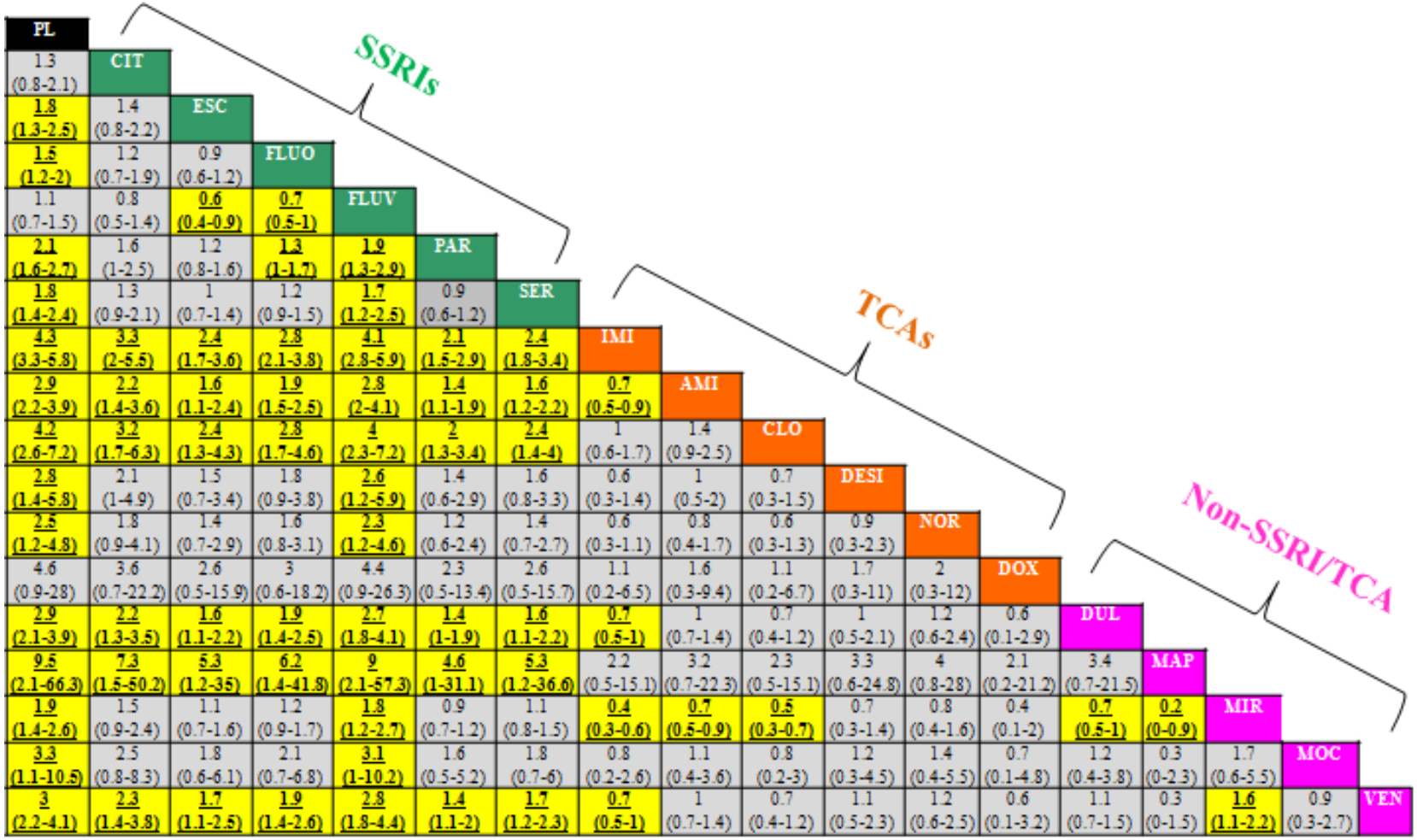
- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class, **Figure 7** shows the following:

    - Regarding SSRIs, pairwise comparisons with TCAs found that all six agents were associated with a lower risk of dizziness compared to amitriptyline, imipramine and clomipramine. Fluvoxamine was also associated with a lower risk when compared to desipramine and nortriptyline, and all remaining comparisons between SSRIs and TCAs followed a similar trend but were associated with inconclusive credible intervals. Pairwise comparisons with non-SSRI/TCAs showed a reduced risk compared to duloxetine, venlafaxine and maprotiline (the latter were associated with little direct evidence and very wide credible intervals). Comparisons between SSRIs identified increased risks of dizziness with escitalopram, fluoxetine, and paroxetine compared to fluvoxamine, as well as paroxetine compared to fluoxetine.

    - Regarding TCAs, comparisons with non-SSRI/TCAs suggest that amitriptyline, imipramine and clomipramine are associated with a greater risk of dizziness than mirtazapine. Imipramine was also associated with an increased risk when compared to venlafaxine. The only difference achieving statistical significance when comparing agents within the TCA class suggests an increased risk with imipramine compared to amitriptyline.

    - Regarding non-SSRI/TCAs, comparisons between interventions in this class suggested an increased risk of dizziness with duloxetine, maprotiline and venlafaxine when compared to mirtazapine; all other comparisons were inconclusive.

Figure 7: League Table Summary of Pairwise Comparisons, Dizziness



PL																
1.3 (0.8-2.1)	CIT															
1.8 (1.3-2.5)	1.4 (0.8-2.2)	ESC														
1.5 (1.2-2)	1.2 (0.7-1.9)	0.9 (0.6-1.2)	FLUO													
1.1 (0.7-1.5)	0.8 (0.5-1.4)	**0.6 (0.4-0.9)**	**0.7 (0.5-1)**	FLUV												
2.1 (1.6-2.7)	1.6 (1-2.5)	1.2 (0.8-1.6)	**1.3 (1-1.7)**	**1.9 (1.3-2.9)**	PAR											
1.8 (1.4-2.4)	1.3 (0.9-2.1)	1 (0.7-1.4)	1.2 (0.9-1.5)	**1.7 (1.2-2.5)**	0.9 (0.6-1.2)	SER										
4.3 (3.3-5.8)	**3.3 (2-5.5)**	**2.4 (1.7-3.6)**	**2.8 (2.1-3.8)**	**4.1 (2.8-5.9)**	**2.1 (1.5-2.9)**	**2.4 (1.8-3.4)**	IMI									
2.9 (2.2-3.9)	**2.2 (1.4-3.6)**	**1.6 (1.1-2.4)**	**1.9 (1.5-2.5)**	**2.8 (2-4.1)**	**1.4 (1.1-1.9)**	**1.6 (1.2-2.2)**	**0.7 (0.5-0.9)**	AMI								
4.2 (2.6-7.2)	**3.2 (1.7-6.3)**	**2.4 (1.3-4.3)**	**2.8 (1.7-4.6)**	**4 (2.3-7.2)**	**2 (1.3-3.4)**	**2.4 (1.4-4)**	1 (0.6-1.7)	1.4 (0.9-2.5)	CLO							
2.8 (1.4-5.8)	2.1 (1-4.9)	1.5 (0.7-3.4)	1.8 (0.9-3.8)	**2.6 (1.2-5.9)**	1.4 (0.6-2.9)	1.6 (0.8-3.3)	0.6 (0.3-1.4)	1 (0.5-2)	0.7 (0.3-1.5)	DESI						
2.5 (1.2-4.8)	1.8 (0.9-4.1)	1.4 (0.7-2.9)	1.6 (0.8-3.1)	**2.3 (1.2-4.6)**	1.2 (0.6-2.4)	1.4 (0.7-2.7)	0.6 (0.3-1.1)	0.8 (0.4-1.7)	0.6 (0.3-1.3)	0.9 (0.3-2.3)	NOR					
4.6 (0.9-28)	3.6 (0.7-22.2)	2.6 (0.5-15.9)	3 (0.6-18.2)	4.4 (0.9-26.3)	2.3 (0.5-13.4)	2.6 (0.5-15.7)	1.1 (0.2-6.5)	1.6 (0.3-9.4)	1.1 (0.2-6.7)	1.7 (0.3-11)	2 (0.3-12)	DOX				
2.9 (2.1-3.9)	**2.2 (1.3-3.5)**	**1.6 (1.1-2.2)**	**1.9 (1.4-2.5)**	**2.7 (1.8-4.1)**	**1.4 (1-1.9)**	**1.6 (1.1-2.2)**	**0.7 (0.5-1)**	1 (0.7-1.4)	0.7 (0.4-1.2)	1 (0.5-2.1)	1.2 (0.6-2.4)	0.6 (0.1-2.9)	DUL			
9.5 (2.1-66.3)	**7.3 (1.5-50.2)**	**5.3 (1.2-35)**	**6.2 (1.4-41.8)**	**9 (2.1-57.3)**	**4.6 (1-31.1)**	**5.3 (1.2-36.6)**	2.2 (0.5-15.1)	3.2 (0.7-22.3)	2.3 (0.5-15.1)	3.3 (0.6-24.8)	4 (0.8-28)	2.1 (0.2-21.2)	3.4 (0.7-21.5)	MAP		
1.9 (1.4-2.6)	1.5 (0.9-2.4)	1.1 (0.7-1.6)	1.2 (0.9-1.7)	**1.8 (1.2-2.7)**	0.9 (0.7-1.2)	1.1 (0.8-1.5)	**0.4 (0.3-0.6)**	**0.7 (0.5-0.9)**	**0.5 (0.3-0.7)**	0.7 (0.3-1.4)	0.8 (0.4-1.6)	0.4 (0.1-2)	**0.7 (0.5-1)**	**0.2 (0-0.9)**	MIR	
3.3 (1.1-10.5)	2.5 (0.8-8.3)	1.8 (0.6-6.1)	2.1 (0.7-6.8)	**3.1 (1-10.2)**	1.6 (0.5-5.2)	1.8 (0.7-6)	0.8 (0.2-2.6)	1.1 (0.4-3.6)	0.8 (0.2-3)	1.2 (0.3-4.5)	1.4 (0.4-5.5)	0.7 (0.1-4.8)	1.2 (0.4-3.8)	0.3 (0-2.3)	1.7 (0.6-5.5)	MOC
3 (2.2-4.1)	**2.3 (1.4-3.8)**	**1.7 (1.1-2.5)**	**1.9 (1.4-2.6)**	**2.8 (1.8-4.4)**	**1.4 (1.1-2)**	**1.7 (1.2-2.3)**	**0.7 (0.5-1)**	1 (0.7-1.4)	0.7 (0.4-1.2)	1.1 (0.5-2.3)	1.2 (0.6-2.5)	0.6 (0.1-3.2)	1.1 (0.7-1.5)	0.3 (0-1.5)	**1.6 (1.1-2.2)**	0.9 (0.3-2.7)	VEN

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of dizziness with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and treatment rankings***. Table 5 presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons. SUCRA values and treatment rankings corresponded to the observation that placebo was associated with the lowest risk of dizziness. SSRIs were associated with qualitatively better SUCRA values and treatment rankings relative to the TCAs and non-SSRI/TCA agents. Fluvoxamine and citalopram were associated with the most favorable estimates after placebo.

Table 5:
Summary Measures, Dizziness

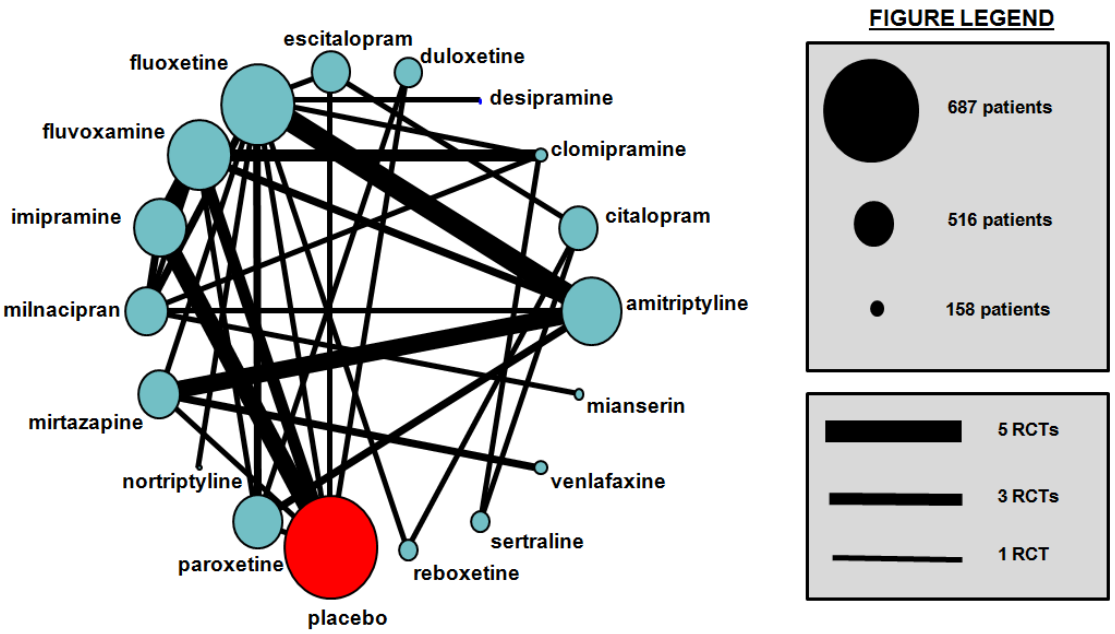
Treatment	SUCRA (%)	median rank (95% CrI)
Placebo	89.5%	4 (1-6)
SSRIs		
Fluvoxamine	87.12%	4 (2-7)
Citalopram	77.70%	6 (2-13)
Fluoxetine	71.24%	8 (5-12)
Sertraline	61.27%	11 (7-15)
Escitalopram	60.83%	11 (6-15)
Paroxetine	51.72%	13 (9-16)
TCAs		
Nortriptyline	44.14%	15 (6-22)
Desipramine	37.19%	17 (7-24)
Amitriptyline	33.37%	18 (14-21)
Doxepin	24.13%	22 (4-26)
Clomipramine	18.67%	22 (17-25)
Imipramine	17%	22 (19-24)
Non-SSRI/TCA		
Mirtazapine	56.37%	12 (8-16)
Duloxetine	34.74%	17 (14-21)
Venlafaxine	32.16%	18 (14-22)
Moclobemide	32%	19 (5-26)
Maprotiline	8.49%	25 (14-26)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of dizziness.

4.1.3.3 Findings, Hypotension

Figure 8 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs.[42,45-47,54,57,61,62,71-73,75,77,78,81,83,88,92,99,110,114,115,123,127,134,138,142,145,146,170,176,186-196] A total of 18 interventions were associated with RCTs that reported data on hypotension, with the numbers of trials and randomized patients per treatment ranging from 1–15 (median 54, IQR 2-8) and 24–788 (median 356, IQR 162-558), respectively. Comparisons between fluoxetine and amitriptyline, fluvoxamine and imipramine, amitripyline and mirtazapine, and imipramine versus placebo were most prevalent. Again, several comparisons were informed by just one study, and several comparisons between active treatments were not informed by head-to-head trials.

Figure 8 - Network Diagram, Hypotension:
Including Data from 46 studies, 6,807 participants (423 events)



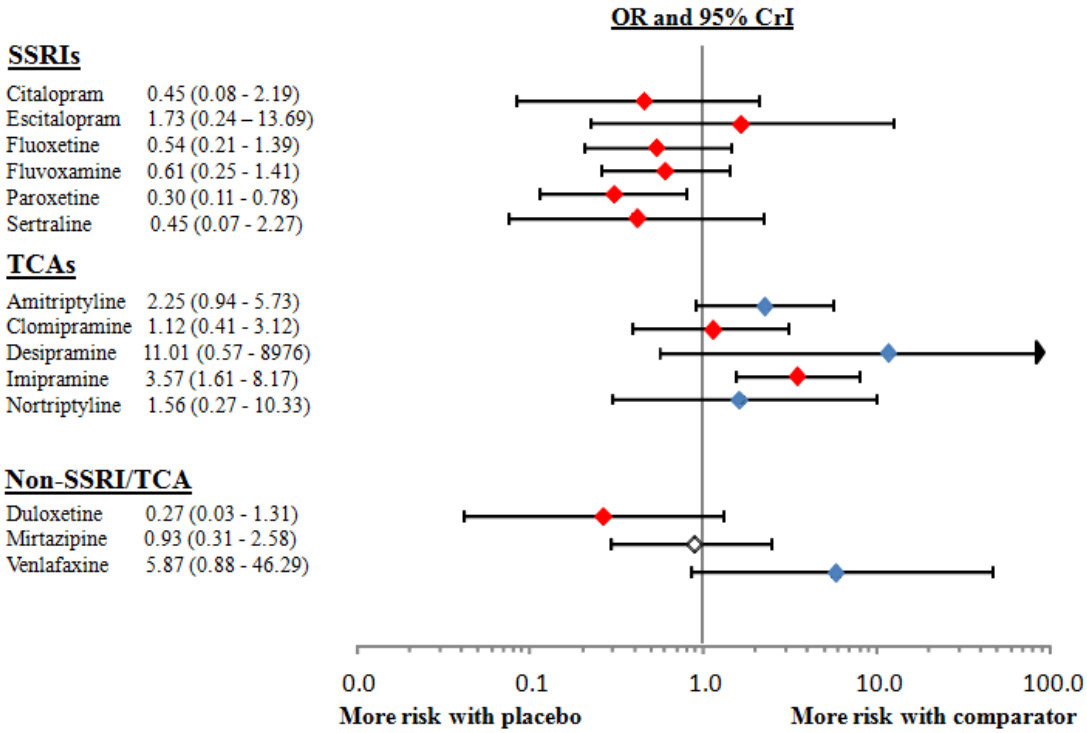
Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Both fixed and random effects models were adequate fits to the data (residual deviances of 91.1 and 89.5 compared to 98 unconstrained data points; random effects was chosen as the primary model (DIC 428.6, compared to 426.8 for fixed effects). **Figure 9** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while **Figure 10** summarizes all possible pairwise comparisons between included regimens. Our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be observed from **Figure 9**:

    - Amongst SSRIs, one agent (paroxetine) was associated with a reduced risk of hypotension. Comparisons involving the five remaining agents were associated with wide and inconclusive credible intervals; four were associated with summary estimates suggesting a trend toward reduction in the risk of hypotension (citalopram, fluoxetine, fluvoxamine, sertraline), while one suggested more hypotension (escitalopram).
    - Amongst TCAs, imipramine was associated with a significant increase in the number of patients experiencing hypotension. The remaining four agents were all associated with point estimates suggesting more risk of hypotension which were accompanied by wide and inconclusive credible intervals.
    - Amongst the three non-SSRI/TCA agents, all comparisons were associated with inconclusive credible intervals. One agent (mirtazapine) was associated with a summary estimate near 1, while the remaining two (duloxetine, venlafaxine) had point estimates suggesting effects in opposing directions.
    - Based on the pattern of summary estimates seen when considering the agents by serotonin affinity grouping (red=high, blue=moderate, white=low), there doesn't appear to be clear evidence of a relationship between serotonin affinity level and the occurrence of hypotension.

Figure 9: Forest Plot of Comparisons versus Placebo, Hypotension – Summary Odds Ratios and Credible Intervals



Summary estimates from network meta-analysis comparing the frequency of hypotension. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

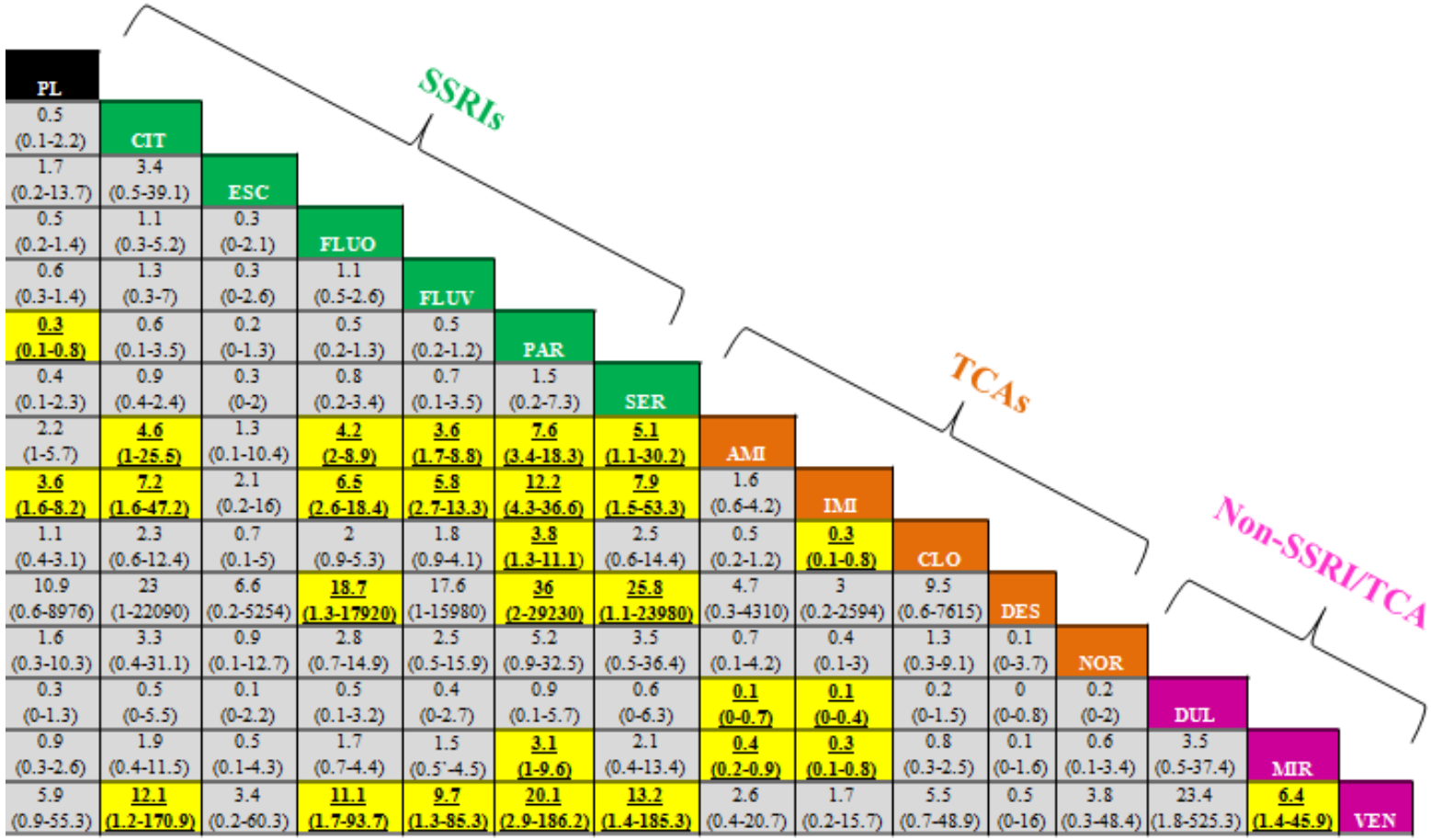
- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class, **Figure 10** shows the following (it should be noted that given the reduced number of studies reporting this outcome and its low incidente rate, comparisons are generally associated with notably wider credible intervals than for other outcomes):

    - Regarding SSRIs, five of six agents (with the exception of escitalopram) were associated with statistically significant reductions of hypotension compared to both amitriptyline and imipramine. Other statistically significant reductions of some of the SSRIs compared to clomipramine, despiramine, mirtazapine and venlafaxine were also noted (though associated with large amounts of uncertainty given the underlying data). None of the comparisons between the individual SSRIs showed statistically significant differences.

    - Regarding TCAs, in addition to the increased risks versus SSRIs, both amitriptyline and imipramine were also associated with increased risks of hypotension compared to duloxetine and mirtazapine. Imipramine was found to place patients at an increased risk compared to clomipramine.

    - Regarding non-SSRI/TCAs, venlafaxine was found to be associated with a greater risk of hypotension compared to mirtazapine; all other comparisons between agents in this grouping were associated with wide and inconclusive credible intervals.

Figure 10: League Table Summary of Pairwise Comparisons, Hypotension



PL	CIT	ESC	FLUO	FLUV	PAR	SER	AMI	IMI	CLO	DES	NOR	DUL	MIR	VEN
0.5 (0.1-2.2)														
1.7 (0.2-13.7)	3.4 (0.5-39.1)													
0.5 (0.2-1.4)	1.1 (0.3-5.2)	0.3 (0-2.1)												
0.6 (0.3-1.4)	1.3 (0.3-7)	0.3 (0-2.6)	1.1 (0.5-2.6)											
0.3 (0.1-0.8)	0.6 (0.1-3.5)	0.2 (0-1.3)	0.5 (0.2-1.3)	0.5 (0.2-1.2)										
0.4 (0.1-2.3)	0.9 (0.4-2.4)	0.3 (0-2)	0.8 (0.2-3.4)	0.7 (0.1-3.5)	1.5 (0.2-7.3)									
2.2 (1-5.7)	**4.6 (1-25.5)**	1.3 (0.1-10.4)	**4.2 (2-8.9)**	**3.6 (1.7-8.8)**	**7.6 (3.4-18.3)**	**5.1 (1.1-30.2)**								
3.6 (1.6-8.2)	**7.2 (1.6-47.2)**	2.1 (0.2-16)	**6.5 (2.6-18.4)**	**5.8 (2.7-13.3)**	**12.2 (4.3-36.6)**	**7.9 (1.5-53.3)**	1.6 (0.6-4.2)							
1.1 (0.4-3.1)	2.3 (0.6-12.4)	0.7 (0.1-5)	2 (0.9-5.3)	1.8 (0.9-4.1)	**3.8 (1.3-11.1)**	2.5 (0.6-14.4)	0.5 (0.2-1.2)	**0.3 (0.1-0.8)**						
10.9 (0.6-8976)	23 (1-22090)	6.6 (0.2-5254)	**18.7 (1.3-17920)**	17.6 (1-15980)	**36 (2-29230)**	**25.8 (1.1-23980)**	4.7 (0.3-4310)	3 (0.2-2594)	9.5 (0.6-7615)					
1.6 (0.3-10.3)	3.3 (0.4-31.1)	0.9 (0.1-12.7)	2.8 (0.7-14.9)	2.5 (0.5-15.9)	5.2 (0.9-32.5)	3.5 (0.5-36.4)	0.7 (0.1-4.2)	0.4 (0.1-3)	1.3 (0.3-9.1)	0.1 (0-3.7)				
0.3 (0-1.3)	0.5 (0-5.5)	0.1 (0-2.2)	0.5 (0.1-3.2)	0.4 (0-2.7)	0.9 (0.1-5.7)	0.6 (0-6.3)	**0.1 (0-0.7)**	**0.1 (0-0.4)**	0.2 (0-1.5)	0 (0-0.8)	0.2 (0-2)			
0.9 (0.3-2.6)	1.9 (0.4-11.5)	0.5 (0.1-4.3)	1.7 (0.7-4.4)	1.5 (0.5-4.5)	**3.1 (1-9.6)**	2.1 (0.4-13.4)	**0.4 (0.2-0.9)**	**0.3 (0.1-0.8)**	0.8 (0.3-2.5)	0.1 (0-1.6)	0.6 (0.1-3.4)	3.5 (0.5-37.4)		
5.9 (0.9-55.3)	**12.1 (1.2-170.9)**	3.4 (0.2-60.3)	**11.1 (1.7-93.7)**	**9.7 (1.3-85.3)**	**20.1 (2.9-186.2)**	**13.2 (1.4-185.3)**	2.6 (0.4-20.7)	1.7 (0.2-15.7)	5.5 (0.7-48.9)	0.5 (0-16)	3.8 (0.3-48.4)	23.4 (1.8-525.3)	**6.4 (1.4-45.9)**	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of hypotension with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and treatment rankings***. **Table 6** presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons. SUCRA values and treatment rankings corresponded to the observation that SSRIs generally appeared to be associated with a lower risk of hypotension than placebo or agents from other classes. Imipramine, venlafaxine and desipramine were found with the least favorable SUCRA values amongst the treatments of interest.

Table 6:
Summary Measures, Hypotension

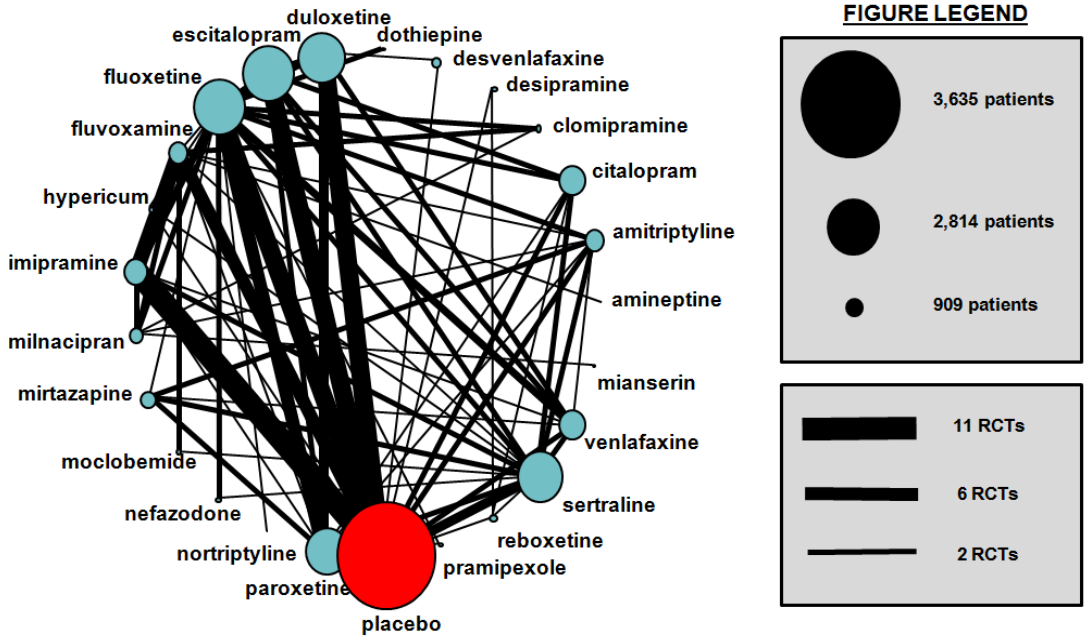
Treatment	SUCRA(%)	median rank (95% CrI)
Placebo	49.5%	10 (4-14)
SSRIs		
Paroxetine	88.0%	3 (1-7)
Sertraline	76.4%	4 (1-13)
Fluoxetine	73.8%	5 (2-9)
Citalopram	73.7%	5 (1-12)
Fluvoxamine	69.2%	6 (3-11)
Escitalopram	34.3%	13 (3-18)
TCAs		
Clomipramine	44.9%	10 (6-15)
Nortriptyline	37.1%	12 (3-17)
Amitriptyline	22.0%	14 (11-18)
Imipramine	13.1%	16 (13-18)
Desipramine	8.8%	18 (7-18)
Non-SSRI/TCA		
Duloxetine	85.0%	2 (1-12)
Mirtazapine	53.0%	9 (4-14)
Venlafaxine	10.4%	17 (10-18)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of hypotension.

4.1.3.4 Findings, Insomnia

Figure 11 presents a network diagram summarizing pairwise comparisons that were available within the set of included RCTs.[41,42,46-48,50,53,55-58,60,61,63,65,68-71,76,78,81,82,86,87,89-91,95-99,101-103,106,112-124,126-133,137-139,142-144,146,150,153,155,157,160,161,165,167,168,170,171,173-179,181-185,191-193,196-217] A total of 25 interventions were associated with RCTs that reported data on insomnia, with the numbers of trials and randomized patients per treatment ranging from 1 – 39 (median 9, IQR 2-18) and 20 – 3,637 (median 876, IQR 160-1,849), respectively. Comparisons of each of imipramine, fluoxetine, escitalopram and duloxetine with placebo, as well as imipramine with fluvoxamine were most prevalent. Again many comparisons were informed by just one study, and many comparisons were not informed by any existing RCTs.

Figure 11 - Network Diagram, Insomnia:
Including Data from 119 studies, 25,459 participants (2,721 events)

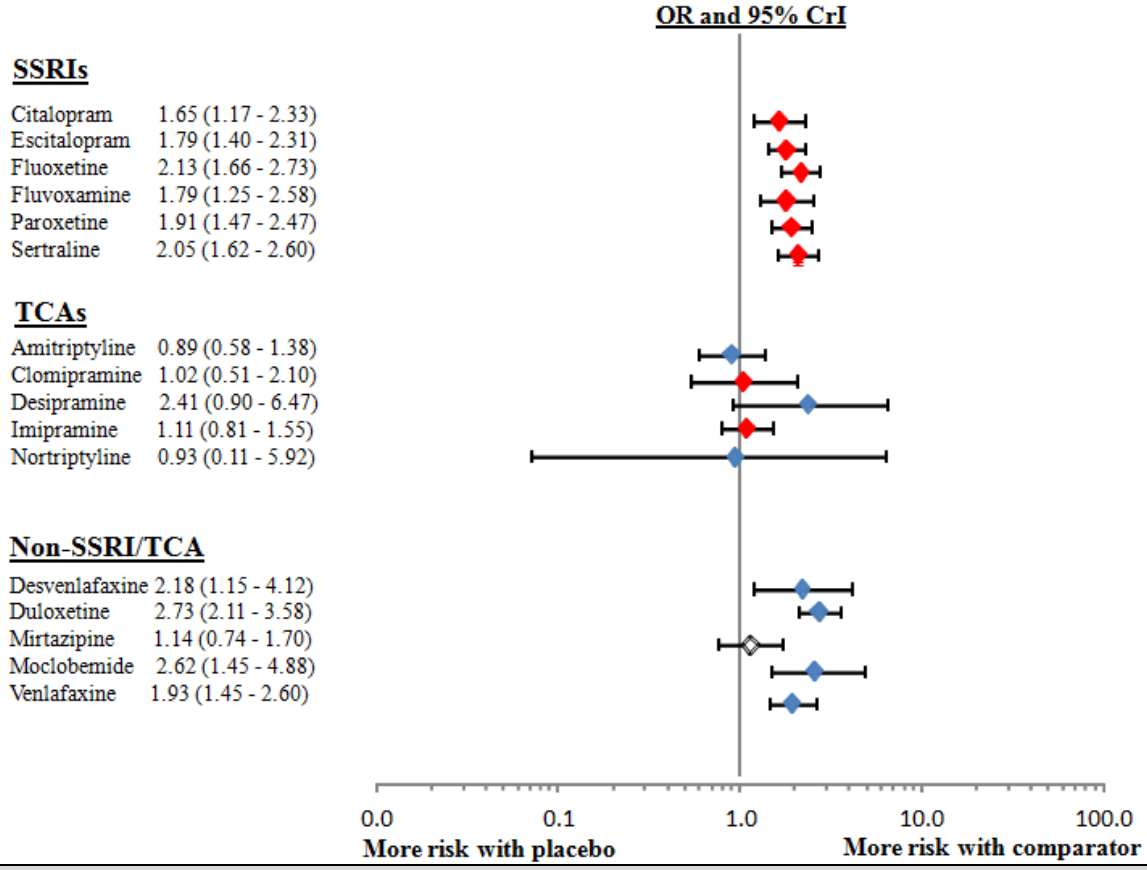


Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Both fixed and random effects models were adequate fits to the data (residual deviances of 284.3 and 271.0 compared to 271 unconstrained data points; random effects was chosen as the primary model (DIC 1416.6, compared to 1416.0 for fixed effects). **Figure 12** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while **Figure 13** summarizes all possible pairwise comparisons between included interventions. Results are presented sequentially, and our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be noted from **Figure 12**:
    - Amongst SSRIs, all six agents were associated with an increased risk of insomnia (range of ORs 1.65-2.13).
    - Amongst TCAs, four of the five agents in the treatment network (amitriptyline, clomipramine, imipramine, nortriptyline) were associated with summary estimates near 1 along with inconclusive credible intervals. One agent (desipramine) had a summary estimate suggesting an increased risk of insomnia with a credible interval which was wide and included the null difference value of 1 (OR 2.41, 95% CrI 0.90-6.47).
    - Amongst non-SSRI/TCA agents, four of the five agents in the treatment network (desvenlafaxine, duloxetine, moclobemide, venlafaxine) were associated with an increased risk of insomnia (range of ORs 1.93-2.73).
    - Based on the pattern of summary estimates seen when considering the agents by serotonin affinity grouping, (red=high, blue=moderate, white=low), there doesn't appear to be clear evidence of a relationship between serotonin affinity and the occurrence of insomnia.

Figure 12: Forest Plot of Comparisons versus Placebo, Insomnia – Summary Odds Ratios and Credible Intervals



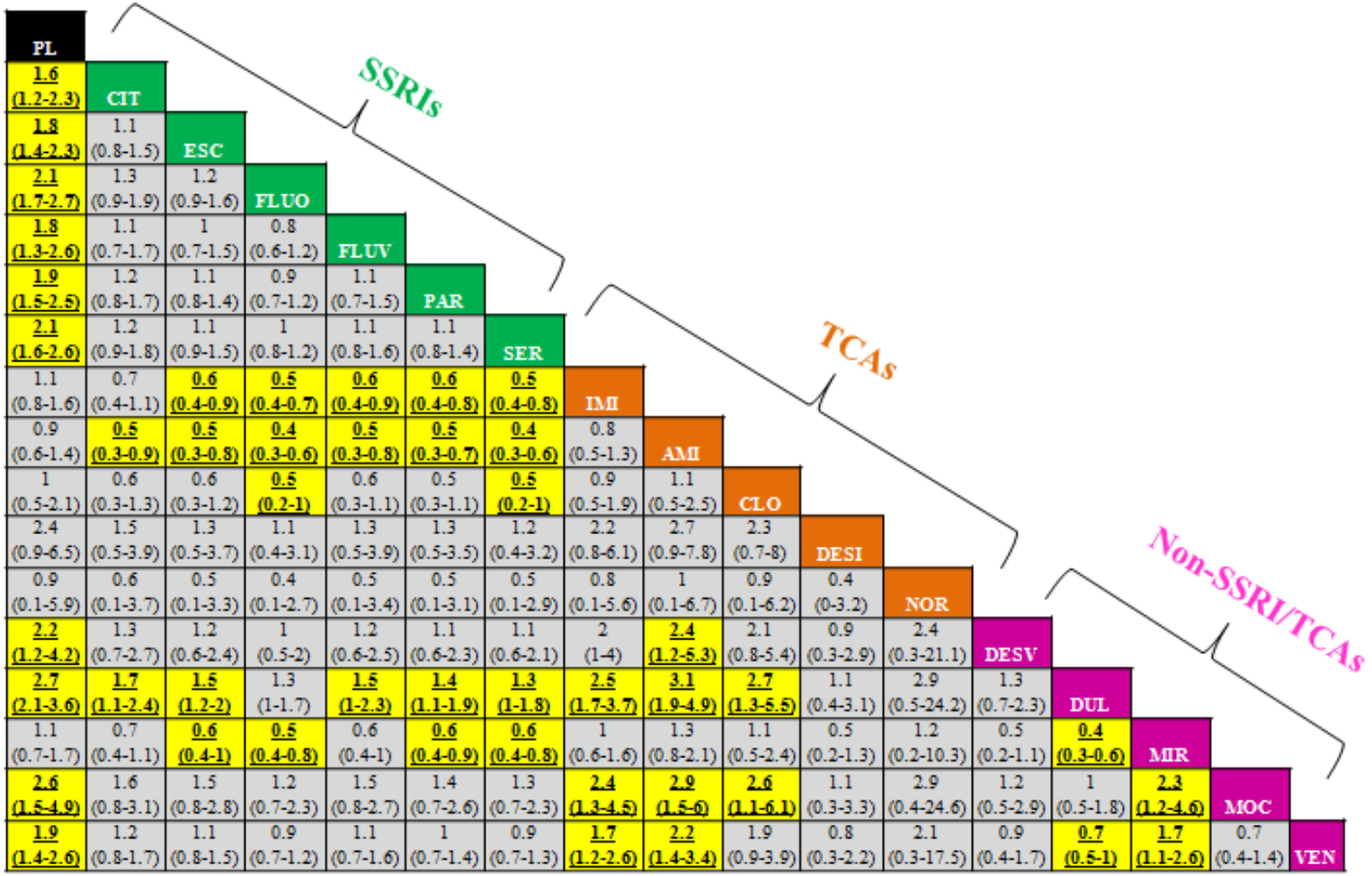
Summary estimates from network meta-analysis comparing the frequency of insomnia. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class, **Figure 13** shows the following:
    - Regarding SSRIs, these agents were consistently associated with increased risks of insomnia relative to the TCAs amitriptyline and imipramine (fluoxetine and sertraline were also associated with a greater risk compared to clomipramine). Several were also associated with an increased risk compared to mirtazapine and a reduced risk compared to duloxetine. Comparing between agents within the SSRI class, no important differences were observed.

    - Regarding TCAs, in addition to the above noted reductions in risk of insomnia compared to SSRIs for amitriptyline, imipramine and clomipramine, findings also suggested less risk for each of these three agents compared to both of the non-SSRI/TCAs duloxetine and moclobemide. There was also a reduced risk for amitriptyline and imipramine when compared to venlafaxine. All comparisons involving desipramine were inconclusive, as were comparisons between the agents within this class.

    - Comparing between non-SSRI/TCA agents, statistically significant increases in the risk of insomnia were observed for duloxetine compared to venlafaxine, and for mirtazapine compared to venlafaxine, duloxetine and moclobemide.

Figure 13: League table Summary of Pairwise Comparisons, Insomnia



PL														
1.6 (1.2-2.3)	CIT													
1.8 (1.4-2.3)	1.1 (0.8-1.5)	ESC												
2.1 (1.7-2.7)	1.3 (0.9-1.9)	1.2 (0.9-1.6)	FLUO											
1.8 (1.3-2.6)	1.1 (0.7-1.7)	1 (0.7-1.5)	0.8 (0.6-1.2)	FLUV										
1.9 (1.5-2.5)	1.2 (0.8-1.7)	1.1 (0.8-1.4)	0.9 (0.7-1.2)	1.1 (0.7-1.5)	PAR									
2.1 (1.6-2.6)	1.2 (0.9-1.8)	1.1 (0.9-1.5)	1 (0.8-1.2)	1.1 (0.8-1.6)	1.1 (0.8-1.4)	SER								
1.1 (0.8-1.6)	0.7 (0.4-1.1)	**0.6 (0.4-0.9)**	**0.5 (0.4-0.7)**	**0.6 (0.4-0.9)**	**0.6 (0.4-0.8)**	**0.5 (0.4-0.8)**	IMI							
0.9 (0.6-1.4)	**0.5 (0.3-0.9)**	**0.5 (0.3-0.8)**	**0.4 (0.3-0.6)**	**0.5 (0.3-0.8)**	**0.5 (0.3-0.7)**	**0.4 (0.3-0.6)**	0.8 (0.5-1.3)	AMI						
1 (0.5-2.1)	0.6 (0.3-1.3)	0.6 (0.3-1.2)	**0.5 (0.2-1)**	0.6 (0.3-1.1)	0.5 (0.3-1.1)	**0.5 (0.2-1)**	0.9 (0.5-1.9)	1.1 (0.5-2.5)	CLO					
2.4 (0.9-6.5)	1.5 (0.5-3.9)	1.3 (0.5-3.7)	1.1 (0.4-3.1)	1.3 (0.5-3.9)	1.3 (0.5-3.5)	1.2 (0.4-3.2)	2.2 (0.8-6.1)	2.7 (0.9-7.8)	2.3 (0.7-8)	DESI				
0.9 (0.1-5.9)	0.6 (0.1-3.7)	0.5 (0.1-3.3)	0.4 (0.1-2.7)	0.5 (0.1-3.4)	0.5 (0.1-3.1)	0.5 (0.1-2.9)	0.8 (0.1-5.6)	1 (0.1-6.7)	0.9 (0.1-6.2)	0.4 (0-3.2)	NOR			
2.2 (1.2-4.2)	1.3 (0.7-2.7)	1.2 (0.6-2.4)	1 (0.5-2)	1.2 (0.6-2.5)	1.1 (0.6-2.3)	1.1 (0.6-2.1)	2 (1-4)	**2.4 (1.2-5.3)**	2.1 (0.8-5.4)	0.9 (0.3-2.9)	2.4 (0.3-21.1)	DESV		
2.7 (2.1-3.6)	**1.7 (1.1-2.4)**	**1.5 (1.2-2)**	1.3 (1-1.7)	**1.5 (1-2.3)**	**1.4 (1.1-1.9)**	**1.3 (1-1.8)**	**2.5 (1.7-3.7)**	**3.1 (1.9-4.9)**	**2.7 (1.3-5.5)**	1.1 (0.4-3.1)	2.9 (0.5-24.2)	1.3 (0.7-2.3)	DUL	
1.1 (0.7-1.7)	0.7 (0.4-1.1)	**0.6 (0.4-1)**	**0.5 (0.4-0.8)**	0.6 (0.4-1)	**0.6 (0.4-0.9)**	**0.6 (0.4-0.8)**	1 (0.6-1.6)	1.3 (0.8-2.1)	1.1 (0.5-2.4)	0.5 (0.2-1.3)	1.2 (0.2-10.3)	0.5 (0.2-1.1)	**0.4 (0.3-0.6)**	MIR
2.6 (1.5-4.9)	1.6 (0.8-3.1)	1.5 (0.8-2.8)	1.2 (0.7-2.3)	1.5 (0.8-2.7)	1.4 (0.7-2.6)	1.3 (0.7-2.3)	**2.4 (1.3-4.5)**	**2.9 (1.5-6)**	**2.6 (1.1-6.1)**	1.1 (0.3-3.3)	2.9 (0.4-24.6)	1.2 (0.5-2.9)	1 (0.5-1.8)	**2.3 (1.2-4.6)**
1.9 (1.4-2.6)	1.2 (0.8-1.7)	1.1 (0.8-1.5)	0.9 (0.7-1.2)	1.1 (0.7-1.6)	1 (0.7-1.4)	0.9 (0.7-1.3)	**1.7 (1.2-2.6)**	**2.2 (1.4-3.4)**	1.9 (0.9-3.9)	0.8 (0.3-2.2)	2.1 (0.3-17.5)	0.9 (0.4-1.7)	**0.7 (0.5-1)**	**1.7 (1.1-2.6)**

MOC															
0.7 (0.4-1.4)	VEN														

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of insomnia with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and median treatment rankings***. **Table 7** presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons. SUCRA values and median treatment rankings of TCAs were qualitatively better compared to those for SSRIs and non-SSRIs/TCAs, while those for mirtazapine also suggested less risk compared to SSRIs. Amitriptyline was associated with a higher SUCRA value than placebo given its slight risk reduction compared to placebo and correspondingly narrow credible interval.

Table 7:
Secondary Measures of Effect, Insomnia

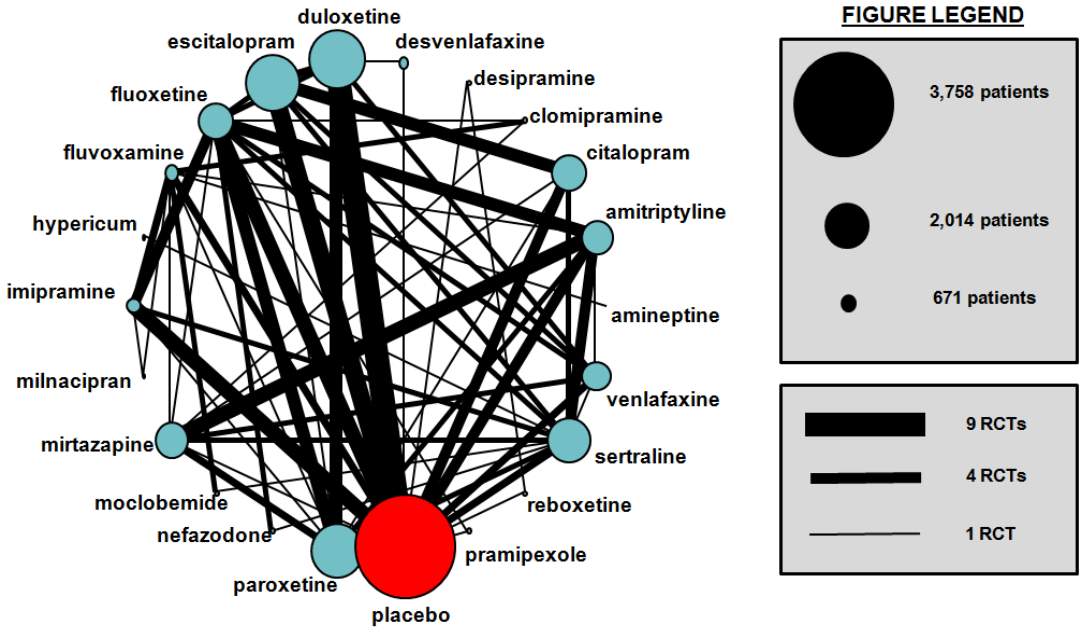
Treatment	SUCRA(%)	median rank (95% CrI)
Placebo	82.6%	5 (2-9)
SSRIs		
Citalopram	53.4%	12 (7-19)
Escitalopram	47.5%	13 (9-19)
Fluvoxamine	46.3%	13 (8-21)
Paroxetine	41.2%	15 (10-20)
Sertraline	34.2%	17 (12-21)
Fluoxetine	30.7%	18 (13-22)
TCAs		
Amitriptyline	86.4%	4 (1-9)
Clomipramine	78.1%	5 (1-17)
Imipramine	76.4%	7 (3-11)
Nortriptyline	70.8%	4 (1-24)
Desipramine	30.9%	20 (4-24)
Non-SSRI/TCA		
Mirtazapine	75.3%	7 (2-12)
Venlafaxine	39.6%	15 (10-21)
Desvenlafaxine	32.1%	18 (8-24)
Moclobemide	21.4%	21 (10-24)
Duloxetine	15.4%	22 (18-24)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of insomnia.

4.3.1.5 Findings, Fatigue

Figure 14 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs.[41,48,49,52-55,57,58,61,65,68-71,75,76,78,79,81,82,86,87,89,91-93,95-97,102-104,106-108,111-113,115-117,120,123,124,126-128,131,132,137-140,143,144,148,150,153,157,164-171,173-175,178-185,198,199,202,204,209,213,215,217-220] A total of 22 interventions were associated with RCTs that reported data on fatigue, with the numbers of trials and randomized patients per treatment ranging from 1 – 30 (median 10, IQR 1-17) and 20 – 2,953 (median 595, IQR 116-1,756), respectively. Comparisons between duloxetine and placebo, escitalopram and placebo, fluoxetine with placebo and amitriptyline and mirtazapine were most prevalent. Again many comparisons were informed by just one study, and many comparisons were not informed by any existing RCTs.

Figure 14 - Network Diagram, Fatigue:
Including Data from 98 studies, 21,939 participants (1,992 events)

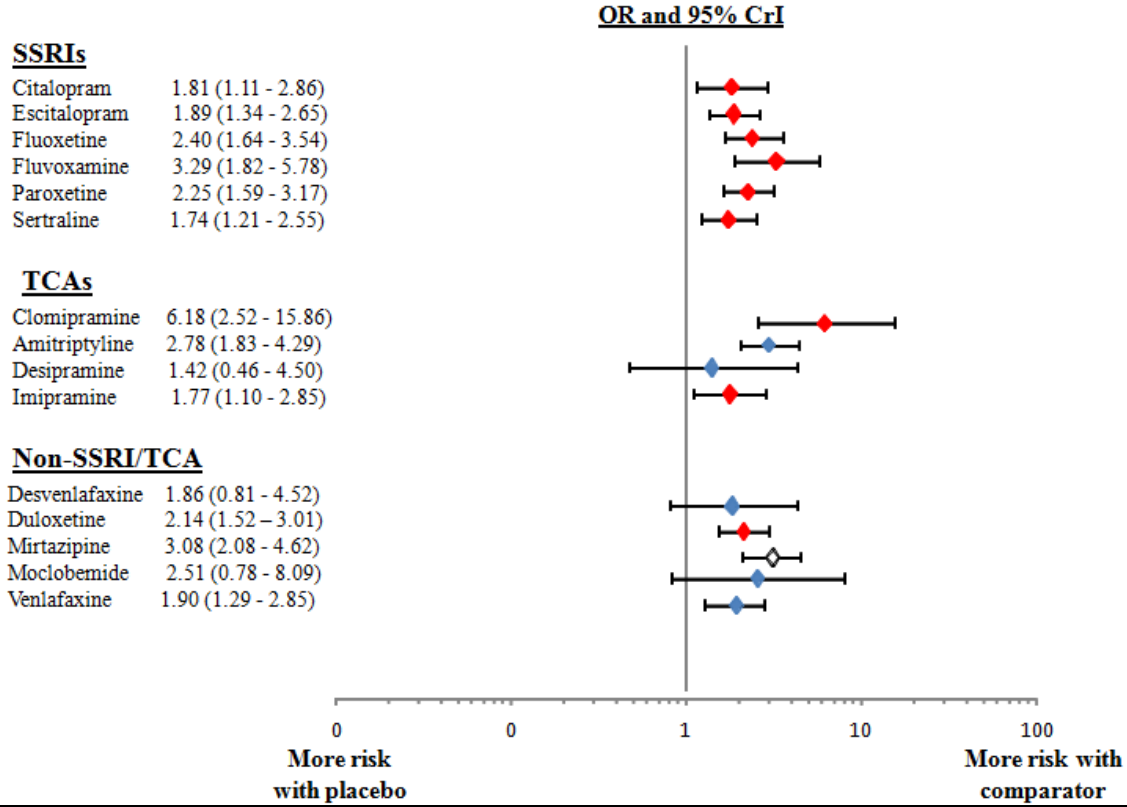


Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Both fixed and random effects models were reasonable fits to the data (residual deviances of 253.1 and 216.1 compared to 224 unconstrained data points; random effects was chosen as the primary model (DIC 1144.3, compared to 1153.9 for fixed effects). **Figure 15** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while **Figure 16** summarizes all possible pairwise comparisons between included regimens. Results are presented sequentially, and our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be observed from **Figure 15**:
    - Amongst SSRIs, all six agents were associated with an increased risk of fatigue (range of ORs 1.74-3.29).
    - Amongst TCAs, three of four agents (clomipramine, amitriptyline, imipramine) were associated with significantly increased risks (range of ORs 1.77-6.18). One agent was associated with an inconclusive comparison (desipramine).
    - Amongst the non-SSRI/TCA agents, three of five agents (duloxetine, mirtazapine, venlafaxine) were associated with an increased risk of fatigue (range of ORs 1.80-3.26), while two agents were associated with increased risk estimates but wide credible intervals that included a possible null difference (desvenlafaxine, moclobemide).
    - Based on the pattern of summary estimates seen when considering the agents by serotonin affinity grouping (red=high, blue=moderate, white=low), there doesn't appear to be evidence of a relationship between serotonin affinity and the occurrence of fatigue.

Figure 15: Forest Plot of Comparisons versus Placebo, Fatigue – Summary Odds Ratios and Credible Intervals

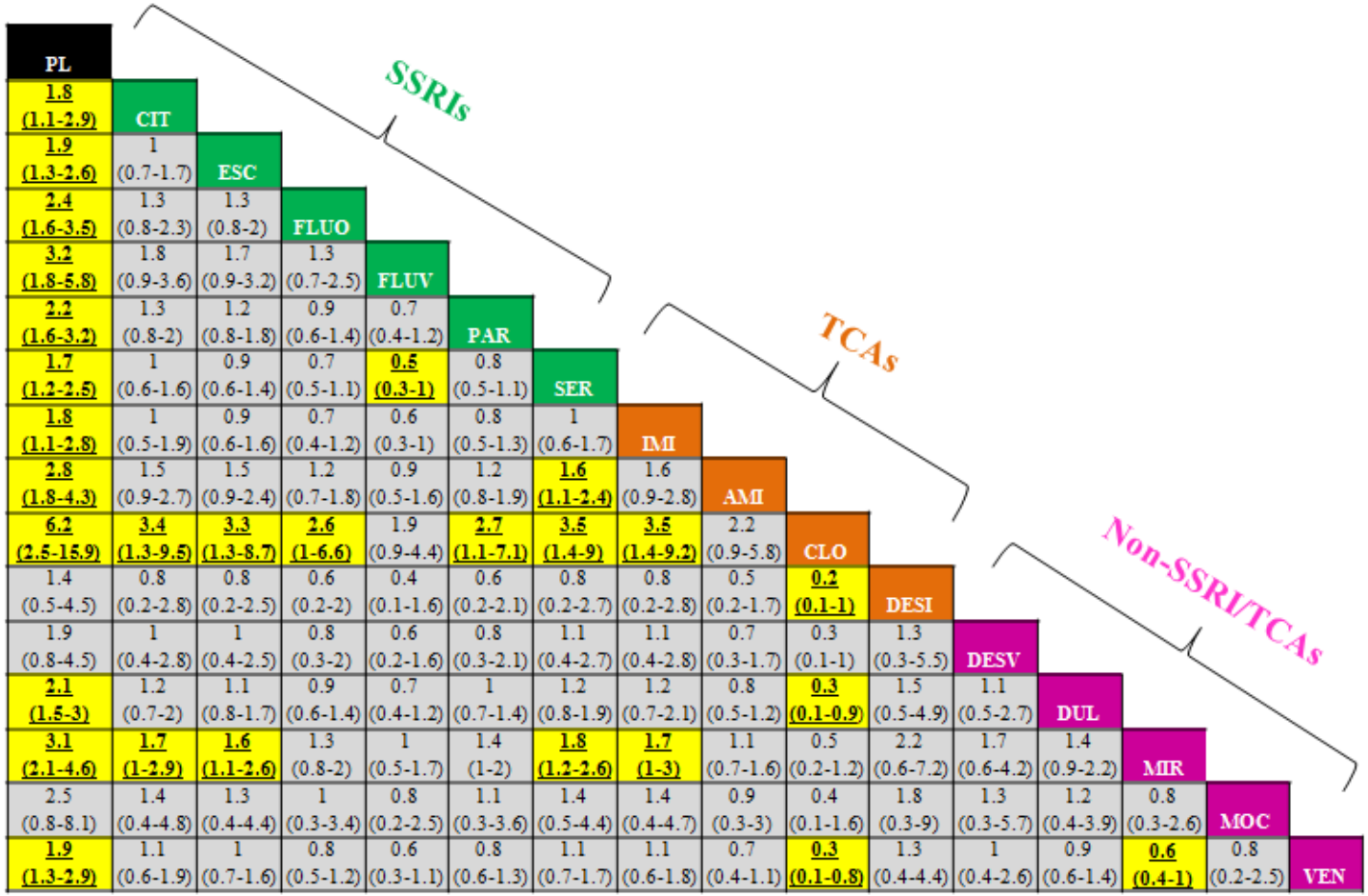


Summary estimates from network meta-analysis comparing the frequency of fatigue. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class, **Figure 16** shows the following:

    - Regarding SSRIs, no increased risk of fatigue was observed with any particular agent relative to agents from other classes. Regarding comparisons between SSRIs, fluvoxamine was associated with an increased risk of fatigue compared to sertraline.
    - Regarding TCAs, comparisons of clomipramine were generally associated with wide credible intervals, however many of these estimates still were associated with a statistically significant increase in the risk of fatigue compared with the majority of the other therapies (range of ORs 2.9-6.2). Amitriptyline was associated with an increased risk of fatigue compared to sertraline, and imipramine was associated with a reduced risk of fatigue compared to fluvoxamine and mirtazapine. Regarding comparisons between TCAs, imipramine and desipramine were associated with a smaller risk of fatigue than clomipramine.
    - Regarding non-SSRI/TCA agents, mirtazapine was associated with a greater risk of fatigue compared to four of six SSRIs (escitalopram, paroxetine, citalopram, sertraline), as well as venlafaxine. All comparisons involving moclobemide were inconclusive. Credible intervals associated with all comparisons between all non-SSRI/TCA agents were inconclusive.

Figure 16: League Table Summary of Pairwise Comparisons, Fatigue



PL	CIT	ESC	FLUO	FLUV	PAR	SER	IMI	AMI	CLO	DESI	DESV	DUL	MIR	MOC	VEN
1.8 (1.1-2.9)	CIT														
1.9 (1.3-2.6)	1 (0.7-1.7)	ESC													
2.4 (1.6-3.5)	1.3 (0.8-2.3)	1.3 (0.8-2)	FLUO												
3.2 (1.8-5.8)	1.8 (0.9-3.6)	1.7 (0.9-3.2)	1.3 (0.7-2.5)	FLUV											
2.2 (1.6-3.2)	1.3 (0.8-2)	1.2 (0.8-1.8)	0.9 (0.6-1.4)	0.7 (0.4-1.2)	PAR										
1.7 (1.2-2.5)	1 (0.6-1.6)	0.9 (0.6-1.4)	0.7 (0.5-1.1)	**0.5 (0.3-1)**	0.8 (0.5-1.1)	SER									
1.8 (1.1-2.8)	1 (0.5-1.9)	0.9 (0.6-1.6)	0.7 (0.4-1.2)	0.6 (0.3-1)	0.8 (0.5-1.3)	1 (0.6-1.7)	IMI								
2.8 (1.8-4.3)	1.5 (0.9-2.7)	1.5 (0.9-2.4)	1.2 (0.7-1.8)	0.9 (0.5-1.6)	1.2 (0.8-1.9)	**1.6 (1.1-2.4)**	1.6 (0.9-2.8)	AMI							
6.2 (2.5-15.9)	**3.4 (1.3-9.5)**	**3.3 (1.3-8.7)**	**2.6 (1-6.6)**	1.9 (0.9-4.4)	**2.7 (1.1-7.1)**	**3.5 (1.4-9)**	**3.5 (1.4-9.2)**	2.2 (0.9-5.8)	CLO						
1.4 (0.5-4.5)	0.8 (0.2-2.8)	0.8 (0.2-2.5)	0.6 (0.2-2)	0.4 (0.1-1.6)	0.6 (0.2-2.1)	0.8 (0.2-2.7)	0.8 (0.2-2.8)	0.5 (0.2-1.7)	**0.2 (0.1-1)**	DESI					
1.9 (0.8-4.5)	1 (0.4-2.8)	1 (0.4-2.5)	0.8 (0.3-2)	0.6 (0.2-1.6)	0.8 (0.3-2.1)	1.1 (0.4-2.7)	1.1 (0.4-2.8)	0.7 (0.3-1.7)	0.3 (0.1-1)	1.3 (0.3-5.5)	DESV				
2.1 (1.5-3)	1.2 (0.7-2)	1.1 (0.8-1.7)	0.9 (0.6-1.4)	0.7 (0.4-1.2)	1 (0.7-1.4)	1.2 (0.8-1.9)	1.2 (0.7-2.1)	0.8 (0.5-1.2)	**0.3 (0.1-0.9)**	1.5 (0.5-4.9)	1.1 (0.5-2.7)	DUL			
3.1 (2.1-4.6)	**1.7 (1-2.9)**	**1.6 (1.1-2.6)**	1.3 (0.8-2)	1 (0.5-1.7)	1.4 (1-2)	**1.8 (1.2-2.6)**	**1.7 (1-3)**	1.1 (0.7-1.6)	0.5 (0.2-1.2)	2.2 (0.6-7.2)	1.7 (0.6-4.2)	1.4 (0.9-2.2)	MIR		
2.5 (0.8-8.1)	1.4 (0.4-4.8)	1.3 (0.4-4.4)	1 (0.3-3.4)	0.8 (0.2-2.5)	1.1 (0.3-3.6)	1.4 (0.5-4.4)	1.4 (0.4-4.7)	0.9 (0.3-3)	0.4 (0.1-1.6)	1.8 (0.3-9)	1.3 (0.3-5.7)	1.2 (0.4-3.9)	0.8 (0.3-2.6)	MOC	
1.9 (1.3-2.9)	1.1 (0.6-1.9)	1 (0.7-1.6)	0.8 (0.5-1.2)	0.6 (0.3-1.1)	0.8 (0.6-1.3)	1.1 (0.7-1.7)	1.1 (0.6-1.8)	0.7 (0.4-1.1)	**0.3 (0.1-0.8)**	1.3 (0.4-4.4)	1 (0.4-2.6)	0.9 (0.6-1.4)	**0.6 (0.4-1)**	0.8 (0.2-2.5)	VEN

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of fatigue with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and treatment rankings***. **Table 8** presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons. Placebo was associated with the largest SUCRA value and most favorable ranking, while clomipramine appears to be associated with the largest risk of fatigue. All three classes were otherwise associated with similar ranges of SUCRA and median ranks.

Table 8:
Additional Summary Measures, Fatigue

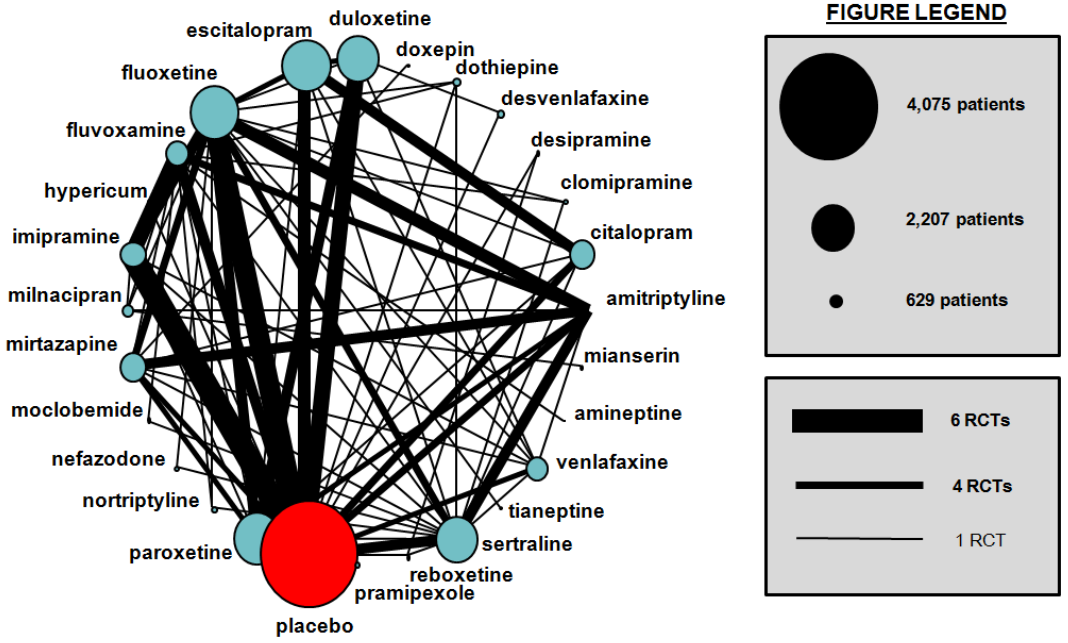
Treatment	SUCRA (%)	median rank (95% CrI)
Placebo	89.9%	3 (2-5)
SSRIs		
Sertraline	65.7%	8 (4-14)
Citalopram	61.8%	9 (4-17)
Escitalopram	59.2%	9 (4-16)
Paroxetine	43.4%	13 (7-18)
Fluoxetine	37.7%	14 (8-19)
Fluvoxamine	21.3%	18 (10-21)
TCAs		
Desipramine	68.1%	5 (2-20)
Imipramine	63.1%	8 (3-16)
Amitriptyline	27.6%	17 (10-20)
Clomipramine	5.3%	21 (16-22)
Non-SSRI/TCA		
Venlafaxine	58.1%	10 (4-16)
Desvenlafaxine	56.2%	9 (2-20)
Duloxetine	47.6%	12 (6-18)
Moclobemide	40.1%	15 (2-22)
Mirtazapine	20.6%	18 (13-21)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of fatigue.

4.1.3.6 Findings, Drowsiness

Figure 17 presents a network diagram summarizing pairwise comparisons that were available within our set of included RCTs.[41-48,50,52,54-57,59,61,63,65-71,73-82,85-89,92,99,100,102-107,109,111-124,126-140,142-145,147-157,160,162,165-169,171,174-180,186,187,190-192,195-197,199-202,205-209,213,215,221,222 95,96,181-185,217] A total of 27 interventions were associated with RCTs that reported data on drowsiness, with the numbers of trials and randomized patients per treatment ranging from 1–44 (median 4, IQR 1-21) and 20–4,079 (median 226, IQR 105-1,864), respectively. Comparisons of placebo against imipramine and fluoxetine as well as between imipramine and fluvoxamine were most prevalent. Many comparisons between treatments were again informed by just a single trial, and many comparisons were not supported by existing RCTs.

Figure 17 - Network Diagram, Drowsiness:
Including Data from 145 studies, 29,378 participants (3,412 events)

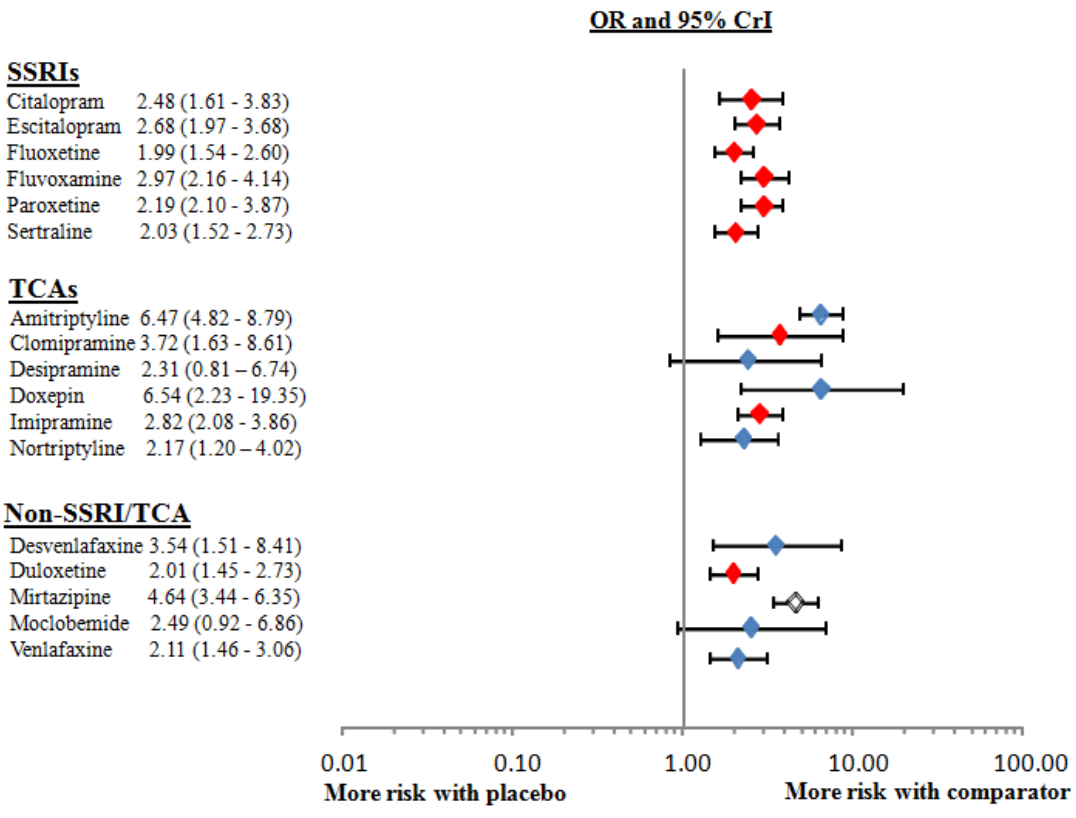


Joining lines indicate where head-to-head RCTs between agents were identified. Adjoining lines are sized to be proportional to the number of studies identified for each comparison. Treatment nodes are proportionally sized to reflect the number of patients randomized to each agent.

Only the random effects model was a reasonable fit to the data (residual deviances of 410.3 and 343.0 for random and fixed effects models compared to 328 unconstrained data points); random effects was chosen as the primary model (DIC 1745.3, compared to 1767.9 for fixed effects). **Figure 18** provides a summary of the odds ratios against the reference group, placebo, derived from network meta-analysis, while **Figure 19** summarizes all pairwise comparisons between interventions. Our findings suggest the following:

- ***Comparisons against placebo***. Considering the agents by class, the following results can be observed from **Figure 18**.
    - Regarding SSRIs, all six agents were associated with statistically significant increases in the risk of drowsiness (range of ORs 1.99-2.97).
    - Regarding TCAs, five of six agents were associated with statistically significant increased risks (range of ORs 2.17-6.54). One agent (desipramine) also showed a similar trend, though the lower bound of its credible interval included 1 (OR 2.31, 95% CrI 0.81-6.74).
    - Regarding non-SSRI/TCAs, four of five agents showed increased risks of drowsiness (range of ORs 2.01-4.64). Similar to despramine, moclobemide also showed a similar trend but had a credible interval which narrowly included 1 (OR 2.49, 95% CrI 0.92-6.86).
    - Based on the pattern of summary estimates seen when considering the agents by serotonin affinity grouping (red=high, blue=moderate, white=low), there doesn't appear to be evidence of a relationship between serotonin affinity and the occurrence of fatigue.

Figure 18: Forest Plot of Comparisons versus Placebo, Drowsiness – Summary Odds Ratios and Credible Intervals



Summary estimates from network meta-analysis comparing the frequency of drowsiness. Antidepressants are organized by class. Colored diamonds for each summary estimate reflect the serotonin affinity of each agent (red=high, blue=moderate, white=low). Estimates were generated using a random effects model.

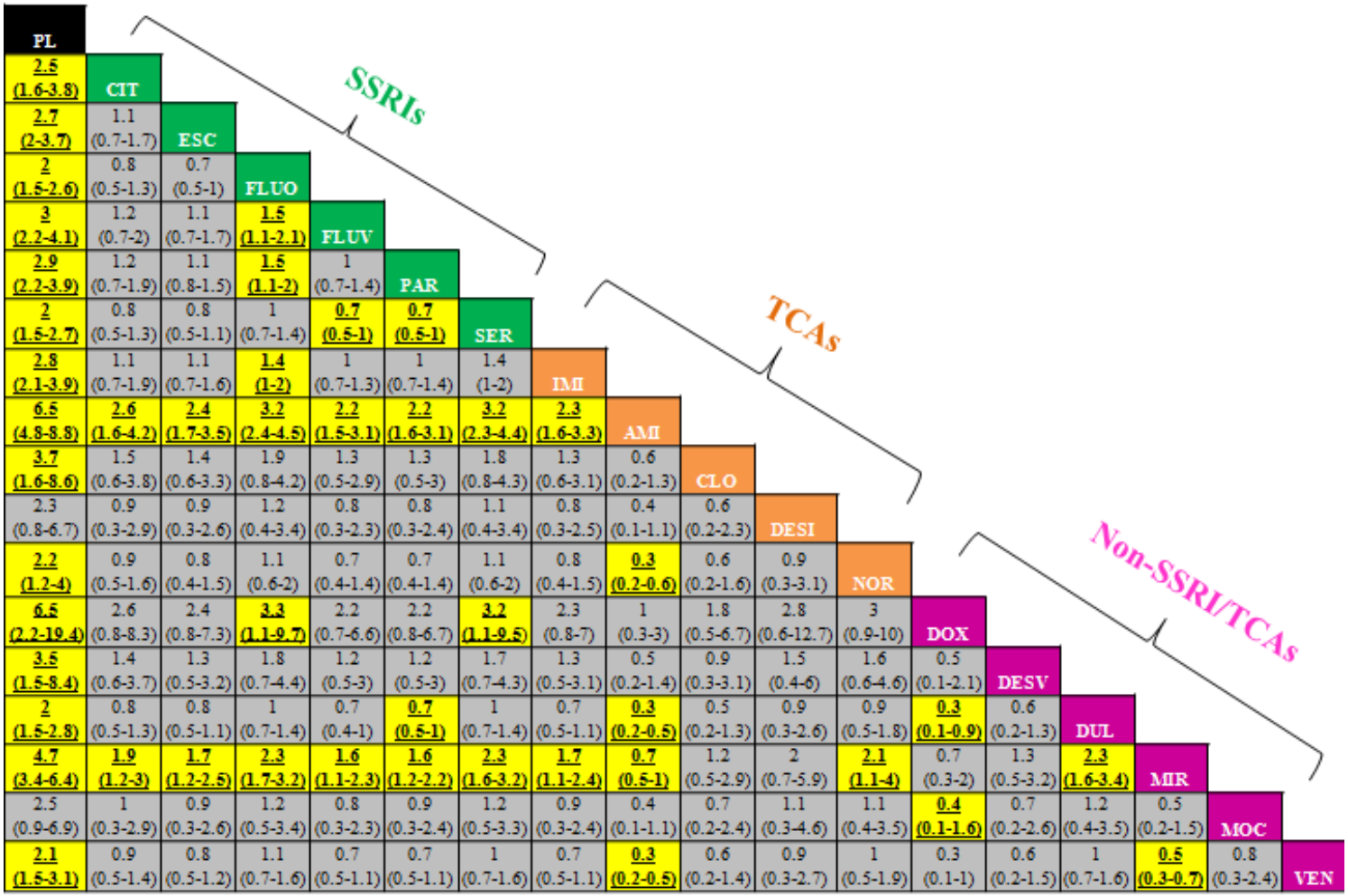
- ***Comparisons between active agents***. Considering findings from comparisons of the agents by class, **Figure 19** shows the following:

    - Regarding SSRIs, comparisons with agents in the TCA category showed SSRIs were consistently associated with a lesser risk of drowsiness when compared against amitriptyline; a similar trend was noted for comparisons against clomipramine, however all credible intervals were wide and inconclusive. Fluoxetine was also associated with a lower risk compared to imipramine. Comparisons with non-SSRI/TCAs found all SSRIs to be associated with a lower risk compared to mirtazapine; a similar trend was noted for comparisons against venlafaxine, however all credible intervals were wide and inconclusive. Paroxetine was associated with a greater risk of drowsiness compared to duloxetine. When comparing the different SSRIs against each other, fluoxetine was associated with a lower risk of drowsiness compared to each of fluvoxamine and paroxetine, and sertraline was associated with less risk compared to each of fluvoxamine and paroxetine.

    - Regarding TCAs, comparisons with non-SSRI/TCAs showed that amitriptyline was associated with a greater risk of drowsiness than duloxetine, mirtazapine and venlafaxine; imipramine and nortriptyline were also associated with an increased risk compared to mirtazapine. Comparisons between the different TCAs were mostly inconclusive, however estimates suggested increased risks with amitriptyline compared to imipramine and nortriptyline.

    - Regarding non-SSRI/TCAs, comparisons between the different agents in this grouping suggested increased risks with doxepin and mirtazapine compared to duloxetine, as well as mirtazapine compared to venlafaxine. All other comparisons were inconclusive.

Figure 19: League Table Summary of Pairwise Comparisons, Drowsiness



PL	CIT	ESC	FLUO	FLUV	PAR	SER	IMI	AMI	CLO	DESI	NOR	DOX	DESV	DUL	MIR	MOC	VEN
2.5 (1.6-3.8)																	
2.7 (2-3.7)	1.1 (0.7-1.7)																
2 (1.5-2.6)	0.8 (0.5-1.3)	0.7 (0.5-1)															
3 (2.2-4.1)	1.2 (0.7-2)	1.1 (0.7-1.7)	**1.5 (1.1-2.1)**														
2.9 (2.2-3.9)	1.2 (0.7-1.9)	1.1 (0.8-1.5)	**1.5 (1.1-2)**	1 (0.7-1.4)													
2 (1.5-2.7)	0.8 (0.5-1.3)	0.8 (0.5-1.1)	1 (0.7-1.4)	**0.7 (0.5-1)**	**0.7 (0.5-1)**												
2.8 (2.1-3.9)	1.1 (0.7-1.9)	1.1 (0.7-1.6)	**1.4 (1-2)**	1 (0.7-1.3)	1 (0.7-1.4)	1.4 (1-2)											
6.5 (4.8-8.8)	**2.6 (1.6-4.2)**	**2.4 (1.7-3.5)**	**3.2 (2.4-4.5)**	**2.2 (1.5-3.1)**	**2.2 (1.6-3.1)**	**3.2 (2.3-4.4)**	**2.3 (1.6-3.3)**										
3.7 (1.6-8.6)	1.5 (0.6-3.8)	1.4 (0.6-3.3)	1.9 (0.8-4.2)	1.3 (0.5-2.9)	1.3 (0.5-3)	1.8 (0.8-4.3)	1.3 (0.6-3.1)	0.6 (0.2-1.3)									
2.3 (0.8-6.7)	0.9 (0.3-2.9)	0.9 (0.3-2.6)	1.2 (0.4-3.4)	0.8 (0.3-2.3)	0.8 (0.3-2.4)	1.1 (0.4-3.4)	0.8 (0.3-2.5)	0.4 (0.1-1.1)	0.6 (0.2-2.3)								
2.2 (1.2-4)	0.9 (0.5-1.6)	0.8 (0.4-1.5)	1.1 (0.6-2)	0.7 (0.4-1.4)	0.7 (0.4-1.4)	1.1 (0.6-2)	0.8 (0.4-1.5)	**0.3 (0.2-0.6)**	0.6 (0.2-1.6)	0.9 (0.3-3.1)							
6.5 (2.2-19.4)	2.6 (0.8-8.3)	2.4 (0.8-7.3)	**3.3 (1.1-9.7)**	2.2 (0.7-6.6)	2.2 (0.8-6.7)	**3.2 (1.1-9.5)**	2.3 (0.8-7)	1 (0.3-3)	1.8 (0.5-6.7)	2.8 (0.6-12.7)	3 (0.9-10)						
3.5 (1.5-8.4)	1.4 (0.6-3.7)	1.3 (0.5-3.2)	1.8 (0.7-4.4)	1.2 (0.5-3)	1.2 (0.5-3)	1.7 (0.7-4.3)	1.3 (0.5-3.1)	0.5 (0.2-1.4)	0.9 (0.3-3.1)	1.5 (0.4-6)	1.6 (0.6-4.6)	0.5 (0.1-2.1)					
2 (1.5-2.8)	0.8 (0.5-1.3)	0.8 (0.5-1.1)	1 (0.7-1.4)	0.7 (0.4-1)	**0.7 (0.5-1)**	1 (0.7-1.4)	0.7 (0.5-1.1)	**0.3 (0.2-0.5)**	0.5 (0.2-1.3)	0.9 (0.3-2.6)	0.9 (0.5-1.8)	**0.3 (0.1-0.9)**	0.6 (0.2-1.3)				
4.7 (3.4-6.4)	**1.9 (1.2-3)**	**1.7 (1.2-2.5)**	**2.3 (1.7-3.2)**	**1.6 (1.1-2.3)**	**1.6 (1.2-2.2)**	**2.3 (1.6-3.2)**	**1.7 (1.1-2.4)**	**0.7 (0.5-1)**	1.2 (0.5-2.9)	2 (0.7-5.9)	**2.1 (1.1-4)**	0.7 (0.3-2)	1.3 (0.5-3.2)	**2.3 (1.6-3.4)**			
2.5 (0.9-6.9)	1 (0.3-2.9)	0.9 (0.3-2.6)	1.2 (0.5-3.4)	0.8 (0.3-2.3)	0.9 (0.3-2.4)	1.2 (0.5-3.3)	0.9 (0.3-2.4)	0.4 (0.1-1.1)	0.7 (0.2-2.4)	1.1 (0.3-4.6)	1.1 (0.4-3.5)	**0.4 (0.1-1.6)**	0.7 (0.2-2.6)	1.2 (0.4-3.5)	0.5 (0.2-1.5)		
2.1 (1.5-3.1)	0.9 (0.5-1.4)	0.8 (0.5-1.2)	1.1 (0.7-1.6)	0.7 (0.5-1.1)	0.7 (0.5-1.1)	1 (0.7-1.6)	0.7 (0.5-1.1)	**0.3 (0.2-0.5)**	0.6 (0.2-1.4)	0.9 (0.3-2.7)	1 (0.5-1.9)	0.3 (0.1-1)	0.6 (0.2-1.5)	1 (0.7-1.6)	**0.5 (0.3-0.7)**	0.8 (0.3-2.4)	

The treatment at the top of each column is the reference group for comparisons in that column, while the comparator is the lower treatment in the league table; a value <1 suggests fewer cases of drowsiness with the comparator than with the reference group. Statistically significant differences (i.e. estimates with a 95% credible interval excluding 1) are bolded, underlined, and highlighted in yellow. Estimates have been rounded to one decimal place in order to fit all information.

- ***SUCRA and treatment rankings***. **Table 9** presents the SUCRA values and median treatment rankings from analysis of the included studies. These values were supportive of findings from pairwise comparisons. SUCRA values and treatment rankings corresponded to the observation that placebo was associated with the least risk of dizziness, and that SSRIs were associated with qualitatively more favorable values than the other two classes. Regarding specific agents, fluoxetine, sertraline and sertraline were associated with the three most favorable SUCRA values suggestive of a lower increase in the risk of drowsiness.

Table 9:
Summary Effect Measures, Drowsiness

Treatment	SUCRA (%)	median rank (95% CrI)
Placebo	94.4%	2 (1-4)
SSRIs		
Fluoxetine	71.1%	8 (5-13)
Sertraline	69.8%	9 (4-14)
Citalopram	54.1%	13 (5-21)
Escitalopram	47.5%	15 (8-20)
Paroxetine	41.3%	16 (11-21)
Fluvoxamine	39.8%	17 (11-21)
TCAs		
Nortriptyline	62.8%	10 (3-21)
Desipramine	57.2%	11 (2-25)
Imipramine	43.7%	16 (9-21)
Clomipramine	31.3%	20 (6-26)
Doxepin	12.8%	25 (11-27)
Amitriptyline	7.9%	25 (22-27)
Non-SSRI/TCA		
Duloxetine	70.3%	8 (4-15)
Venlafaxine	66.3%	10 (4-17)
Moclobemide	53.5%	13 (2-25)
Desvenlafaxine	34.3%	20 (5-26)
Mirtazapine	18.1%	22 (19-25)

Agents are arranged by class and by decreasing SUCRA value. Larger SUCRA values (i.e. nearer 100%) and smaller rankings (i.e. nearer 1) suggest lower risk of drowsiness.

4.1.3.7 Additional Analyses:
Evaluations of Heterogeneity and Consistency

To supplement our primary unadjusted analyses, we also performed meta-regression analysis to adjust for control group risk across studies. Based on model fit statistics, none of these models were found to improve the fit of the model to the data for any of our clinical outcomes. Analyses performed for each of the outcomes of interest to assess the assumption of consistency between direct and indirect evidence showed no evidence of inconsistency in any of our analyses; again, in all cases we found that inspection of fit statistics generated by the alternative model formulations to be of no gain (and typically worse) in terms of fit. **Appendices 3-4** provide relevant statistical summaries from these analyses.

4.2 Associations of Affinity with Fractures and Bone Mineral Density

4.2.1 Literature Search Results

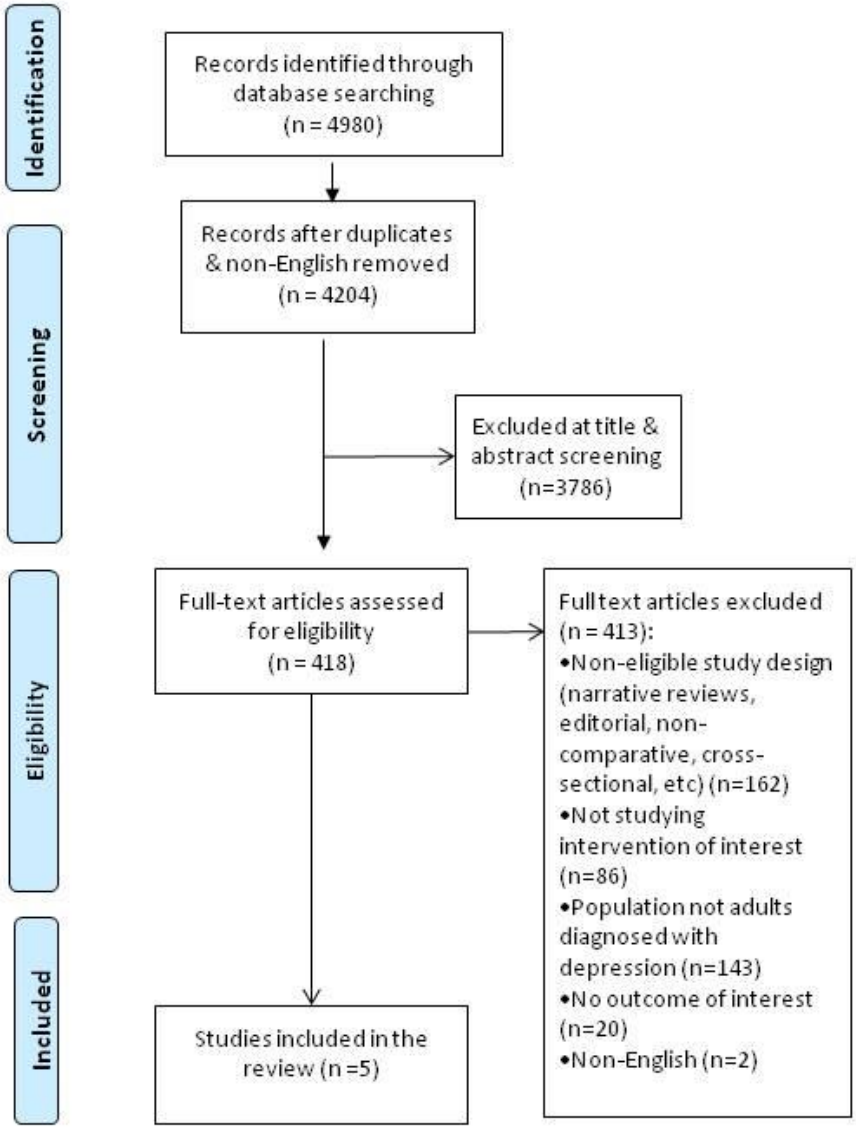
Figure 20 presents a PRISMA flow diagram documenting the literature selection process for our search to identify relevant observational studies addressing a possible long-term association of serotonin affinity with the outcomes of interest. In total, 5 cohort studies[17,18,223-225] were included to address the potential existence of a long-term association between the serotonin affinity level of antidepressants and its impact on fractures and changes in bone mineral density.

4.2.2 Study Design Features, Intervention Groups, Outcomes Reported

Table 10 provides a summary of key characteristics of the included observational studies Overviews of key characteristics are as follows:

- ***Study Design and Analysis***: Amongst the studies where duration of follow-up was reported, follow-up ranged from a minimum of 6 weeks to a maximum of an average 5 years. None were industry funded. One study employed propensity score matching techniques to achieve balance between treatment groups on a broad range of demographics, while others generally employed multivariable adjustment using logistic or linear regression to account for between-group differences in relevant risk factors.

Figure 20: PRISMA Flow Diagram, Observational Studies



- ***Study Populations***: All included studies enrolled patients with depressive symptoms. It was common for the control group to be non-users of antidepressants who did not display depressive symptoms, though one study did include a depressed control group.[17] The mean age of patients in most studies was indicative of an elderly study population (many pre-specified this in their eligibility criteria), while one small study[224] was performed in younger subjects (mean age of 37 years). Both the duration and severity of depression were not consistently reported from study to study. The degree of co-medication varied across studies in terms of current/past use of other benzodiazepines and other relevant agents, and the extent of reporting of this information across studies was variable (a detailed account is provided in **Appendix 5**). Some studies were performed in

community dwelling subjects while others were performed in nursing home residents. Two studies enrolled large sample sizes of 60,746[18] and 10,844,[17] respectively, while the remainder of studies were mostly small (**Table 10**). Studies commonly consisted of a majority of female participants.

- ***Interventions***: A total of 4 studies presented between-group comparisons of antidepressant users at the class level (e.g. SSRI users vs TCA users vs non-users), while 1 provided data at the individual agent level. Overall 5 studies included a high serotonin affinity group (i.e. SSRI users); exposure groups which were purely treated with agents of moderate affinity only or low affinity only were not identified, as comparator groups in many studies were reported at the class level (e.g. TCA users) where agents are a mixture of agents of varied affinity levels and the number of patients receiving the different agents was not consistently clear. Only one study directly addressed serotonin affinity in its approach to analysis, however their categories of dissociation constants to define affinity categories partially differed from our a priori approach.[17]

- ***Outcomes reported***: Overall 2 studies reported information on the occurrence of falls, 2 on fractures, and 2 on changes in bone mineral density over time at one or more body sites.. The occurrence of falls and fractures were commonly reported in the format of adjusted rate ratios, while changes in bone mineral density over time were reported as mean change scores at the different body sites assessed. Analyses comparing the frequency of fractures between different exposure groups commonly were based on multivariable analyses adjusting for a broad range of risk factors related to patient demographics, comorbidities and past or current drug exposures..

Table 11 provides a brief overview of study characteristics, methods and findings, while tables provided in **Appendix 5** summarize study methods and patient characteristics in more depth with regard to co-medications, demographics, and other features.

Table 10: Summary of Observational Study Characteristics

Trial Characteristic	Categories	# of Included Studies
Study Design	Prospective/retrospective cohort	5 (100%)
Gender	% female participants, range	67.7%-100% (one not reported)
Age	Median (range) in years	70.4 (37-77 years; not reported in one study)
Geographic Location	US	3 (60%)
	Europe	1 (20%)
	Not reported	1 (20%)
Industry sponsored	# yes/no	0/5
Publication year	Median and range	Medians 2008/2011 (range 1981-2012)
Study sample size	Range	40 - 60,746 (one not reported)
	# fewer than 100 total patients	2 (40%)
	# more than 1000 total patients	2 (40%)
Outcomes studied	Falls	2 (40%)
	Fractures	2(40%)
	Change in BMD, one or more body sites	2(40%)

4.2.3 Risk of Bias Assessments, Observational Studies

Risk of bias assessments of the included observational studies based on the Downs and Black scale identified are provided in **Appendix 5**. In brief, all full text articles provided clear statements of their objectives, their outcome measures, patient characteristics, and assessed valid and reliable outcome measures. Reporting of study findings and provision of measures of uncertainty were judged adequate in most studies. None of the studies were randomised or involved blinding of subjects. The most common limitations of the observational studies were limited adjustments for potentially important confounders, lack of clarity in some instances about the representativeness of study populations and settings, and small sample size.

4.2.4 Overview of Study Findings

Following review of the included observational studies, a decision as to whether to meta-analyze data was discussed. Given that patient age, presence of comorbidities, severity of illness, and extent of co-medication use were found to vary considerably across studies, meta-analysis of study-level data was judged inappropriate. The following sections provide a narrative summary of study findings for the outcomes of interest; **Table 11** provides a summary of study level findings.

Table 11: Overview of Included Observational Studies				
Author, Design; Study Purpose	**Sample Period; Outcome(s)**	**Exposure Groups and Sample Size**	**Confounder adjustment in analyses**	**Brief Summary of Findings**
Gagnee et al[17] (2011); Cohort study, single community site (US); Compare fracture rates across exposure groups and see if serotonin affinity of antidepressants explains differences	1994-2004 ; Fractures	Antidepressants with i) Low ii) Medium iii) High affinity ; Total sample size of 2,711 participants per group	Propensity matching to address confounding by indication ; models considered demographic measures, psychiatric conditions, and risk factors for fracture	Based on the data, variations in the fracture risk between antidepressants could not be explained by their associated serotonin affinity level, and it other factors including depression severity warrant consideration.
Coupland et al[18] (2011); Cohort study, 560 tertiary care sites (US); Study association of antidepressants and risk of harms in depressed elderly patients	1996-2008 ; Fractures, Falls	Non-users of antidepressants ; users of SSRIs ; users of TCAs ; users of other antidepressants ; Total of 60,746 patients	Age, gender, history of depression, depression severity, deprivation, smoking, baseline comorbidities, co-medications used	There was a lack of evidence suggesting that TCAs are associated with a greater risk of adverse outcomes relative to other treatments, but that SSRIs may be associated with a greater risk of certain outcomes including both falls and fractures.
Thapa et al[223] (1998) Cohort; 80 nursing homes (US); Compare rate of falls between new users of TCAs and SSRIs.	Varied across groups ; began between 1993-96 ; Falls	Non-users of antidepressants ; new users of SSRIs ; new users of TCAs ; new users of trazodone ; Sample size for depressed subgroup not reported (2,428 overall)	Age, sex, race, body mass index, ambulatory status, cognitive impairment, activity level, co-medication use	The rate of falls was similar between older and newer antidepressants, and that use of newer agents is unlikely to modify the rate of falls in nursing home residents.
Winterhalder et al[224] (2012); Cohort, single tertiary care site (Switzerland); Study longitudinal changes in trabecular volumetric BMD in young depressed patients receiving SSRI vs. other antidepressants	Not reported ; BMD	SSRI users ; NSRI and TCA users Total sample size of 40 patients	None reported	The negative effect of SSRIs on BMD seen in other studies was not observed due to both the lower serotonergic activity of the SSRIs used, the short follow-up time of 12 months, and the younger age of the study population
Choi et al[225] (2011) (abstract); Cohort, setting not reported; Study association of SSRI use & BMD change in postmenopausal depressed women	Not reported ; BMD	SSRI users ; non-users of antidepressants. Total sample size of 81	None reported	Analyses suggested a more rapid decline in BMD in the SSRI group compared to the anti-depressant free group at the right femur, left femur, and lumbar area. SSRI use may be associated with more rapid decline of BMD in postmenopausal women.
BMD=bone mineral density ; SSRI=selected serotonin reuptake inhibitor ; TCA=tricyclic antidepressants. ***A detailed summary of study characteristics and patient characteristics is provided in the appendices to this report.***				

4.2.3.1 Findings: Incidence of Falls and Fractures

Gagne et al[17] (2011) reported findings from a propensity score matched cohort study that assessed the comparative safety of antidepressant treatments in Medicare beneficiaries in two US states treated between 1994-2004. The study consisted of four groups: secondary amine tricyclics, tertiary amine tricyclics, selective serotonin reuptake inhibitors, and atypical antidepressants. A total of 2,711 patients per group were included following propensity score matching from a total of more than 70,000 subjects. The authors explored whether variations in fracture rates were associated with (i) type of antidepressant exposure; and (ii) serotonin transport affinity of antidepressants, which in the study were classified as *low* (K_i>100nmol/L), *medium* (K_i 10-100nmol/L) or *high* (K_i<10nmol/L)(these categories differed some from those chosen for this review, whose ranges were <10, 10-1,000, and>1,000nmol/L, respectively); both short-term and long-term analyses were performed. Balance of demographics between groups in the matched sample was high on many demographics including age, gender, race, comorbidities (including dementia, ADHD, Parkinson`s disease, Alzheimer`s disease and sleep disorders), osteoporosis related risk factors (rheumatiod arthritis, history of a prior fracture or visit for a fall), and use of risk-modifying medications for falls (benzodiazipines, anticonvulsants, glucocorticoids, thiazolidinedione, etc). Mean age for the propensity-matched sample was 77 years, and 84% were female.The authors also performed analyses assessing the incident fracture rates per 1,000 person years observed when co-stratifying antidepressant agents by both sedation potential as described elsewhere[226] and by serotonin affinity. While the fracture rate rose with increasing affinity in the grouping of drugs with low sedative potential, this did not hold true in drugs with medium or high sedative potential, and the authors concluded that no discernable pattern was present. Prior to the study the authors hypothesized there would exist an association between serotonin affinity and fracture risk in long-term analyses only, however short-term analyses and long-term analyses generated similar findings. The authors noted that differences between groups for fracture-free time diverged early during follow-up. The authors concluded that, based on their findings, variations in the fracture risk between antidepressants could not be explained by their associated serotonin affinity level, and it was suggested that other factors including depression severity warrant consideration.

Coupland et al[18] (2011) reported findings from a cohort study of depressed individuals from 570 general practices the UK aged 65 years or more (N=60,746) which studied the association between antidepressant use and the risk of several harms, two of which were falls and fractures. Patients with a newly diagnosed episode of depression between 1996-2007 were included, and patient follow-up concluded in 2008. The study consisted of a control group of individuals not taking any antidepressants, those taking TCAs (mainly amitriptyline, dosulepin, lofepramine and trazodone;), those taking SSRIs (mainly citalopram, fluoxetine, paroxetine, sertraline and escitalopram; all high affinity for serotonin), and those taking other antidepressants (mainly venlafaxine and mirtazapine). The mean age of patients overall was 75.0 years, 66.7% were female, and the median duration of antidepressant use was one year. Doses were typically lowest for TCAs in terms of defined daily doses. Statistical analyses were performed using a time-to-event approach and incorporated a wide range of patient covariates including age at study entry, gender, year of depression diagnosis, existence of a past depression diagnosis, severity of index depression diagnosis, smoking status, a broad range of comorbidities at baseline (hypertension,

cancer, stroke, dementia, Parkinson's disease, coronary heart disease, etc), use of additional medications (statins, NSAIDs, antipsychotics, antihypertensive agents, hypnotics, anxiolytics, anticonvulsants, etc), and a history of falls prior to study entry. Based on this approach to modeling, each of the SSRI (HR 1.66, 95% CI 1.58 - 1.73) TCA (HR 1.30, 95% CI 1.23 - 1.38) and other antidepressants (HR 1.39, 95% CI 1.28 - 1.52) groups were associated with elevated risks of falls and fractures. Compared to TCAs, SSRIs were associated with statistically significantly higher rates of both falls (HR 1.27, CI 95% CI 1.20-1.35) and fractures (HR 1.26, 95% CI 1.15-1.37); the grouping of other antidepressants showed only an increased risk for the occurrence of fractures (HR 1.31, 95% CI 1.15-1.50). Analyses by individual antidepressant agent amongst the 11 most commonly prescribed agents showed that SSRIs were associated with the largest increase in the risk of falls, while findings regarding fractures showed relatively similar associations. Analyses according to drug dose showed a trend between escalating doses of TCAs and SSRIs with the risk of falls, but not with the risk of fractures. The authors concluded that there was a lack of evidence suggesting that TCAs are associated with a greater risk of adverse outcomes relative to other treatments, but that SSRIs may be associated with a greater risk of certain outcomes including both falls and fractures.

Thapa et al[223] (1998) reported findings from a retrospective inception cohort of US nursing home residents (53 sites) that assessed the occurrence of falls and injurious falls in new users of TCAs (n=665; included nortriptyline (moderate affinity), amitriptyline (moderate affinity), doxepin (moderate affinity) and imipramine(high affinity)), SSRIs (n=612; all high affinity agents), trazodone (n=304; moderate affinity), and non-users (n=847). Non-users were randomly chosen from nursing home residents not on antidepressants, and matched by date of admission and index date of antidepressant therapy initiation. Study follow-up continued for antidepressant users until they left the nursing home due to either death, discharge, transfer or extended hospital stay elsewhere, or at the time antidepressant medications were halted for 2 weeks or more. For non-users, follow-up continued until time of departure from the nursing time, time starting antidepressant therapy, or the time the matched user's follow-up ended. The users group was different from the non-users group in several ways including presence of greater mobility, increased co-medication use (benzodiazepines, antipsychotics, other sedative/hypnotic agents), and approximately double the extent of falls in the prior 3 months. In the full cohort, each of the classes of agents was associated with an increased rate of fall occurrence relative to the non-users group; rate ratios were 2.0 (95% CI 1.8-2.2) for TCAs, 1.8 (1.6-2.0) for SSRIs, 1.2 (1.0-1.4) for trazodone. The increased rates of fall remained present for the first 6 months of treatment and beyond. Amongst the study cohort, a subgroup of 910 were diagnosed with depression as their primary indication (366 TCAs, 492 SSRIs, 103 trazodone), however demographic and medication information was only available from the full cohort. Patients were aged 65 years and older, the mean age was 82 years, 75% of subjects were females, and 60% used wheelchairs or were chair/bed bound. For those with depression or depressive symptoms, rate ratios for TCAs, SSRIs and trazodone were 1.8 (1.6-2.0), 1.7 (1.6-1.9), and 1.1 (0.9-1.3) compared to no intervention. The authors calculated adjusted rate ratios for falls every 60 days for up to approximately 270 days of follow-up, and found that the pattern of risk was generally consistent across time points.The authors concluded that the rate of falls was similar between older and newer antidepressants, and that use of newer agents is unlikely to modify the rate of falls in nursing home residents.

4.2.4.2 Changes in Bone Mineral Density

Winterhalder et al[224] (2012) assessed 12-month changes in bone mineral density and bone geometry of the radius and tybia in a total of 26 SSRI users and 14 SNRI/TCA users of mean age of 37 years seen at a clinic in Switzerland. Overall, 85% of patients were female, and patients with any history of previous antidepressant use, bisphosphonate use, glucocorticoid use, or several comoribidities (e.g. bone metabolic disease, hyper-hypoparathyroidism, chronic renal insufficiency, cancer, pregnancy, or lactation) were excluded. Those in the SSRI group were receiving one of fluoxetine (n=1), paroxetine (5), citalopram (7), sertraline (3), or escitalopram (10) (all high affinity agents), while patients in the SNRI/TCA group received one of venlafaxine (7), duloxetine (3), amitriptyline (3) or trimipramine (1) (all moderate affinity agents with the exception of duloxetine (high affinity)). Groups were similar with regard to age, height and Beck depression score at baseline, though patients in the non-SSRI group had a greater mean body mass and a shorter mean duration of therapy at baseline (10.2 months vs 7.9 months). Over 12 months of follow-up, minimal changes in measures of bone mineral density or bone geometry were observed in the SSRI group, while patients receiving SNRI/TCA agents were associated with statistically significant changes in trabecular bone mineral density at the tibia and radious of 1.8% and 1.0%; the authors note that the clinical relevance of this change is not clear. The authors noted that the negative effect of SSRIs on BMD seen in other studies is likely not observed in this work due to both the lower serotonergic activity of the SSRIs used and the relatively short follow-up time of 12-14 months, as well as the younger age of the study population (and related small number of patients with a low BMD for age). Other cited study limitations potentially impacting the ability to identify differences included the small sample size and the fact that some patients were already on treatment prior to baseline assessment.

In addition to the included full text reports, one abstract was also included from our literature search. Information regarding methods for study design, data analysis and patient characteristics was limited. In a small retrospective cohort study, Choi et al[225] assessed changes in bone mineral density in a group of depressed post-menopausal women receiving treatment with SSRIs (n=34) compared to a group of similar women not receiving antidepressants (n=47). BMD was assessed prior to and following diagnosis of depression, and a comparison of BMD changes between groups was performed at average follow-up durations of 18.9 months in the untreated group and 12.4 months in the group receiving SSRIs. The mean age of the cohort was approximately 66 years, and groups were similar with regard to use of calcium agents and hormone replacement therapy. Analyses suggested a more rapid decline in bone mineral density in the SSRI-treated group compared to the anti-depressant free group, as shown by statistically significant differences of change at the sites of the right femur (0.026 (0.23) versus -0.20 (0.43)), left femur (0.032 (0.20) versus -0.20 (0.29)), and lumbar area (0.01 (0.34) versus -0.15 (0.33)). The authors concluded that their findings may implicate SSRIs as being associated with more rapid decline of BMD in postmenopausal women.

4.2.4.3 Existing Systematic Reviews of Observational Data

During protocol development for this work, two existing reviews were identified;[24,25]. Wu et al[24] conducted a meta-analysis of cohort and case-control studies, and included sensitivity analyses limiting studies to those adjusting for BMD and depression; all findings suggested an increased risk of fracture, and the authors note a potential effect of SSRIs (i.e. high affinity agents) on fracture independent of depression and bone mineral density. Eom et al[25] (2012) included similar studies and drew similar conclusions. In the most recently published meta-analysis identified during the conduct of our review, Rabenda et al[26] also investigated the association between use of antidepressants and the risk of fractures. The authors conducted a systematic review of both case-control and cohort studies (published or performed between 1966-2011) that reported risk estimates of fracture associated with use of antidepressants. A total of 34 publications (33 studies [20 case-control and 13 cohort studies] with 1.2 million individuals) were identified. Compared with non-users, there was an increased risk of fractures of all types with the use of antidepressants: random effects relative risk [RR] = 1.39 (95%CI: 1.32-1.47). Use of antidepressants were associated with a risk increase in non-vertebral, hip, and spine fractures, respectively ([non-vertebral fractures: RR = 1.42, 95%CI: 1.34-1.51]; [hip fractures: RR = 1.47, 95%CI: 1.36-1.58]; [spine fractures: RR = 1.38, 95%CI: 1.19-1.61]). The authors showed that both SSRIs and TCAs were associated with an increased risk of fractures of all types, but suggested that studies evaluating SSRI use showed a higher increase in the risk of fractures of all types, non-vertebral, and hip fractures than studies evaluating TCA use.

5. DISCUSSION

5.1 Summary and Interpretations

In this systematic review, we explored the possibility of a bi-modal effect of antidepressant therapies and their levels of serotonin affinity on the risk of fractures, falls, and changes in bone mineral density in depressed patients using a combination of randomized and observational evidence. We used data from antidepressant RCTs to explore whether certain antidepressants may be associated with the occurrence of side effects which may place users, particularly the elderly, at an increased of falling and incurring a larger number of falls (and thus potentially increasing the risk of fractures). Our network meta-analyses of RCT data for vision problems, dizziness, hypotension, insomnia, fatigue and drowsiness confirmed increased risks of all of these outcomes with agents from high, moderate and low serotonin affinity categories. Many of these risks are not surprising and have been described elsewhere.[227-229] Some unexpected findings included observations that (i) TCAs were not always found significantly worse for harms than no treatment (e.g. for hypotension, however considerable uncertainty of findings was present); (ii) that sertraline appeared to cause more vision problems than escitalopram and fluoxetine); (iii) that in some cases the TCA imipramine did not show as much risk for vision problems as expected; (iv) that SSRIs showed significant reductions in the occurrence of hypotension relative to amitriptyline and imipramine. No clear pattern between risk and affinity level was noted, and in many cases there was little difference amongst the agents within a given class. While we identified important differences between some interventions in the risks of these side effects which could potentially be associated with an increased risk of falls (and thus

possibly fractures), the extent to which important variations in the frequency of these side effects may be associated with increased numbers of falls or fractures remains unclear. Additionally, the timing of these outcomes during the conduct of randomized trials is not known, but it remains possible they may occur more commonly during the early part of these studies when dose titration is being established and side effects may be more prevalent. It may be possible that some agents or classes of agents provide effecive treatment more quickly, and thus an earlier return to physical activities with a risk of injury that might not otherwise have been pursued is possible.

Using observational literature to study a possible long-term mechanism involving changes in the strength of bone, we included information from 5 studies, several of which were small, which also did not provide a consistent set of findings which provided clearly supportive evidence of an impact of affinity. Only one study[17] focused specifically on exploring a relationship between serotonin affinity and fracture risk and bone mineral density change. Findings from this study suggested that, from both a short-term and long-term perspective, serotonin affinity on its own cannot explain changes in fracture risk. Other studies were of only moderate duration, and longer durations may be needed to more clearly observe associations between serotonin affinity and changes in bone (and related changes in fracture risk), if such an association exists. A number of studies reported only on users at the class level (i.e. SSRI users, TCA users, etc); while SSRIs as a class consist strictly of agents of high serotonin affinity, other classes consist of a mix of agents of low, moderate and high affinities, and interpretations regarding affinity in these studies were further complicated when a breakdown of specific agents used by patients was not provided. Findings from three recent systematic reviews[24-26] all suggested an increase in the risk of fractures with antidepressants compared to non-use, with a greater risk of the high affinity SSRIs relative to the mixed affinity groupings of TCAs and non-SSRI/TCAs. From exploration of the literature, we are aware that additional literature addressing some aspect of the effect of serotonin affinity on fracture risk is available in patients using antidepressant therapies for other indications, and a more broad synthesis of the evidence across indications may increase the ability to identify important associations. One such example is work from Verdel et al[16] (2010) which reported findings from a case-control study (n=16,717 cases of patients presenting to hospital with a fracture and 61,517 controls) that looked at the association between serotonin affinity of antidepressants used and the occurrence of both osteoporotic and non-osteoporotic fractures in a study where cases were patients presenting to hospital for admission with a first fracture during the study period. Current use of SSRIs, current use of TCAs, and current use of non-SSRI/non-TCA agents were all associated with an increased risk of osteoporotic fractures compared to use of no current use of these agents, and there also existed evidence of sequential increments in the risk of osteoporotic fractures based on comparisons between affinity groupings of antidepressant agents from low to high (low: OR 1.32 with 95% CI 0.98-1.79; moderate: OR 1.43 with 95% CI 1.19-1.72; high: OR 1.86 with 95% CI 1.63-2.13). Non-osteoporotic fractures weren't associated with the same patterns in findings that were noted for osteoporotic fractures, perhaps suggesting an association between antidepressant use and changes in bone mineral density leading to more fractures. We also excluded several other studies because of their cross-sectional design,[230-233] and Other studies were encountered and a systematic search is likely to identify further information.

5.3 Remaining Knowledge Gaps

The study of a potential association between serotonin affinity of antidepressant drugs and the occurrence of changes in bone mineral density and the risk of fractures remains challenging, and observational data from our review did not shed much additional light. The relationship of physical changes related to the depression episode itself as well as the involvement of other comorbidities is complex, and efforts to account for these risk factors does not entirely shed the risk of residual confounding in analyses studying an affinity relationship. The impact of other co-medications such as benzodiazepines on the occurrence of other clinical sequalae (e.g. orthostatic hypotension) which may also impact the frequency of falls is not entirely known, and the extent to which additional falls will lead to fractures (also a possible function of antidepressants used) also remains unclear. It remains possible that other mechanisms beyond serotonin affinity if the antidepressant(s) consumed may play an important role. It is possible that, for example, an increase in the rate of falls and fractures in patients treated with SSRIs (i.e. high serotonin affinity agents) is a consequence of more rapid treatment response or a lesser induced sedation relative to other classes which could lead to a more rapid return to usual physical activity; this increased time 'at risk' could thus explain the presence of more outcomes.

5.4 Limitations of This Review

This review is associated with several limitations. Our network meta-analyses consisted of a large number of antidepressants whose associated trials varied widely in terms of dates of conduct and publication. With regard to the assumption of similarity which is important for the validity of network meta-analyses, RCTs were drawn from Cochrane systematic reviews of antidepressant agents which were conducted according to common protocols. While we are confident in the similarity of these studies and did not find evidence against this based on our analyses for statistical inconsistency of the data, our collaborators are currently in the midst of completing information tables incorporating both study characteristics and risk of bias information. We will provide DSEN owith updates as this information is received, and we will incorporate any necessary changes into the planned peer reviewed publication for this work. Our collaborators were unable to provide study information for the agents bupropion and trazodone, both of which are available for use in Canada. We hope to further expand the data set with our collaborators and incorporate these agents into our treatment network in the near future. Our data sets for network meta-analysis also currently do not include data from two-armed studies where one arm was placebo, and our collaborators from Oxford are currently expanding their data collection and will share this data at a later date; its addition to our current data will likely further reduce the uncertainty around current summary estimates.

We encountered challenges in the collection of observational data in this review. Several studies were small and of somewhat short duration, as it remains possible that lengthier exposure to antidepressants may be needed to observe important changes in bone mineral density and related risk of fractures. Residual confounding remains a significant challenge; it remains a challenge to determine across studies the extent that other factors such as co-medication use, severity of depression, and history of therapy (e.g. $1^{st}/2^{nd}/3^{rd}$ line versus naive users) impact risks along with

the aspect of serotonin affinity. The tendency for studies to be reported by drug class also led to challenges in associating the serotonin affinity level of different exposure groups, a challenge both for our included studies and also to some degree a reason for exclusion of other studies. We did not consider studies to be clearly sufficiently homogenous for the performance of a meta-analysis, and thus we have conservatively summarized the principle characteristics and findings of these studies. Future studies may benefit from including several design efforts including a primary focus on creating exposure groups based on serotonin affinity; encompassing a lengthy follow-up period; looking at both bone mineral density and falls independently; selecting a control group which adequately balances other known risks of falls and reduced bone mineral density; and getting detailed information on all relevant concomitant medication use and past exposures.

6. CONCLUSIONS

Existing reputations of the different classes in terms of side effect profile were generally reinforced by our findings. How often some of these adverse effects may lead to falls and fractures is not known, and is likely a function of patient age and comorbidities. Whether these events occur only early on during drug titration or whether their risk remains relatively consistent throughout their use is an important consideration.In our assessment we did not identify conclusive evidence supporting an association between serotonin affinity and the occurrence of these events; this was expected by our clinical experts. The limited amount of observational evidence we found that allowed consideration of the impact of serotonin affinity on the occurrence of falls, fractures and BMD change neither confirmed or denied a possible association.This DSEN query is of high clinical relevance and importance, however evaluation of the serotonin affinity hypothesis in context of the currently available literature remains challenging given the small amount of literature, study design challenges, residual confounding concerns, and reporting issues in that many studies are reported only at the drug class level. Future studies primarily addressing serotonin affinity and incorporating it in data analysis and reporting plans are needed. Consideration of studies beyond strictly patients with depression may identify additional relevant studies for consideration of the hypothesis of serotonin affinity and its effects on bone mineral density.

Appendix 1: Summary of Medline Literature Search Strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

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1 exp Serotonin Uptake Inhibitors/ (28420)
2 ((Serotonin or 5-HT or 5-Hydroxytryptamine) adj2 Uptake Inhibitor$1).tw. (1726)
3 ((Serotonin or 5-HT or 5-Hydroxytryptamine) adj2 reuptake Inhibitor$1).tw. (9409)
4 (Inhibitor$1 adj2 (serotonin reuptake or serotonin uptake or 5-HT uptake or 5-hydroxytryptamine uptake)).tw. (9353)
5 (SSRI or SSRIs).tw. (5942)
6 or/1-5 (32661)
7 exp Antidepressive Agents/ (112802)
8 (antidepressant$1 or anti-depressant$1 or antidepressive$1 or anti-depressive$1 or thymoanaleptic$1 or thymoleptic$1).tw. (42893)
9 exp Moclobemide/ (633)
10 (Moclobemide or Apo-Moclobemide or Moclobemid or Arima or Aurorex or Aurorix or Deprenorm or Feraken or Manerix or Moclix or Moclobeta or Moclodura or Moclonorm or Novo-Moclobemide or Nu-Moclobemide or PMS-Moclobemide or Rimoc or "Ro 11-1163" or "Ro-11-1163").tw. (1233)
11 71320-77-9.rn. (633)
12 exp Sertraline/ (2149)
13 (Sertraline or Altruline or Apo-Sertraline or Aremis or Besitran or Gen-Sertraline or Gladem or Lustral or Novo-Sertraline or ratio-Sertraline or Rhoxal-sertraline or Sealdin or Zoloft).tw. (2777)
14 79617-96-2.rn. (2149)
15 exp 5-Hydroxytryptophan/ (3857)
16 (5-Hydroxytryptophan or "5-HTP" or Hydroxytryptophan or Oxitriptan or Oxytryptophan or "Tryptophan, 5-Hydroxy-").tw. (3657)
17 56-69-9.rn. (3857)
18 exp Amoxapine/ (320)
19 (Amoxapine or Asendin or Asendis or Demolox or Desmethylloxapine or Defanyl).tw. (372)
20 14028-44-5.rn. (320)
21 exp Bupropion/ (2103)
22 (Bupropion or Amfebutamone or Quomen or Wellbutrin).tw. (2587)
23 34841-39-9.rn. (2103)
24 exp Citalopram/ (3084)
25 (Citalopram or Escitalopram or Lexapro or "Lu-10-171").tw. (4084)
26 59729-33-8.rn. (3084)
27 exp Fluoxetine/ (6930)
28 (Fluoxetin$1 or "Lilly-110140" or Prozac or Sarafem).tw. (8422)
29 54910-89-3.rn. (6930)
30 exp Fluvoxamine/ (1612)
31 (Fluvoxamin$1 or Desiflu or "DU-23000" or Dumirox or Faverin or Fevarin or Floxyfral or Fluvoxadura or Luvox or Novo-Fluvoxamine or Nu-Fluvoxamine or PMS-Fluvoxamine or ratio-Fluvoxamine).tw. (2116)
32 54739-18-3.rn. (1612)
33 exp Maprotiline/ (847)
34 (Maprotiline or "Ba-34,276" or Deprilept or Dibencycladine or Ludiomil or Maprolu or Maprotilin* or Mirpan or Novo-Maprotiline or Psymion).tw. (1000)
35 10262-69-8.rn. (847)
36 exp Mianserin/ (2128)
37 (Mianserin or Lerivon or "Org GB 94" or Tolvon).tw. (1873)

38 24219-97-4.rn. (2128)
39 (nefazodon* or Apo-Nefazodone or Dutonin or Lin-Nefazodone or Menfazona or Nefadar or Rulivan or Serzone).tw. (613)
40 83366-66-9.rn. (463)
41 (Venlafaxin* or Elafax or UNII-GRZ5RCB1QG or Dobupal or Efexor or Effexor or sila-venlafaxine or Trevilor or Vandral or "Wy 45030" or "Wy-45,030").tw. (2407)
42 93413-69-5.rn. (1740)
43 exp Ritanserin/ (617)
44 (Ritanserin or "R-55667").tw. (1217)
45 87051-43-2.rn. (617)
46 exp Sulpiride/ (3521)
47 (Sulpiride or Aiglonyl or Arminol or Deponerton or Desisulpid or Digton or Dogmatil or Dolmatil or Eglonyl or Ekilid or Guastil or Lebopride or Meresa or Neogama or Pontiride or Psicocen or Sulp or Sulperide or Sulpitil or Sulpivert or Sulpor or Synedil or Tepavil or Vertigo-Meresa or vertigo-neogama).tw. (4362)
48 15676-16-1.rn. (3521)
49 exp Trazodone/ (1111)
50 (Trazodone or AF-1161 or Apo-Trazodone or Deprax or Desyrel or Gen-Trazodone or Molipaxin or Novo-Trazodone or Nu-Trazodone or PMS-Trazodone or ratio-Trazodone or Thombran or Tradozone or Trazodon or Trazodon-neuraxpharm or Trazon or Trittico).tw. (1376)
51 19794-93-5.rn. (1111)
52 exp Tryptophan/ (28983)
53 (Tryptophan or Ardeydorm or Ardeytropin or "L-Tryptophan" or "L-Tryptophan-ratiopharm" or Levotryptophan or Lyphan or Naturruhe or Optimax or PMS-Tryptophan or ratio-Tryptophan or Trofan or Tryptacin or Tryptan).tw. (34342)
54 73-22-3.rn. (25740)
55 exp Viloxazine/ (210)
56 (Viloxazine or Emovit or "ICI-58,834" or Vivalan).tw. (293)
57 46817-91-8.rn. (210)
58 exp Paroxetine/ (3264)
59 (Paroxetine or Aropax or "BRL-29060" or "FG-7051" or Paxil or Seroxat).tw. (4093)
60 61869-08-7.rn. (3264)
61 exp Zimeldine/ (463)
62 (Zimeldine or "H-102-09" or Zelmid or Zimelidin).tw. (169)
63 56775-88-3.rn. (463)
64 exp Amitriptyline/ (5784)
65 (Amitriptyline or Amineurin or Amitrip or Amitriptylin beta or Amitriptylin-neuraxpharm or Amitriptyline Hydrochloride or Amitrol or Anapsique or Apo-Amitriptyline or Damilen or Domical or Elavil or Endep or Laroxyl or Lentizol or Novoprotect or Saroten or Sarotex or Syneudon or Triptafen or Tryptanol or Tryptine or Tryptizol).tw. (5367)
66 50-48-6.rn. (5784)
67 exp Clomipramine/ (2619)
68 (Clomipramine or Anafranil or Chlomipramine or Chlorimipramine or Hydiphen).tw. (3096)
69 303-49-1.rn. (2619)
70 exp Desipramine/ (5355)
71 (Desipramine or Apo-Desipramine or Demethylimipramine or Desmethylimipramine or Norpramin or Novo-Desipramine or Nu-Desipramine or Pertofran or Pertofrane or Pertrofran or Petylyl or PMS-Desipramine or ratio-Desipramine).tw. (5954)
72 50-47-5.rn. (5355)
73 exp Dothiepin/ (268)
74 (Dothiepin or Dosulepin or Prothiaden).tw. (306)

75 113-53-1.rn. (268)
76 exp Doxepin/ (742)
77 (Doxepin or Apo-Doxepin or Aponal or Deptran or Desidox or Doneurin or Doxepia or doxepin-biomo or Espadox or Mareen or Novo-Doxepin or Prudoxin or Quitaxon or Sinequan or Sinquan or Xepin or Zonalon).tw. (991)
78 1668-19-5.rn. (742)
79 exp Imipramine/ (9191)
80 (Imipramine or Imidobenzyle or Imizin or Janimine or Melipramine or Norchlorimipramine or Pryleugan or Tofranil).tw. (8755)
81 50-49-7.rn. (9191)
82 exp Iprindole/ (181)
83 Iprindole.tw. (253)
84 5560-72-5.rn. (181)
85 exp Lofepramine/ (102)
86 (Lofepramine or Deftan or Feprapax or Gamanil or Gamonil or "Leo 640" or Lomont or Lopramine).tw. (143)
87 23047-25-8.rn. (102)
88 exp Nortriptyline/ (1932)
89 (Allegron or Apo-Nortriptyline or Aventyl or Desitriptyline or Desmethylamitriptylin or Gen-Nortriptyline or Norfenazin or Nortrilen or Novo-Nortriptyline or Nu-Nortriptyline or Pamelor or Paxtibi or PMS-Nortriptyline or ratio-Nortriptyline).tw. (10)
90 72-69-5.rn. (1932)
91 exp Opipramol/ (209)
92 (Opipramol or Insidon).tw. (186)
93 315-72-0.rn. (209)
94 exp Protriptyline/ (181)
95 (Protriptyline or Vivactil).tw. (311)
96 438-60-8.rn. (181)
97 exp Trimipramine/ (306)
98 (Trimipramine or Apo-Trimip or Eldoral or Herphonal or Novo-Tripramine or Nu-Trimipramine or Rhotrimine or Stangyl or Surmontil or Trimeprimine or Trimidura or Trimineurin or Trimipramin-neurazpharm).tw. (406)
99 739-71-9.rn. (306)
100 (Dibenzepin* or "UNII-510SJZ1Y6L").tw. (118)
101 4498-32-2.rn. (5)
102 (Mirtazapine or Avanza or EINECS 2 or Mepirzapin* or Norset or "Org 3770" or Promyrtil or Remergil or Remergon or Remeron or Rexer or "UNII-A051Q2099Q" or Zispin).tw. (1171)
103 85650-52-8.rn. (0)
104 (Desvenlafaxine or "O-desmethylvenlafaxine" or "DVS 233" or "UNII-NG99554ANW").tw. (205)
105 93413-62-8.rn. (125)
106 (Duloxetine or "(S)-Duloxetine" or Ariclaim or "HSDB 7368" or "LY 248686" or "UNII-O5TNM5N07U" or Xeristar or Yentreve).tw. (1149)
107 116539-59-4.rn. (0)
108 or/7-107 (154994)
109 6 or 108 (161116)
110 exp Fractures, Bone/ (127411)
111 exp Bone Density/ (35366)
112 (fractur* or ((break* or broke$1) adj3 bone$1)).tw. (152808)
113 (bone$1 adj3 (density or dense)).tw. (31095)
114 (bone$1 adj3 mineral content$1).tw. (5447)
115 BMD.tw. (16674)

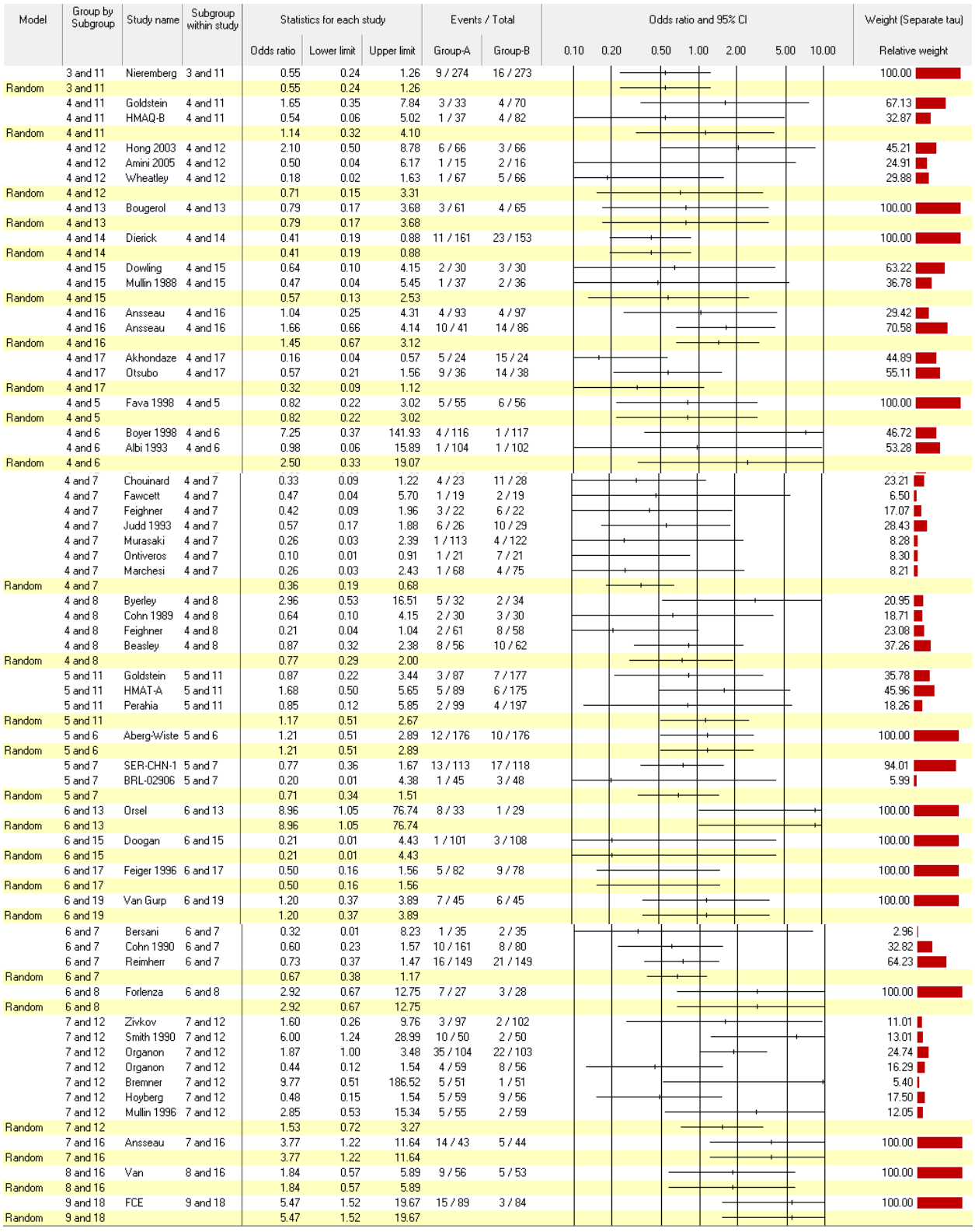
116 exp Bone Resorption/ (29027)
117 (bone$1 adj3 (resorption* or loss$2 or remodeling or form or formed or forms or forming or formation*)).tw. (60772)
118 Osteolysis.tw. (5428)
119 or/110-118 (279007)
120 109 and 119 (430

Appendix 2:
Summary Forest Plots by Outcome and Comparison

Provided in this section are summary forest plots from traditional pairwise meta-analyses that were performed for each outcome and each pairwise comparison for which data was available. These analyses played a role in reviewing the degree of statistical heterogeneity present within each pairwise comparison in the network where multiple studies were available based on review of I^2 values (values >50% were considered to reflect potentially important heterogeneity). Our meta-analyses did not identify high quantities of statistical heterogeneity in our analyses.

Blurred vision:

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 10	Tourian	1 and 10	0.14	0.02	1.06	1 / 161	13 / 298		100.00
Random	1 and 10			0.14	0.02	1.06				
	1 and 11	Goldstein	1 and 11	0.74	0.16	3.43	3 / 70	4 / 70		19.94
	1 and 11	Goldstein	1 and 11	0.28	0.03	2.28	1 / 89	7 / 177		10.54
	1 and 11	HMAQ-B	1 and 11	0.53	0.09	3.00	2 / 75	4 / 82		15.75
	1 and 11	HMAT-A	1 and 11	0.32	0.04	2.67	1 / 90	6 / 175		10.33
	1 and 11	Nieremberg	1 and 11	0.36	0.10	1.26	3 / 137	16 / 273		30.04
	1 and 11	Perahia	1 and 11	0.28	0.01	5.43	1 / 100	4 / 197		5.32
	1 and 11	Tourian	1 and 11	0.48	0.04	5.40	1 / 161	2 / 157		8.09
Random	1 and 11			0.43	0.22	0.85				
	1 and 12	Smith 1990	1 and 12	1.00	0.14	7.39	2 / 50	2 / 50		58.21
	1 and 12	Halikas	1 and 12	0.10	0.01	1.95	1 / 51	5 / 51		26.79
	1 and 12	Bremner	1 and 12	1.00	0.02	51.38	1 / 51	1 / 51		15.01
Random	1 and 12			0.54	0.12	2.50				
	1 and 15	Doogan	1 and 15	0.63	0.08	4.86	2 / 102	3 / 108		100.00
Random	1 and 15			0.63	0.08	4.86				
	1 and 18	FCE	1 and 18	0.99	0.19	5.04	3 / 85	3 / 84		100.00
Random	1 and 18			0.99	0.19	5.04				
	1 and 3	Nieremberg	1 and 3	0.66	0.18	2.48	3 / 137	9 / 274		100.00
Random	1 and 3			0.66	0.18	2.48				
	1 and 4	Goldstein	1 and 4	0.45	0.09	2.35	3 / 70	3 / 33		21.93
	1 and 4	HMAQ-B	1 and 4	0.99	0.09	11.24	2 / 75	1 / 37		10.17
	1 and 4	Byerley	1 and 4	0.86	0.21	3.58	4 / 29	5 / 32		29.75
	1 and 4	Cohn 1989	1 and 4	0.50	0.04	5.83	1 / 29	2 / 30		9.98
	1 and 4	Feighner	1 and 4	2.73	0.51	14.67	5 / 59	2 / 61		21.32
	1 and 4	Fava 1998	1 and 4	0.29	0.01	5.60	1 / 20	5 / 55		6.84
Random	1 and 4			0.85	0.39	1.85				
	1 and 5	Goldstein	1 and 5	0.32	0.03	3.12	1 / 89	3 / 87		31.09
	1 and 5	HMAT-A	1 and 5	0.19	0.02	1.65	1 / 90	5 / 89		34.49
	1 and 5	Perahia	1 and 5	0.33	0.01	8.12	1 / 100	2 / 99		15.70
	1 and 5	Fava 1998	1 and 5	0.24	0.01	4.46	1 / 20	6 / 56		18.72
Random	1 and 5			0.25	0.07	0.90				
	1 and 6	Doogan	1 and 6	3.00	0.12	74.53	2 / 102	1 / 101		19.10
	1 and 6	Reimherr	1 and 6	0.41	0.16	1.02	7 / 150	16 / 149		80.90
Random	1 and 6			0.60	0.13	2.78				
	1 and 7	Reimherr	1 and 7	0.30	0.12	0.73	7 / 150	21 / 149		71.00
	1 and 7	Smith 1990	1 and 7	0.17	0.03	0.81	2 / 50	10 / 50		22.57
	1 and 7	Bremner	1 and 7	0.10	0.01	1.95	1 / 51	5 / 51		6.44
Random	1 and 7			0.24	0.12	0.52				
	1 and 8	Byerley	1 and 8	2.56	0.43	15.12	4 / 29	2 / 34		27.38
	1 and 8	Cohn 1989	1 and 8	0.32	0.03	3.28	1 / 29	3 / 30		19.86
	1 and 8	Feighner	1 and 8	0.58	0.18	1.89	5 / 59	8 / 58		38.91
	1 and 8	Escobar	1 and 8	0.05	0.00	1.08	1 / 14	7 / 16		13.84
Random	1 and 8			0.56	0.16	1.99				
	1 and 9	FCE	1 and 9	0.18	0.05	0.65	3 / 85	15 / 89		100.00
Random	1 and 9			0.18	0.05	0.65				
	10 and 11	Tourian	10 and 11	3.54	0.79	15.87	13 / 298	2 / 157		100.00
Random	10 and 11			3.54	0.79	15.87				
	11 and 14	HMCQ	11 and 14	1.01	0.46	2.20	10 / 164	20 / 330		100.00
Random	11 and 14			1.01	0.46	2.20				
	12 and 14	Guelfi 2001	12 and 14	4.22	0.46	38.60	4 / 78	1 / 79		50.00
	12 and 14	Guelfi 2000	12 and 14	4.22	0.46	38.60	4 / 78	1 / 79		50.00
Random	12 and 14			4.22	0.88	20.18				
	2 and 3	Moore 2005	2 and 3	4.77	0.23	100.16	3 / 153	1 / 144		100.00
Random	2 and 3			4.77	0.23	100.16				
	2 and 4	Zohar 2003	2 and 4	7.17	0.82	62.32	6 / 42	1 / 44		43.99
	2 and 4	Dick 1983	2 and 4	1.17	0.20	6.89	3 / 15	3 / 17		56.01
Random	2 and 4			2.59	0.44	15.16				
	2 and 6	Ekselius	2 and 6	0.53	0.19	1.47	6 / 200	11 / 200		100.00
Random	2 and 6			0.53	0.19	1.47				



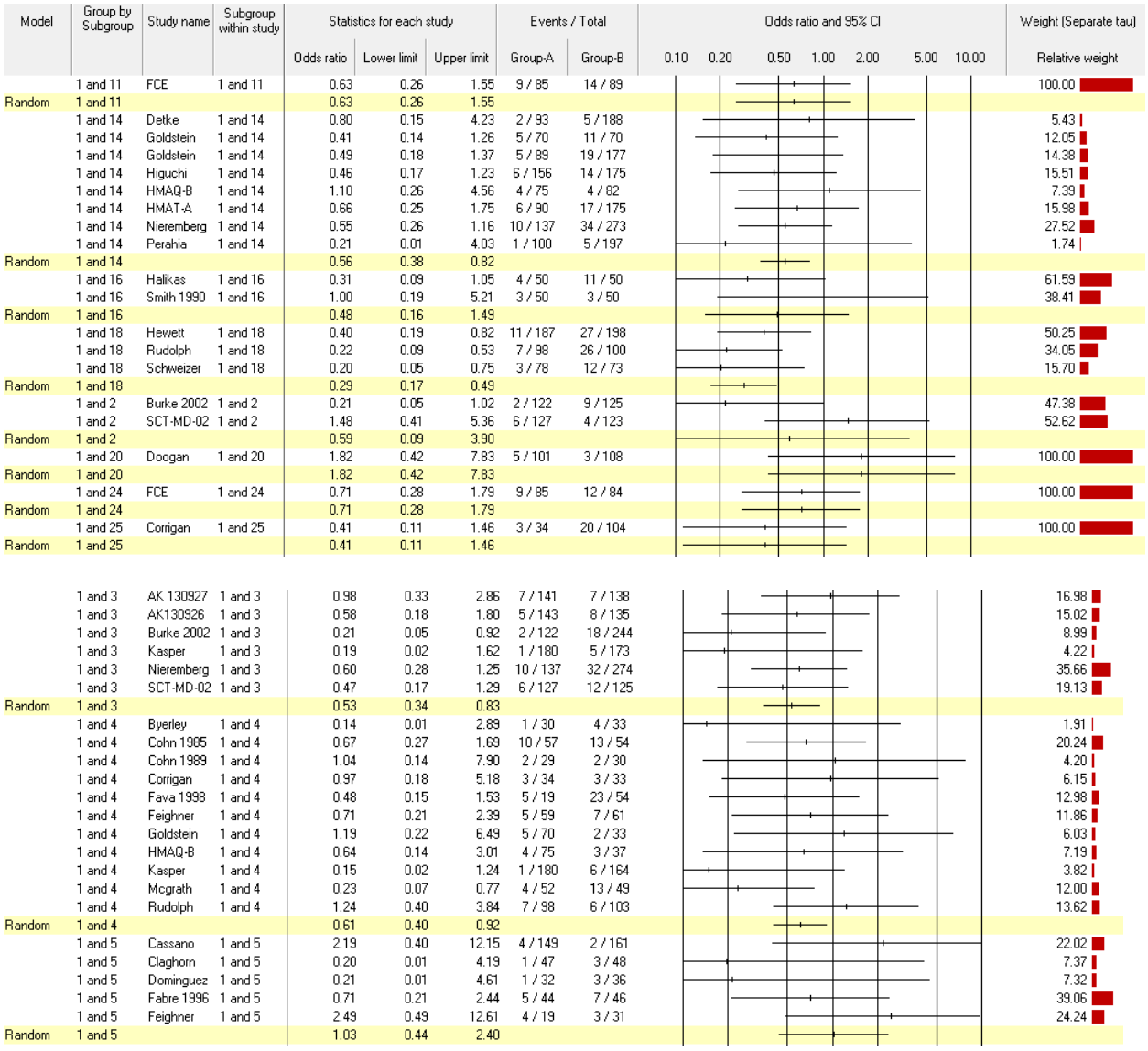
Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	3 and 11	Nieremberg	3 and 11	0.55	0.24	1.26	9 / 274	16 / 273	100.00
Random	3 and 11			0.55	0.24	1.26			
	4 and 11	Goldstein	4 and 11	1.65	0.35	7.84	3 / 33	4 / 70	67.13
	4 and 11	HMAQ-B	4 and 11	0.54	0.06	5.02	1 / 37	4 / 82	32.87
Random	4 and 11			1.14	0.32	4.10			
	4 and 12	Hong 2003	4 and 12	2.10	0.50	8.78	6 / 66	3 / 66	45.21
	4 and 12	Amini 2005	4 and 12	0.50	0.04	6.17	1 / 15	2 / 16	24.91
	4 and 12	Wheatley	4 and 12	0.18	0.02	1.63	1 / 67	5 / 66	29.88
Random	4 and 12			0.71	0.15	3.31			
	4 and 13	Bougerol	4 and 13	0.79	0.17	3.68	3 / 61	4 / 65	100.00
Random	4 and 13			0.79	0.17	3.68			
	4 and 14	Dierick	4 and 14	0.41	0.19	0.88	11 / 161	23 / 153	100.00
Random	4 and 14			0.41	0.19	0.88			
	4 and 15	Dowling	4 and 15	0.64	0.10	4.15	2 / 30	3 / 30	63.22
	4 and 15	Mullin 1988	4 and 15	0.47	0.04	5.45	1 / 37	2 / 36	36.78
Random	4 and 15			0.57	0.13	2.53			
	4 and 16	Ansseau	4 and 16	1.04	0.25	4.31	4 / 93	4 / 97	29.42
	4 and 16	Ansseau	4 and 16	1.66	0.66	4.14	10 / 41	14 / 86	70.58
Random	4 and 16			1.45	0.67	3.12			
	4 and 17	Akhondaze	4 and 17	0.16	0.04	0.57	5 / 24	15 / 24	44.89
	4 and 17	Otsubo	4 and 17	0.57	0.21	1.56	9 / 36	14 / 38	55.11
Random	4 and 17			0.32	0.09	1.12			
	4 and 5	Fava 1998	4 and 5	0.82	0.22	3.02	5 / 55	6 / 56	100.00
Random	4 and 5			0.82	0.22	3.02			
	4 and 6	Boyer 1998	4 and 6	7.25	0.37	141.93	4 / 116	1 / 117	46.72
	4 and 6	Albi 1993	4 and 6	0.98	0.06	15.89	1 / 104	1 / 102	53.28
Random	4 and 6			2.50	0.33	19.07			
	4 and 7	Chouinard	4 and 7	0.33	0.09	1.22	4 / 23	11 / 28	23.21
	4 and 7	Fawcett	4 and 7	0.47	0.04	5.70	1 / 19	2 / 19	6.50
	4 and 7	Feighner	4 and 7	0.42	0.09	1.96	3 / 22	6 / 22	17.07
	4 and 7	Judd 1993	4 and 7	0.57	0.17	1.88	6 / 26	10 / 29	28.43
	4 and 7	Murasaki	4 and 7	0.26	0.03	2.39	1 / 113	4 / 122	8.28
	4 and 7	Ontiveros	4 and 7	0.10	0.01	0.91	1 / 21	7 / 21	8.30
	4 and 7	Marchesi	4 and 7	0.26	0.03	2.43	1 / 68	4 / 75	8.21
Random	4 and 7			0.36	0.19	0.68			
	4 and 8	Byerley	4 and 8	2.96	0.53	16.51	5 / 32	2 / 34	20.95
	4 and 8	Cohn 1989	4 and 8	0.64	0.10	4.15	2 / 30	3 / 30	18.71
	4 and 8	Feighner	4 and 8	0.21	0.04	1.04	2 / 61	8 / 58	23.08
	4 and 8	Beasley	4 and 8	0.87	0.32	2.38	8 / 56	10 / 62	37.26
Random	4 and 8			0.77	0.29	2.00			
	5 and 11	Goldstein	5 and 11	0.87	0.22	3.44	3 / 87	7 / 177	35.78
	5 and 11	HMAT-A	5 and 11	1.68	0.50	5.65	5 / 89	6 / 175	45.96
	5 and 11	Perahia	5 and 11	0.85	0.12	5.85	2 / 99	4 / 197	18.26
Random	5 and 11			1.17	0.51	2.67			
	5 and 6	Aberg-Wiste	5 and 6	1.21	0.51	2.89	12 / 176	10 / 176	100.00
Random	5 and 6			1.21	0.51	2.89			
	5 and 7	SER-CHN-1	5 and 7	0.77	0.36	1.67	13 / 113	17 / 118	94.01
	5 and 7	BRL-02906	5 and 7	0.20	0.01	4.38	1 / 45	3 / 48	5.99
Random	5 and 7			0.71	0.34	1.51			
	6 and 13	Orsel	6 and 13	8.96	1.05	76.74	8 / 33	1 / 29	100.00
Random	6 and 13			8.96	1.05	76.74			
	6 and 15	Doogan	6 and 15	0.21	0.01	4.43	1 / 101	3 / 108	100.00
Random	6 and 15			0.21	0.01	4.43			
	6 and 17	Feiger 1996	6 and 17	0.50	0.16	1.56	5 / 82	9 / 78	100.00
Random	6 and 17			0.50	0.16	1.56			
	6 and 19	Van Gurp	6 and 19	1.20	0.37	3.89	7 / 45	6 / 45	100.00
Random	6 and 19			1.20	0.37	3.89			
	6 and 7	Bersani	6 and 7	0.32	0.01	8.23	1 / 35	2 / 35	2.96
	6 and 7	Cohn 1990	6 and 7	0.60	0.23	1.57	10 / 161	8 / 80	32.82
	6 and 7	Reimherr	6 and 7	0.73	0.37	1.47	16 / 149	21 / 149	64.23
Random	6 and 7			0.67	0.38	1.17			
	6 and 8	Forlenza	6 and 8	2.92	0.67	12.75	7 / 27	3 / 28	100.00
Random	6 and 8			2.92	0.67	12.75			
	7 and 12	Zivkov	7 and 12	1.60	0.26	9.76	3 / 97	2 / 102	11.01
	7 and 12	Smith 1990	7 and 12	6.00	1.24	28.99	10 / 50	2 / 50	13.01
	7 and 12	Organon	7 and 12	1.87	1.00	3.48	35 / 104	22 / 103	24.74
	7 and 12	Organon	7 and 12	0.44	0.12	1.54	4 / 59	8 / 56	16.29
	7 and 12	Bremner	7 and 12	9.77	0.51	186.52	5 / 51	1 / 51	5.40
	7 and 12	Hoyberg	7 and 12	0.48	0.15	1.54	5 / 59	9 / 56	17.50
	7 and 12	Mullin 1996	7 and 12	2.85	0.53	15.34	5 / 55	2 / 59	12.05
Random	7 and 12			1.53	0.72	3.27			
	7 and 16	Ansseau	7 and 16	3.77	1.22	11.64	14 / 43	5 / 44	100.00
Random	7 and 16			3.77	1.22	11.64			
	8 and 16	Van	8 and 16	1.84	0.57	5.89	9 / 56	5 / 53	100.00
Random	8 and 16			1.84	0.57	5.89			
	9 and 18	FCE	9 and 18	5.47	1.52	19.67	15 / 89	3 / 84	100.00
Random	9 and 18			5.47	1.52	19.67			

Hypotension

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 13	Higuchi	1 and 13	4.06	0.83	19.86	7 / 156	2 / 175		100.00
Random	1 and 13			4.06	0.83	19.86				
	1 and 14	Smith 1990	1 and 14	1.00	0.14	7.39	2 / 50	2 / 50		72.21
	1 and 14	Halikas	1 and 14	0.33	0.01	8.21	1 / 51	2 / 51		27.79
Random	1 and 14			0.73	0.13	4.01				
	1 and 3	Kasper	1 and 3	0.48	0.04	5.32	1 / 180	2 / 173		100.00
Random	1 and 3			0.48	0.04	5.32				
	1 and 4	Kasper	1 and 4	0.91	0.06	14.68	1 / 180	1 / 164		100.00
Random	1 and 4			0.91	0.06	14.68				
	1 and 5	Cassano	1 and 5	3.29	0.34	31.96	3 / 149	1 / 161		31.65
	1 and 5	Claghorn	1 and 5	1.02	0.14	7.58	2 / 46	2 / 47		40.78
	1 and 5	Fabre 1996	1 and 5	2.14	0.19	24.51	2 / 44	1 / 46		27.57
Random	1 and 5			1.81	0.50	6.52				
	1 and 6	Higuchi	1 and 6	7.66	0.93	62.98	7 / 156	1 / 164		100.00
Random	1 and 6			7.66	0.93	62.98				
	1 and 8	Smith 1990	1 and 8	0.26	0.05	1.30	2 / 50	7 / 50		100.00
Random	1 and 8			0.26	0.05	1.30				
	1 and 9	Cassano	1 and 9	0.50	0.12	2.05	3 / 149	6 / 153		38.15
	1 and 9	Claghorn	1 and 9	0.36	0.07	1.98	2 / 46	5 / 45		26.21
	1 and 9	Fabre 1996	1 and 9	0.33	0.06	1.75	2 / 44	6 / 48		27.44
	1 and 9	Escobar	1 and 9	0.10	0.00	2.11	1 / 13	5 / 16		8.20
Random	1 and 9			0.36	0.15	0.86				
	10 and 17	Leinonen	10 and 17	0.61	0.28	1.35	17 / 55	22 / 52		100.00
Random	10 and 17			0.61	0.28	1.35				
	14 and 15	Guelfi 2001	14 and 15	0.19	0.02	1.68	1 / 78	5 / 79		50.00
	14 and 15	Guelfi 2000	14 and 15	0.19	0.02	1.68	1 / 78	5 / 79		50.00
Random	14 and 15			0.19	0.04	0.89				
	16 and 17	Endo 1995	16 and 17	0.29	0.01	7.25	1 / 96	2 / 85		100.00
Random	16 and 17			0.29	0.01	7.25				
	2 and 18	Langworth	2 and 18	0.41	0.12	1.35	4 / 164	9 / 156		100.00
Random	2 and 18			0.41	0.12	1.35				
	2 and 3	Moore 2005	2 and 3	0.31	0.01	7.65	1 / 153	2 / 143		100.00
Random	2 and 3			0.31	0.01	7.65				
	2 and 7	Ekselius	2 and 7	1.00	0.46	2.16	14 / 200	14 / 200		100.00
Random	2 and 7			1.00	0.46	2.16				
	3 and 4	Kasper	3 and 4	1.91	0.17	21.23	2 / 173	1 / 164		100.00
Random	3 and 4			1.91	0.17	21.23				
	4 and 10	Ginestet	4 and 10	0.45	0.12	1.78	4 / 28	7 / 26		100.00
Random	4 and 10			0.45	0.12	1.78				
	4 and 11	Bowden	4 and 11	0.10	0.01	2.01	1 / 29	5 / 31		100.00
Random	4 and 11			0.10	0.01	2.01				
	4 and 12	Akhondaze	4 and 12	0.33	0.09	1.29	4 / 24	9 / 24		100.00
Random	4 and 12			0.33	0.09	1.29				
	4 and 14	Wheatley	4 and 14	5.41	0.61	47.62	5 / 66	1 / 67		100.00
Random	4 and 14			5.41	0.61	47.62				
	4 and 17	Ansseau	4 and 17	0.43	0.11	1.71	3 / 93	7 / 97		84.53
	4 and 17	Lee 2002	4 and 17	0.41	0.02	10.35	1 / 32	2 / 40		15.47
Random	4 and 17			0.43	0.12	1.52				
	4 and 18	Massana	4 and 18	0.36	0.14	0.95	7 / 89	15 / 79		100.00
Random	4 and 18			0.36	0.14	0.95				

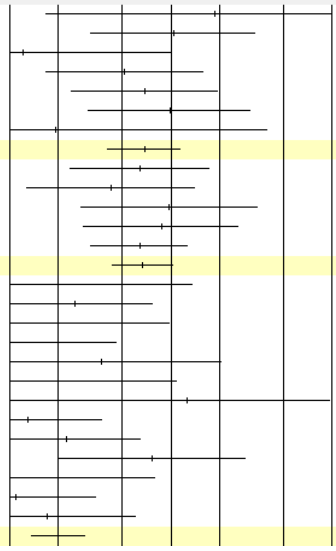
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	4 and 6	De Wilde	4 and 6	0.90	0.12	6.71	2 / 41	2 / 37		33.91
	4 and 6	Schone	4 and 6	1.04	0.25	4.40	4 / 52	4 / 54		66.09
Random	4 and 6			0.99	0.31	3.20				
	4 and 8	Altamura	4 and 8	0.20	0.01	4.57	1 / 14	3 / 16		13.64
	4 and 8	Chouinard	4 and 8	0.06	0.00	1.13	1 / 24	8 / 29		15.64
	4 and 8	De Ronchi	4 and 8	0.48	0.08	2.84	2 / 32	4 / 33		42.50
	4 and 8	Ontiveros	4 and 8	0.18	0.01	4.02	1 / 22	3 / 22		13.91
	4 and 8	Marchesi	4 and 8	0.21	0.01	4.55	1 / 69	3 / 76		14.31
Random	4 and 8			0.24	0.08	0.76				
	5 and 10	Ottevanger	5 and 10	0.12	0.01	1.14	1 / 20	6 / 20		29.67
	5 and 10	de Wilde	5 and 10	0.12	0.01	1.09	1 / 22	6 / 21		29.78
	5 and 10	Dick 1983	5 and 10	1.40	0.33	5.93	7 / 17	5 / 15		40.55
Random	5 and 10			0.33	0.05	1.94				
	5 and 17	Ansseau	5 and 17	0.66	0.27	1.65	8 / 41	23 / 86		100.00
Random	5 and 17			0.66	0.27	1.65				
	5 and 6	Ansseau	5 and 6	4.66	0.53	41.16	5 / 64	1 / 56		100.00
Random	5 and 6			4.66	0.53	41.16				
	5 and 8	Murasaki	5 and 8	0.21	0.02	1.82	1 / 113	5 / 122		67.12
	5 and 8	Kostiukova	5 and 8	0.17	0.01	3.71	1 / 26	3 / 24		32.88
Random	5 and 8			0.19	0.03	1.15				
	5 and 9	Amore 1989	5 and 9	0.29	0.06	1.45	3 / 15	7 / 15		46.63
	5 and 9	Cassano	5 and 9	0.15	0.02	1.29	1 / 161	6 / 153		27.05
	5 and 9	Fabre 1996	5 and 9	0.16	0.02	1.35	1 / 46	6 / 48		26.32
Random	5 and 9			0.21	0.07	0.62				
	5 nd 9	Claghorn	5 nd 9	0.36	0.07	1.94	2 / 47	5 / 45		100.00
Random	5 nd 9			0.36	0.07	1.94				
	6 and 13	Higuchi	6 and 13	0.53	0.05	5.91	1 / 164	2 / 175		100.00
Random	6 and 13			0.53	0.05	5.91				
	6 and 13	Higuchi	6 and 13	0.53	0.05	5.91	1 / 164	2 / 175		100.00
Random	6 and 13			0.53	0.05	5.91				
	6 and 8	SER-CHN-1	6 and 8	0.14	0.04	0.49	3 / 113	19 / 118		79.29
	6 and 8	Hutchinson	6 and 8	0.26	0.02	3.02	1 / 58	2 / 32		20.71
Random	6 and 8			0.16	0.05	0.49				
	7 and 10	Edwards	7 and 10	0.25	0.02	2.71	1 / 17	3 / 15		100.00
Random	7 and 10			0.25	0.02	2.71				
	8 and 14	Smith 1990	8 and 14	3.91	0.77	19.83	7 / 50	2 / 50		21.81
	8 and 14	Organon	8 and 14	3.00	0.12	74.50	2 / 105	1 / 104		5.58
	8 and 14	Organon	8 and 14	0.95	0.13	6.97	2 / 59	2 / 56		14.46
	8 and 14	Hoyberg	8 and 14	1.38	0.51	3.72	11 / 59	8 / 56		58.16
Random	8 and 14			1.71	0.80	3.65				
	8 and 17	Ansseau	8 and 17	2.45	0.83	7.28	12 / 43	6 / 44		100.00
Random	8 and 17			2.45	0.83	7.28				
	9 and 17	Yamashita	9 and 17	9.58	0.51	181.51	5 / 67	1 / 67		34.47
	9 and 17	Tignol 1998	9 and 17	6.47	0.77	54.62	6 / 109	1 / 112		65.53
Random	9 and 17			7.40	1.32	41.65				

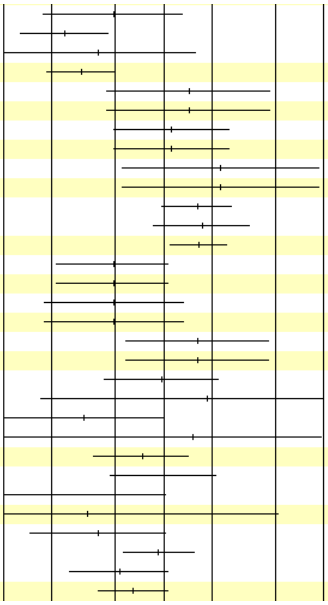
Dizziness

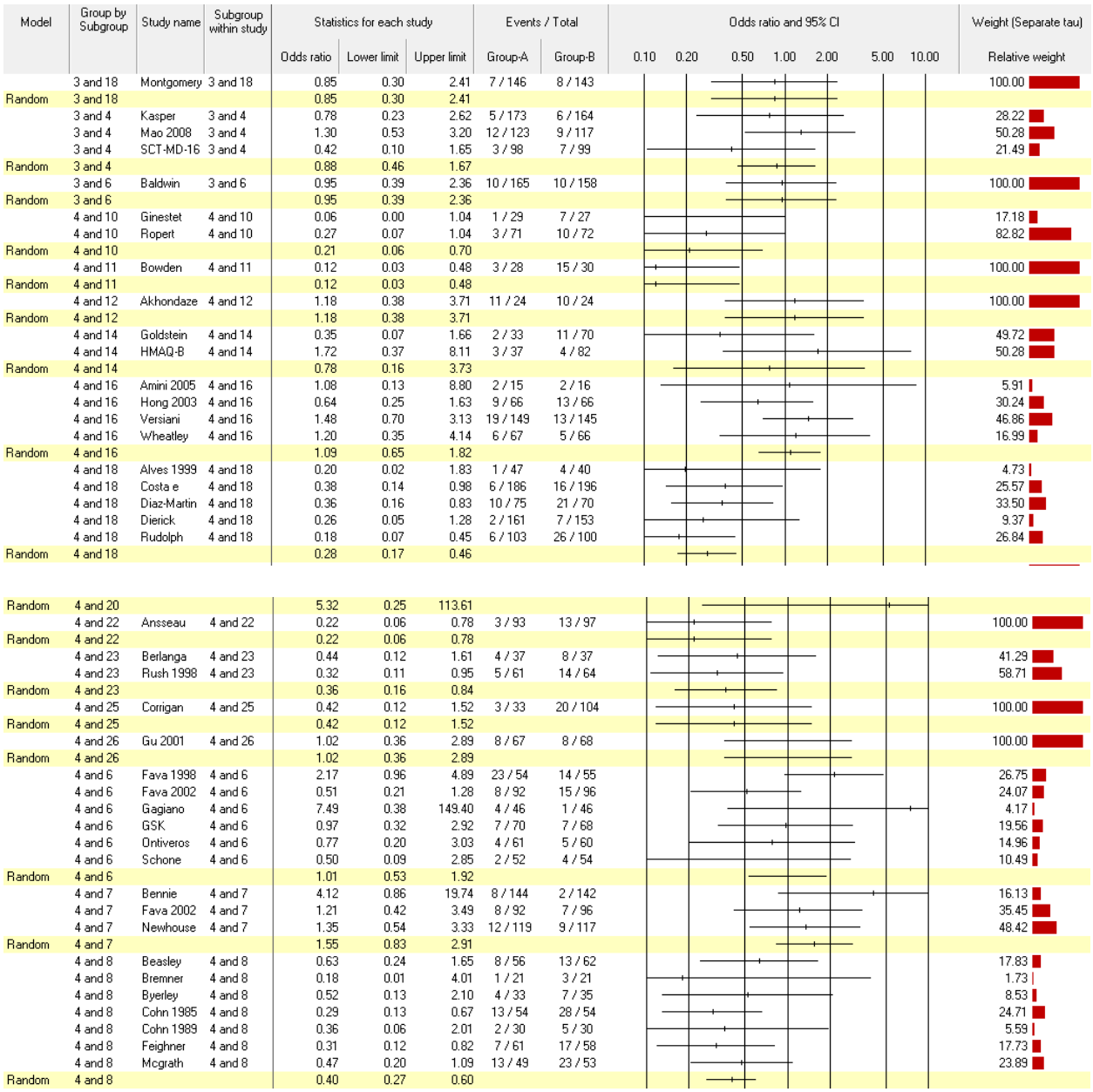


Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	1 and 11	FCE	1 and 11	0.63	0.26	1.55	9 / 85	14 / 89	100.00
Random	1 and 11			0.63	0.26	1.55			
	1 and 14	Detke	1 and 14	0.80	0.15	4.23	2 / 93	5 / 188	5.43
	1 and 14	Goldstein	1 and 14	0.41	0.14	1.26	5 / 70	11 / 70	12.05
	1 and 14	Goldstein	1 and 14	0.49	0.18	1.37	5 / 89	19 / 177	14.38
	1 and 14	Higuchi	1 and 14	0.46	0.17	1.23	6 / 156	14 / 175	15.51
	1 and 14	HMAQ-B	1 and 14	1.10	0.26	4.56	4 / 75	4 / 82	7.39
	1 and 14	HMAT-A	1 and 14	0.66	0.25	1.75	6 / 90	17 / 175	15.98
	1 and 14	Nieremberg	1 and 14	0.55	0.26	1.16	10 / 137	34 / 273	27.52
	1 and 14	Perahia	1 and 14	0.21	0.01	4.03	1 / 100	5 / 197	1.74
Random	1 and 14			0.56	0.38	0.82			
	1 and 16	Halikas	1 and 16	0.31	0.09	1.05	4 / 50	11 / 50	61.59
	1 and 16	Smith 1990	1 and 16	1.00	0.19	5.21	3 / 50	3 / 50	38.41
Random	1 and 16			0.48	0.16	1.49			
	1 and 18	Hewett	1 and 18	0.40	0.19	0.82	11 / 187	27 / 198	50.25
	1 and 18	Rudolph	1 and 18	0.22	0.09	0.53	7 / 98	26 / 100	34.05
	1 and 18	Schweizer	1 and 18	0.20	0.05	0.75	3 / 78	12 / 73	15.70
Random	1 and 18			0.29	0.17	0.49			
	1 and 2	Burke 2002	1 and 2	0.21	0.05	1.02	2 / 122	9 / 125	47.38
	1 and 2	SCT-MD-02	1 and 2	1.48	0.41	5.36	6 / 127	4 / 123	52.62
Random	1 and 2			0.59	0.09	3.90			
	1 and 20	Doogan	1 and 20	1.82	0.42	7.83	5 / 101	3 / 108	100.00
Random	1 and 20			1.82	0.42	7.83			
	1 and 24	FCE	1 and 24	0.71	0.28	1.79	9 / 85	12 / 84	100.00
Random	1 and 24			0.71	0.28	1.79			
	1 and 25	Corrigan	1 and 25	0.41	0.11	1.46	3 / 34	20 / 104	100.00
Random	1 and 25			0.41	0.11	1.46			
	1 and 3	AK 130927	1 and 3	0.98	0.33	2.86	7 / 141	7 / 138	16.98
	1 and 3	AK130926	1 and 3	0.58	0.18	1.80	5 / 143	8 / 135	15.02
	1 and 3	Burke 2002	1 and 3	0.21	0.05	0.92	2 / 122	18 / 244	8.99
	1 and 3	Kasper	1 and 3	0.19	0.02	1.62	1 / 180	5 / 173	4.22
	1 and 3	Nieremberg	1 and 3	0.60	0.28	1.25	10 / 137	32 / 274	35.66
	1 and 3	SCT-MD-02	1 and 3	0.47	0.17	1.29	6 / 127	12 / 125	19.13
Random	1 and 3			0.53	0.34	0.83			
	1 and 4	Byerley	1 and 4	0.14	0.01	2.89	1 / 30	4 / 33	1.91
	1 and 4	Cohn 1985	1 and 4	0.67	0.27	1.69	10 / 57	13 / 54	20.24
	1 and 4	Cohn 1989	1 and 4	1.04	0.14	7.90	2 / 29	2 / 30	4.20
	1 and 4	Corrigan	1 and 4	0.97	0.18	5.18	3 / 34	3 / 33	6.15
	1 and 4	Fava 1998	1 and 4	0.48	0.15	1.53	5 / 19	23 / 54	12.98
	1 and 4	Feighner	1 and 4	0.71	0.21	2.39	5 / 59	7 / 61	11.86
	1 and 4	Goldstein	1 and 4	1.19	0.22	6.49	5 / 70	2 / 33	6.03
	1 and 4	HMAQ-B	1 and 4	0.64	0.14	3.01	4 / 75	3 / 37	7.19
	1 and 4	Kasper	1 and 4	0.15	0.02	1.24	1 / 180	6 / 164	3.82
	1 and 4	Mcgrath	1 and 4	0.23	0.07	0.77	4 / 52	13 / 49	12.00
	1 and 4	Rudolph	1 and 4	1.24	0.40	3.84	7 / 98	6 / 103	13.62
Random	1 and 4			0.61	0.40	0.92			
	1 and 5	Cassano	1 and 5	2.19	0.40	12.15	4 / 149	2 / 161	22.02
	1 and 5	Claghorn	1 and 5	0.20	0.01	4.19	1 / 47	3 / 48	7.37
	1 and 5	Dominguez	1 and 5	0.21	0.01	4.61	1 / 32	3 / 36	7.32
	1 and 5	Fabre 1996	1 and 5	0.71	0.21	2.44	5 / 44	7 / 46	39.06
	1 and 5	Feighner	1 and 5	2.49	0.49	12.61	4 / 19	3 / 31	24.24
Random	1 and 5			1.03	0.44	2.40			

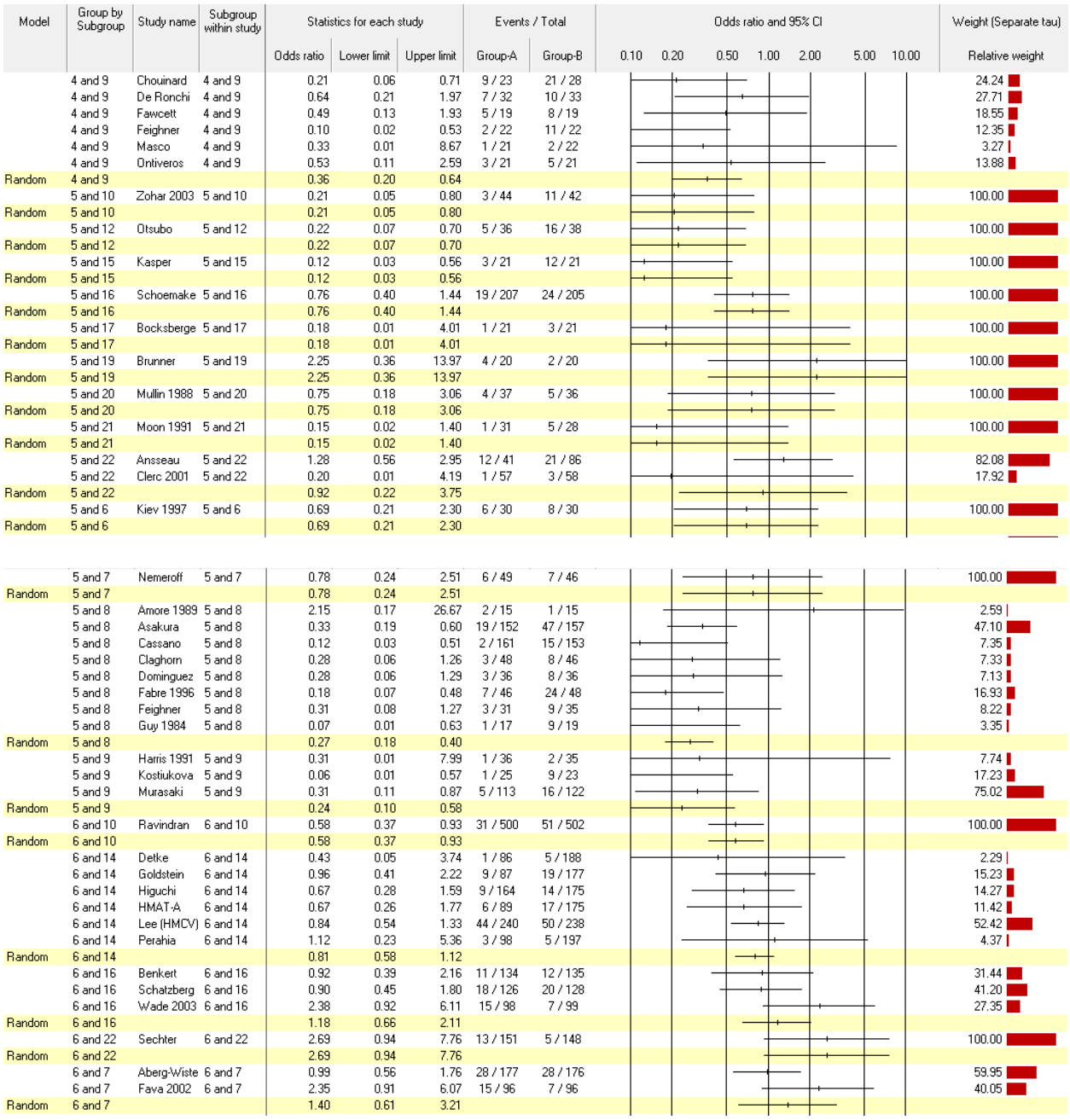
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 6	Detke	1 and 6	1.87	0.17	20.98	2 / 93	1 / 86		4.74
	1 and 6	Fava 1998	1 and 6	1.05	0.32	3.43	5 / 19	14 / 55		19.67
	1 and 6	Feighner	1 and 6	0.12	0.01	1.03	1 / 40	7 / 40		6.03
	1 and 6	Goldstein	1 and 6	0.52	0.17	1.61	5 / 89	9 / 87		21.51
	1 and 6	Higuchi	1 and 6	0.69	0.24	1.98	6 / 156	9 / 164		24.84
	1 and 6	HMAT-A	1 and 6	0.99	0.31	3.19	6 / 90	6 / 89		20.22
	1 and 6	Perahia	1 and 6	0.19	0.01	4.05	1 / 100	3 / 98		2.98
Random	1 and 6			0.69	0.41	1.16				
	1 and 7	Coleman	1 and 7	0.64	0.24	1.76	7 / 121	10 / 115		19.38
	1 and 7	Croft 1999	1 and 7	0.42	0.13	1.41	4 / 119	9 / 118		13.35
	1 and 7	Doogan	1 and 7	0.98	0.27	3.49	5 / 101	5 / 99		12.02
	1 and 7	Lydiard	1 and 7	0.87	0.28	2.67	6 / 129	7 / 132		15.54
	1 and 7	Reimherr	1 and 7	0.64	0.32	1.29	15 / 150	22 / 149		39.72
Random	1 and 7			0.67	0.43	1.04				
	1 and 8	Byerley	1 and 8	0.07	0.00	1.38	1 / 30	7 / 35		1.73
	1 and 8	Cassano	1 and 8	0.25	0.08	0.78	4 / 149	15 / 153		11.64
	1 and 8	Claghorn	1 and 8	0.06	0.00	1.00	1 / 47	8 / 46		1.77
	1 and 8	Cohn 1985	1 and 8	0.20	0.08	0.47	10 / 57	28 / 54		19.70
	1 and 8	Cohn 1989	1 and 8	0.37	0.07	2.08	2 / 29	5 / 30		4.96
	1 and 8	Dominguez	1 and 8	0.06	0.00	1.10	1 / 32	8 / 36		1.75
	1 and 8	Escobar	1 and 8	1.27	0.07	22.72	1 / 12	1 / 15		1.78
	1 and 8	Fabre 1996	1 and 8	0.13	0.04	0.38	5 / 44	24 / 48		12.46
	1 and 8	Feighner	1 and 8	0.22	0.08	0.66	5 / 59	17 / 58		12.76
	1 and 8	Feighner	1 and 8	0.77	0.20	2.94	4 / 19	9 / 35		8.26
	1 and 8	Feighner	1 and 8	0.10	0.01	0.81	1 / 40	8 / 38		3.25
	1 and 8	Mcgrath	1 and 8	0.11	0.03	0.35	4 / 52	23 / 53		11.08
	1 and 8	Schweizer	1 and 8	0.17	0.05	0.61	3 / 78	14 / 73		8.85
Random	1 and 8			0.20	0.13	0.29				
	1 and 9	Lydiard	1 and 9	0.48	0.18	1.33	6 / 129	12 / 131		24.71
	1 and 9	Reimherr	1 and 9	0.24	0.13	0.46	15 / 150	47 / 149		62.64
	1 and 9	Smith 1990	1 and 9	0.39	0.10	1.61	3 / 50	7 / 50		12.65
Random	1 and 9			0.30	0.18	0.50				
	10 and 16	Richou	10 and 16	1.45	0.44	4.77	7 / 86	5 / 87		100.00
Random	10 and 16			1.45	0.44	4.77				
	11 and 24	FCE	11 and 24	1.12	0.49	2.58	14 / 89	12 / 84		100.00
Random	11 and 24			1.12	0.49	2.58				
	13 and 16	Marttila	13 and 16	2.27	0.55	9.45	6 / 72	3 / 78		100.00
Random	13 and 16			2.27	0.55	9.45				
	14 and 18	HMCQ	14 and 18	1.63	0.98	2.73	30 / 164	41 / 340		65.21
	14 and 18	Perahia	14 and 18	1.75	0.86	3.53	23 / 166	14 / 166		34.79
Random	14 and 18			1.67	1.10	2.53				
	16 and 18	Guelfi 2001	16 and 18	0.48	0.21	1.09	11 / 78	20 / 79		100.00
Random	16 and 18			0.48	0.21	1.09				
	2 and 16	Leinonen	2 and 16	0.49	0.18	1.35	6 / 133	12 / 137		100.00
Random	2 and 16			0.49	0.18	1.35				
	2 and 24	Langworth	2 and 24	1.62	0.58	4.58	10 / 164	6 / 156		100.00
Random	2 and 24			1.62	0.58	4.58				
	2 and 3	Burke 2002	2 and 3	0.97	0.42	2.24	9 / 125	18 / 244		55.60
	2 and 3	Moore 2005	2 and 3	1.88	0.17	20.96	2 / 152	1 / 142		8.08
	2 and 3	SCT-MD-02	2 and 3	0.32	0.10	1.01	4 / 123	12 / 125		31.70
	2 and 3	Yevtushenk	2 and 3	1.52	0.06	37.74	2 / 215	1 / 109		4.62
Random	2 and 3			0.73	0.37	1.47				
	2 and 7	Ekselius	2 and 7	1.00	0.46	2.16	14 / 200	14 / 200		62.50
	2 and 7	Hsu 2011	2 and 7	0.05	0.00	1.04	1 / 21	7 / 21		37.50
Random	2 and 7			0.34	0.02	5.32				
	3 and 14	Khan 2007	3 and 14	0.39	0.14	1.05	6 / 137	14 / 133		20.49
	3 and 14	Nieremberg	3 and 14	0.93	0.56	1.56	32 / 274	34 / 273		47.16
	3 and 14	Wade 2007	3 and 14	0.53	0.26	1.08	13 / 143	24 / 151		32.34
Random	3 and 14			0.65	0.39	1.08				



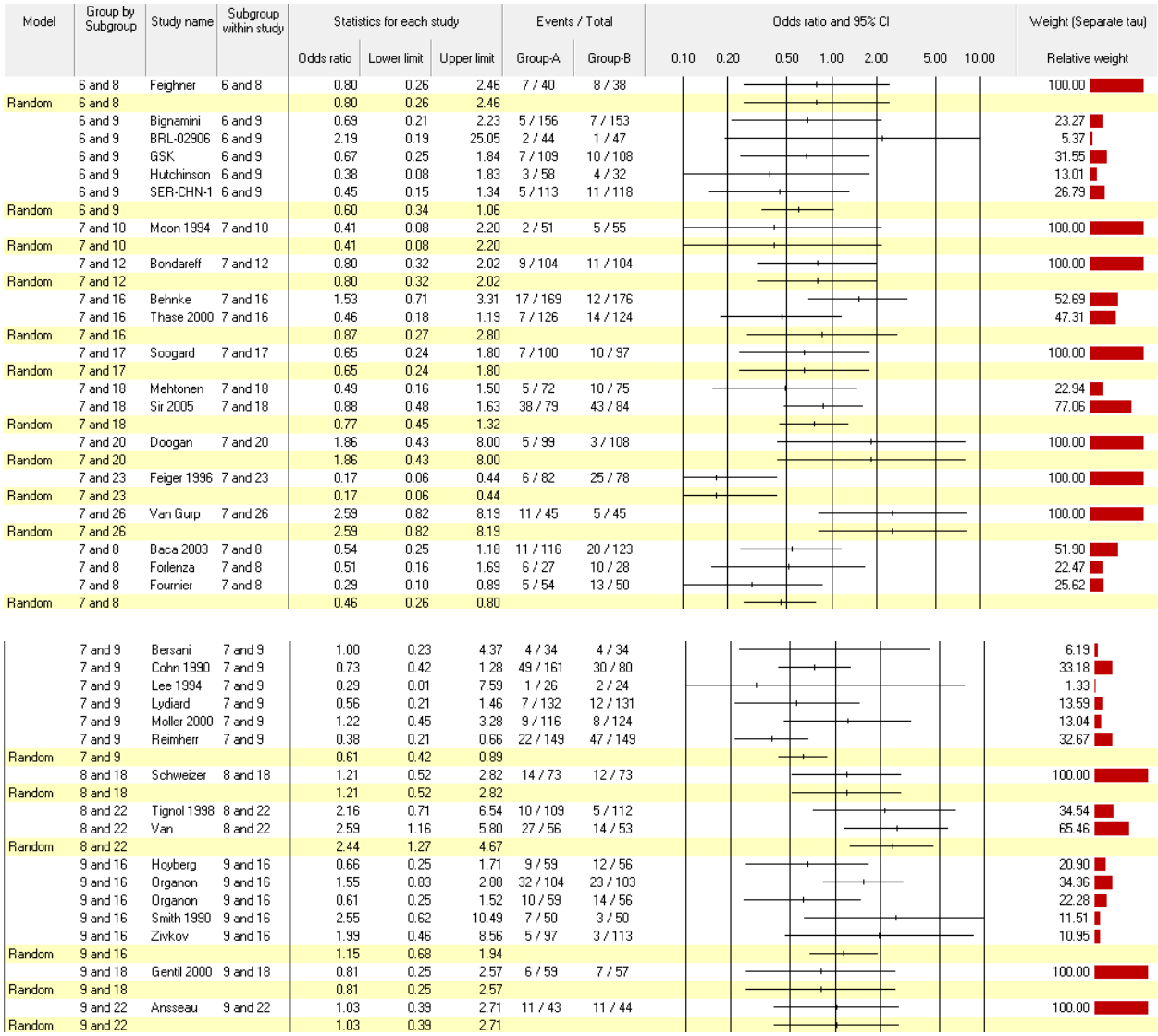




Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	3 and 18	Montgomery	3 and 18	0.85	0.30	2.41	7 / 146	8 / 143	100.00
Random	3 and 18			0.85	0.30	2.41			
	3 and 4	Kasper	3 and 4	0.78	0.23	2.62	5 / 173	6 / 164	28.22
	3 and 4	Mao 2008	3 and 4	1.30	0.53	3.20	12 / 123	9 / 117	50.28
	3 and 4	SCT-MD-16	3 and 4	0.42	0.10	1.65	3 / 98	7 / 99	21.49
Random	3 and 4			0.88	0.46	1.67			
	3 and 6	Baldwin	3 and 6	0.95	0.39	2.36	10 / 165	10 / 158	100.00
Random	3 and 6			0.95	0.39	2.36			
	4 and 10	Ginestet	4 and 10	0.06	0.00	1.04	1 / 29	7 / 27	17.18
	4 and 10	Ropert	4 and 10	0.27	0.07	1.04	3 / 71	10 / 72	82.82
Random	4 and 10			0.21	0.06	0.70			
	4 and 11	Bowden	4 and 11	0.12	0.03	0.48	3 / 28	15 / 30	100.00
Random	4 and 11			0.12	0.03	0.48			
	4 and 12	Akhondaze	4 and 12	1.18	0.38	3.71	11 / 24	10 / 24	100.00
Random	4 and 12			1.18	0.38	3.71			
	4 and 14	Goldstein	4 and 14	0.35	0.07	1.66	2 / 33	11 / 70	49.72
	4 and 14	HMAQ-B	4 and 14	1.72	0.37	8.11	3 / 37	4 / 82	50.28
Random	4 and 14			0.78	0.16	3.73			
	4 and 16	Amini 2005	4 and 16	1.08	0.13	8.80	2 / 15	2 / 16	5.91
	4 and 16	Hong 2003	4 and 16	0.64	0.25	1.63	9 / 66	13 / 66	30.24
	4 and 16	Versiani	4 and 16	1.48	0.70	3.13	19 / 149	13 / 145	46.86
	4 and 16	Wheatley	4 and 16	1.20	0.35	4.14	6 / 67	5 / 66	16.99
Random	4 and 16			1.09	0.65	1.82			
	4 and 18	Alves 1999	4 and 18	0.20	0.02	1.83	1 / 47	4 / 40	4.73
	4 and 18	Costa e	4 and 18	0.38	0.14	0.98	6 / 186	16 / 196	25.57
	4 and 18	Diaz-Martin	4 and 18	0.36	0.16	0.83	10 / 75	21 / 70	33.50
	4 and 18	Dierick	4 and 18	0.26	0.05	1.28	2 / 161	7 / 153	9.37
	4 and 18	Rudolph	4 and 18	0.18	0.07	0.45	6 / 103	26 / 100	26.84
Random	4 and 18			0.28	0.17	0.46			
Random	4 and 20			5.32	0.25	113.61			
	4 and 22	Ansseau	4 and 22	0.22	0.06	0.78	3 / 93	13 / 97	100.00
Random	4 and 22			0.22	0.06	0.78			
	4 and 23	Berlanga	4 and 23	0.44	0.12	1.61	4 / 37	8 / 37	41.29
	4 and 23	Rush 1998	4 and 23	0.32	0.11	0.95	5 / 61	14 / 64	58.71
Random	4 and 23			0.36	0.16	0.84			
	4 and 25	Corrigan	4 and 25	0.42	0.12	1.52	3 / 33	20 / 104	100.00
Random	4 and 25			0.42	0.12	1.52			
	4 and 26	Gu 2001	4 and 26	1.02	0.36	2.89	8 / 67	8 / 68	100.00
Random	4 and 26			1.02	0.36	2.89			
	4 and 6	Fava 1998	4 and 6	2.17	0.96	4.89	23 / 54	14 / 55	26.75
	4 and 6	Fava 2002	4 and 6	0.51	0.21	1.28	8 / 92	15 / 96	24.07
	4 and 6	Gagiano	4 and 6	7.49	0.38	149.40	4 / 46	1 / 46	4.17
	4 and 6	GSK	4 and 6	0.97	0.32	2.92	7 / 70	7 / 68	19.56
	4 and 6	Ontiveros	4 and 6	0.77	0.20	3.03	4 / 61	5 / 60	14.96
	4 and 6	Schone	4 and 6	0.50	0.09	2.85	2 / 52	4 / 54	10.49
Random	4 and 6			1.01	0.53	1.92			
	4 and 7	Bennie	4 and 7	4.12	0.86	19.74	8 / 144	2 / 142	16.13
	4 and 7	Fava 2002	4 and 7	1.21	0.42	3.49	8 / 92	7 / 96	35.45
	4 and 7	Newhouse	4 and 7	1.35	0.54	3.33	12 / 119	9 / 117	48.42
Random	4 and 7			1.55	0.83	2.91			
	4 and 8	Beasley	4 and 8	0.63	0.24	1.65	8 / 56	13 / 62	17.83
	4 and 8	Bremner	4 and 8	0.18	0.01	4.01	1 / 21	3 / 21	1.73
	4 and 8	Byerley	4 and 8	0.52	0.13	2.10	4 / 33	7 / 35	8.53
	4 and 8	Cohn 1985	4 and 8	0.29	0.13	0.67	13 / 54	28 / 54	24.71
	4 and 8	Cohn 1989	4 and 8	0.36	0.06	2.01	2 / 30	5 / 30	5.59
	4 and 8	Feighner	4 and 8	0.31	0.12	0.82	7 / 61	17 / 58	17.73
	4 and 8	Mcgrath	4 and 8	0.47	0.20	1.09	13 / 49	23 / 53	23.89
Random	4 and 8			0.40	0.27	0.60			



Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	4 and 9	Chouinard	4 and 9	0.21	0.06	0.71	9 / 23	21 / 28	24.24
	4 and 9	De Ronchi	4 and 9	0.64	0.21	1.97	7 / 32	10 / 33	27.71
	4 and 9	Fawcett	4 and 9	0.49	0.13	1.93	5 / 19	8 / 19	18.55
	4 and 9	Feighner	4 and 9	0.10	0.02	0.53	2 / 22	11 / 22	12.35
	4 and 9	Masco	4 and 9	0.33	0.01	8.67	1 / 21	2 / 22	3.27
	4 and 9	Ontiveros	4 and 9	0.53	0.11	2.59	3 / 21	5 / 21	13.88
Random	4 and 9			0.36	0.20	0.64			
	5 and 10	Zohar 2003	5 and 10	0.21	0.05	0.80	3 / 44	11 / 42	100.00
Random	5 and 10			0.21	0.05	0.80			
	5 and 12	Otsubo	5 and 12	0.22	0.07	0.70	5 / 36	16 / 38	100.00
Random	5 and 12			0.22	0.07	0.70			
	5 and 15	Kasper	5 and 15	0.12	0.03	0.56	3 / 21	12 / 21	100.00
Random	5 and 15			0.12	0.03	0.56			
	5 and 16	Schoemake	5 and 16	0.76	0.40	1.44	19 / 207	24 / 205	100.00
Random	5 and 16			0.76	0.40	1.44			
	5 and 17	Bocksberge	5 and 17	0.18	0.01	4.01	1 / 21	3 / 21	100.00
Random	5 and 17			0.18	0.01	4.01			
	5 and 19	Brunner	5 and 19	2.25	0.36	13.97	4 / 20	2 / 20	100.00
Random	5 and 19			2.25	0.36	13.97			
	5 and 20	Mullin 1988	5 and 20	0.75	0.18	3.06	4 / 37	5 / 36	100.00
Random	5 and 20			0.75	0.18	3.06			
	5 and 21	Moon 1991	5 and 21	0.15	0.02	1.40	1 / 31	5 / 28	100.00
Random	5 and 21			0.15	0.02	1.40			
	5 and 22	Ansseau	5 and 22	1.28	0.56	2.95	12 / 41	21 / 86	82.08
	5 and 22	Clerc 2001	5 and 22	0.20	0.01	4.19	1 / 57	3 / 58	17.92
Random	5 and 22			0.92	0.22	3.75			
	5 and 6	Kiev 1997	5 and 6	0.69	0.21	2.30	6 / 30	8 / 30	100.00
Random	5 and 6			0.69	0.21	2.30			
	5 and 7	Nemeroff	5 and 7	0.78	0.24	2.51	6 / 49	7 / 46	100.00
Random	5 and 7			0.78	0.24	2.51			
	5 and 8	Amore 1989	5 and 8	2.15	0.17	26.67	2 / 15	1 / 15	2.59
	5 and 8	Asakura	5 and 8	0.33	0.19	0.60	19 / 152	47 / 157	47.10
	5 and 8	Cassano	5 and 8	0.12	0.03	0.51	2 / 161	15 / 153	7.35
	5 and 8	Claghorn	5 and 8	0.28	0.06	1.26	3 / 48	8 / 46	7.33
	5 and 8	Dominguez	5 and 8	0.28	0.06	1.29	3 / 36	8 / 36	7.13
	5 and 8	Fabre 1996	5 and 8	0.18	0.07	0.48	7 / 46	24 / 48	16.93
	5 and 8	Feighner	5 and 8	0.31	0.08	1.27	3 / 31	9 / 35	8.22
	5 and 8	Guy 1984	5 and 8	0.07	0.01	0.63	1 / 17	9 / 19	3.35
Random	5 and 8			0.27	0.18	0.40			
	5 and 9	Harris 1991	5 and 9	0.31	0.01	7.99	1 / 36	2 / 35	7.74
	5 and 9	Kostiukova	5 and 9	0.06	0.01	0.57	1 / 25	9 / 23	17.23
	5 and 9	Murasaki	5 and 9	0.31	0.11	0.87	5 / 113	16 / 122	75.02
Random	5 and 9			0.24	0.10	0.58			
	6 and 10	Ravindran	6 and 10	0.58	0.37	0.93	31 / 500	51 / 502	100.00
Random	6 and 10			0.58	0.37	0.93			
	6 and 14	Detke	6 and 14	0.43	0.05	3.74	1 / 86	5 / 188	2.29
	6 and 14	Goldstein	6 and 14	0.96	0.41	2.22	9 / 87	19 / 177	15.23
	6 and 14	Higuchi	6 and 14	0.67	0.28	1.59	9 / 164	14 / 175	14.27
	6 and 14	HMAT-A	6 and 14	0.67	0.26	1.77	6 / 89	17 / 175	11.42
	6 and 14	Lee (HMCV)	6 and 14	0.84	0.54	1.33	44 / 240	50 / 238	52.42
	6 and 14	Perahia	6 and 14	1.12	0.23	5.36	3 / 98	5 / 197	4.37
Random	6 and 14			0.81	0.58	1.12			
	6 and 16	Benkert	6 and 16	0.92	0.39	2.16	11 / 134	12 / 135	31.44
	6 and 16	Schatzberg	6 and 16	0.90	0.45	1.80	18 / 126	20 / 128	41.20
	6 and 16	Wade 2003	6 and 16	2.38	0.92	6.11	15 / 98	7 / 99	27.35
Random	6 and 16			1.18	0.66	2.11			
	6 and 22	Sechter	6 and 22	2.69	0.94	7.76	13 / 151	5 / 148	100.00
Random	6 and 22			2.69	0.94	7.76			
	6 and 7	Aberg-Wiste	6 and 7	0.99	0.56	1.76	28 / 177	28 / 176	59.95
	6 and 7	Fava 2002	6 and 7	2.35	0.91	6.07	15 / 96	7 / 96	40.05
Random	6 and 7			1.40	0.61	3.21			



Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	6 and 8	Feighner	6 and 8	0.80	0.26	2.46	7 / 40	8 / 38	100.00
Random	6 and 8			0.80	0.26	2.46			
	6 and 9	Bignamini	6 and 9	0.69	0.21	2.23	5 / 156	7 / 153	23.27
	6 and 9	BRL-02906	6 and 9	2.19	0.19	25.05	2 / 44	1 / 47	5.37
	6 and 9	GSK	6 and 9	0.67	0.25	1.84	7 / 109	10 / 108	31.55
	6 and 9	Hutchinson	6 and 9	0.38	0.08	1.83	3 / 58	4 / 32	13.01
	6 and 9	SER-CHN-1	6 and 9	0.45	0.15	1.34	5 / 113	11 / 118	26.79
Random	6 and 9			0.60	0.34	1.06			
	7 and 10	Moon 1994	7 and 10	0.41	0.08	2.20	2 / 51	5 / 55	100.00
Random	7 and 10			0.41	0.08	2.20			
	7 and 12	Bondareff	7 and 12	0.80	0.32	2.02	9 / 104	11 / 104	100.00
Random	7 and 12			0.80	0.32	2.02			
	7 and 16	Behnke	7 and 16	1.53	0.71	3.31	17 / 169	12 / 176	52.69
	7 and 16	Thase 2000	7 and 16	0.46	0.18	1.19	7 / 126	14 / 124	47.31
Random	7 and 16			0.87	0.27	2.80			
	7 and 17	Soogard	7 and 17	0.65	0.24	1.80	7 / 100	10 / 97	100.00
Random	7 and 17			0.65	0.24	1.80			
	7 and 18	Mehtonen	7 and 18	0.49	0.16	1.50	5 / 72	10 / 75	22.94
	7 and 18	Sir 2005	7 and 18	0.88	0.48	1.63	38 / 79	43 / 84	77.06
Random	7 and 18			0.77	0.45	1.32			
	7 and 20	Doogan	7 and 20	1.86	0.43	8.00	5 / 99	3 / 108	100.00
Random	7 and 20			1.86	0.43	8.00			
	7 and 23	Feiger 1996	7 and 23	0.17	0.06	0.44	6 / 82	25 / 78	100.00
Random	7 and 23			0.17	0.06	0.44			
	7 and 26	Van Gurp	7 and 26	2.59	0.82	8.19	11 / 45	5 / 45	100.00
Random	7 and 26			2.59	0.82	8.19			
	7 and 8	Baca 2003	7 and 8	0.54	0.25	1.18	11 / 116	20 / 123	51.90
	7 and 8	Forlenza	7 and 8	0.51	0.16	1.69	6 / 27	10 / 28	22.47
	7 and 8	Fournier	7 and 8	0.29	0.10	0.89	5 / 54	13 / 50	25.62
Random	7 and 8			0.46	0.26	0.80			
	7 and 9	Bersani	7 and 9	1.00	0.23	4.37	4 / 34	4 / 34	6.19
	7 and 9	Cohn 1990	7 and 9	0.73	0.42	1.28	49 / 161	30 / 80	33.18
	7 and 9	Lee 1994	7 and 9	0.29	0.01	7.59	1 / 26	2 / 24	1.33
	7 and 9	Lydiard	7 and 9	0.56	0.21	1.46	7 / 132	12 / 131	13.59
	7 and 9	Moller 2000	7 and 9	1.22	0.45	3.28	9 / 116	8 / 124	13.04
	7 and 9	Reimherr	7 and 9	0.38	0.21	0.66	22 / 149	47 / 149	32.67
Random	7 and 9			0.61	0.42	0.89			
	8 and 18	Schweizer	8 and 18	1.21	0.52	2.82	14 / 73	12 / 73	100.00
Random	8 and 18			1.21	0.52	2.82			
	8 and 22	Tignol 1998	8 and 22	2.16	0.71	6.54	10 / 109	5 / 112	34.54
	8 and 22	Van	8 and 22	2.59	1.16	5.80	27 / 56	14 / 53	65.46
Random	8 and 22			2.44	1.27	4.67			
	9 and 16	Hoyberg	9 and 16	0.66	0.25	1.71	9 / 59	12 / 56	20.90
	9 and 16	Organon	9 and 16	1.55	0.83	2.88	32 / 104	23 / 103	34.36
	9 and 16	Organon	9 and 16	0.61	0.25	1.52	10 / 59	14 / 56	22.28
	9 and 16	Smith 1990	9 and 16	2.55	0.62	10.49	7 / 50	3 / 50	11.51
	9 and 16	Zivkov	9 and 16	1.99	0.46	8.56	5 / 97	3 / 113	10.95
Random	9 and 16			1.15	0.68	1.94			
	9 and 18	Gentil 2000	9 and 18	0.81	0.25	2.57	6 / 59	7 / 57	100.00
Random	9 and 18			0.81	0.25	2.57			
	9 and 22	Ansseau	9 and 22	1.03	0.39	2.71	11 / 43	11 / 44	100.00
Random	9 and 22			1.03	0.39	2.71			

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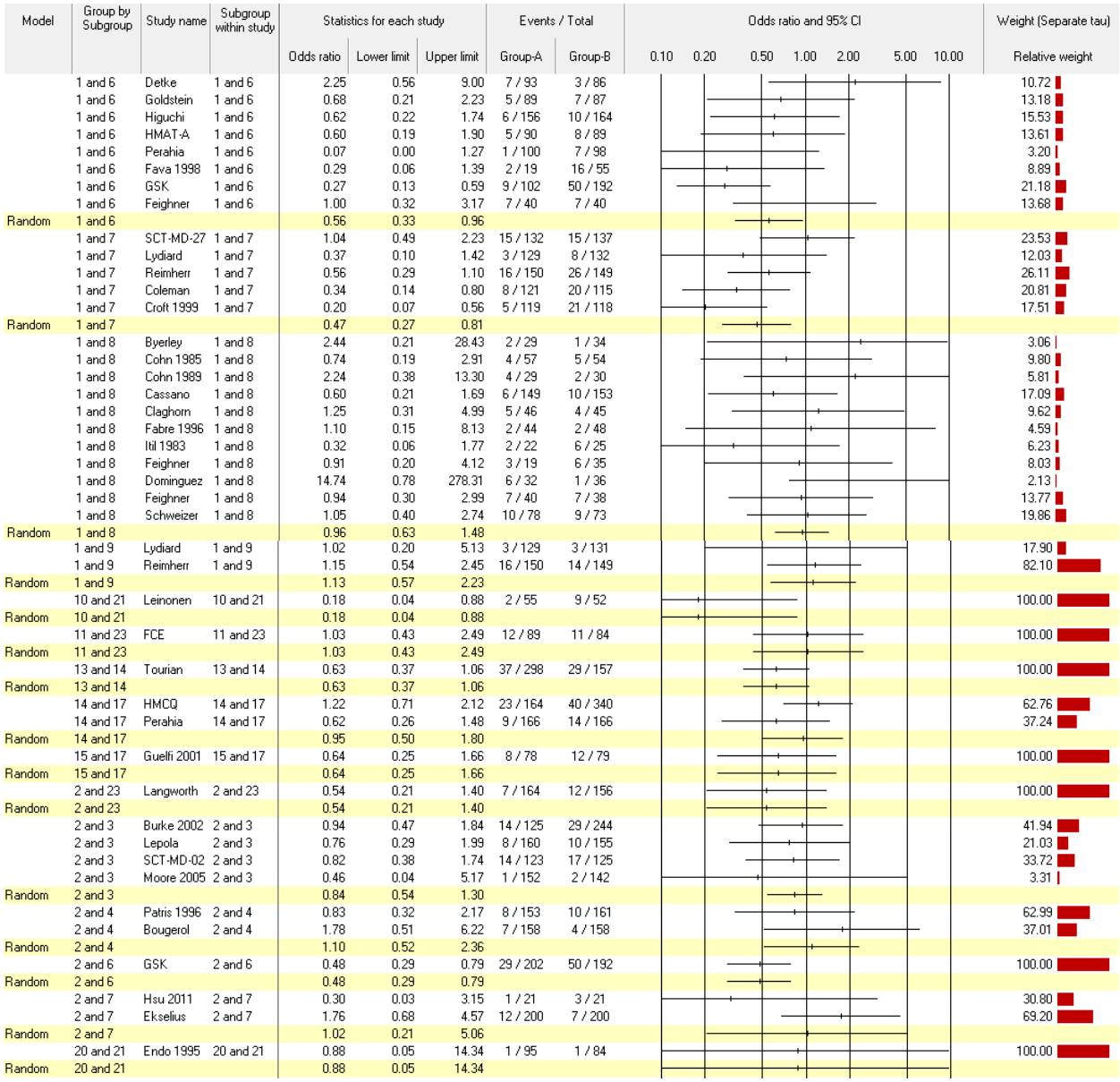
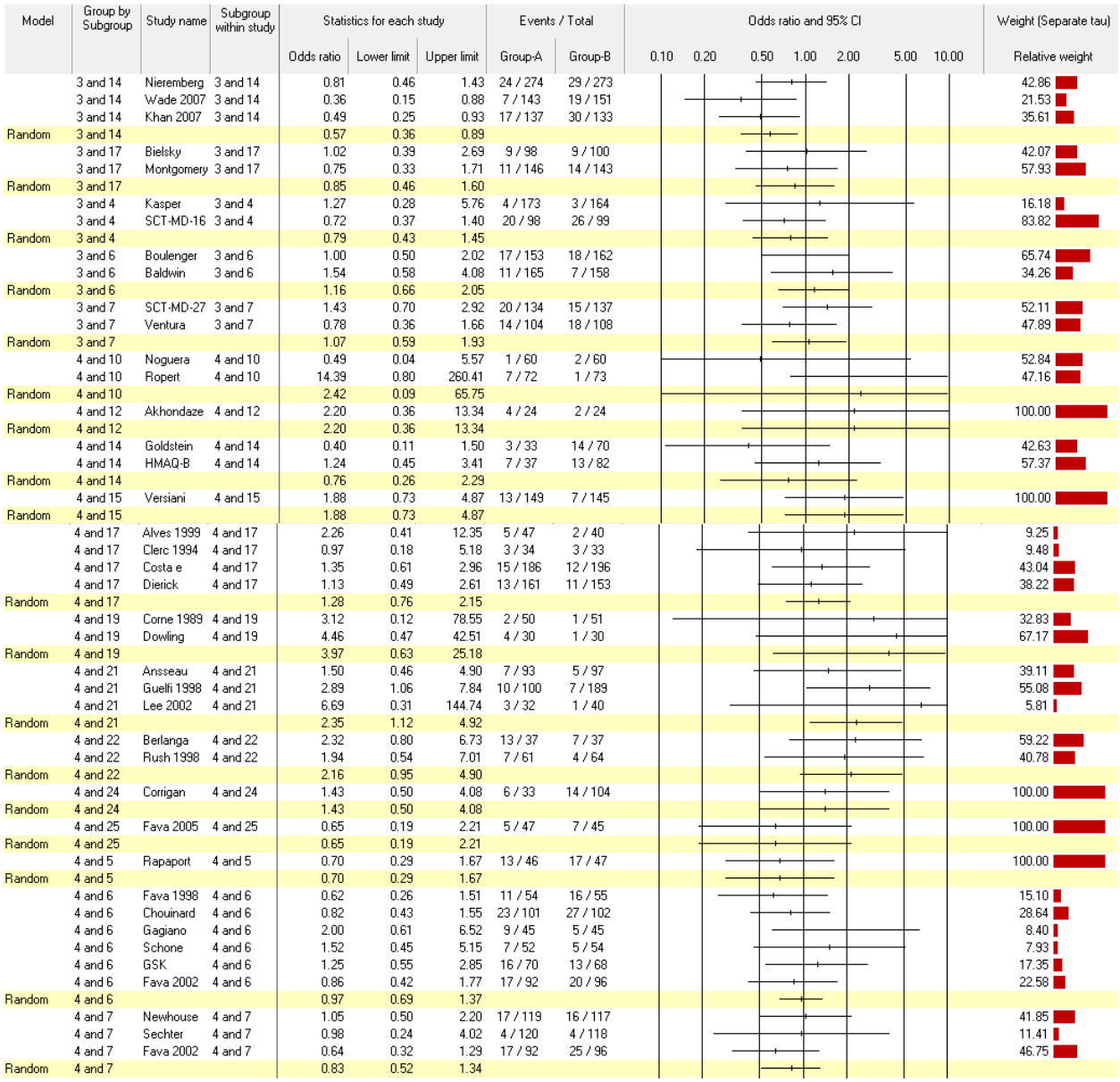
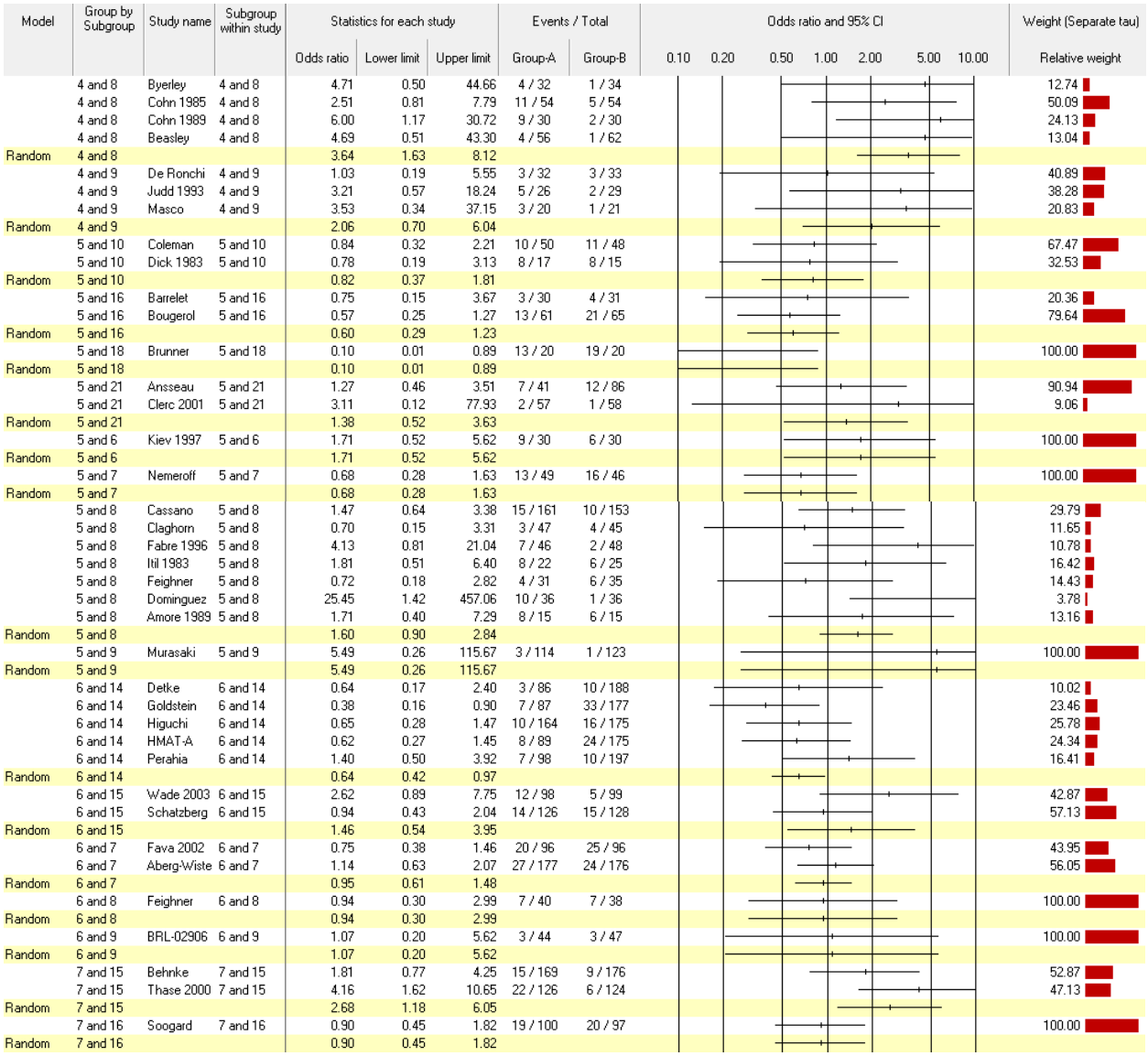
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 11	FCE	1 and 11	0.58	0.22	1.54	7 / 85	12 / 89		100.00
Random	1 and 11			0.58	0.22	1.54				
	1 and 13	Tourian	1 and 13	0.23	0.09	0.59	5 / 161	37 / 298		100.00
Random	1 and 13			0.23	0.09	0.59				
	1 and 14	Tourian	1 and 14	0.14	0.05	0.38	5 / 161	29 / 157		11.99
	1 and 14	Nieremberg	1 and 14	0.81	0.40	1.64	12 / 137	29 / 273		15.54
	1 and 14	Goldstein	1 and 14	0.31	0.10	0.91	5 / 70	14 / 70		10.82
	1 and 14	HMAQ-B	1 and 14	0.46	0.17	1.28	6 / 75	13 / 82		11.46
	1 and 14	Detke	1 and 14	1.45	0.53	3.94	7 / 93	10 / 188		11.73
	1 and 14	Goldstein	1 and 14	0.26	0.10	0.69	5 / 89	33 / 177		11.98
	1 and 14	Higuchi	1 and 14	0.40	0.15	1.04	6 / 156	16 / 175		12.14
	1 and 14	HMAT-A	1 and 14	0.37	0.14	1.01	5 / 90	24 / 175		11.73
	1 and 14	Perahia	1 and 14	0.10	0.01	1.72	1 / 100	10 / 197		2.61
Random	1 and 14			0.41	0.25	0.67				
	1 and 17	Hewett	1 and 17	0.64	0.26	1.57	8 / 187	13 / 198		48.26
	1 and 17	Schweizer	1 and 17	0.57	0.24	1.36	10 / 78	15 / 73		51.74
Random	1 and 17			0.60	0.32	1.13				
	1 and 2	Burke 2002	1 and 2	0.27	0.09	0.84	4 / 122	14 / 125		18.54
	1 and 2	Lepola	1 and 2	0.38	0.10	1.45	3 / 154	8 / 160		13.33
	1 and 2	SCT-MD-02	1 and 2	0.52	0.21	1.30	8 / 127	14 / 123		29.37
	1 and 2	GSK	1 and 2	0.58	0.26	1.27	9 / 102	29 / 202		38.76
Random	1 and 2			0.46	0.28	0.75				
	1 and 23	FCE	1 and 23	0.60	0.22	1.62	7 / 85	11 / 84		100.00
Random	1 and 23			0.60	0.22	1.62				
	1 and 24	Corrigan	1 and 24	0.19	0.02	1.54	1 / 34	14 / 104		100.00
Random	1 and 24			0.19	0.02	1.54				
	1 and 25	Fava 2005	1 and 25	0.88	0.27	2.87	6 / 43	7 / 45		100.00
Random	1 and 25			0.88	0.27	2.87				
	1 and 3	Nieremberg	1 and 3	1.00	0.48	2.07	12 / 137	24 / 274		16.74
	1 and 3	AK130926	1 and 3	1.11	0.50	2.50	14 / 143	12 / 135		14.44
	1 and 3	SCT-MD-35	1 and 3	0.32	0.06	1.61	2 / 133	6 / 131		4.68
	1 and 3	Burke 2002	1 and 3	0.25	0.09	0.73	4 / 122	29 / 244		9.52
	1 and 3	Lepola	1 and 3	0.29	0.08	1.07	3 / 154	10 / 155		6.79
	1 and 3	SCT-MD-02	1 and 3	0.43	0.18	1.03	8 / 127	17 / 125		12.83
	1 and 3	Kasper	1 and 3	0.96	0.24	3.90	4 / 180	4 / 173		6.04
	1 and 3	SCT-MD-27	1 and 3	0.73	0.36	1.50	15 / 132	20 / 134		16.98
	1 and 3	AK 130927	1 and 3	0.40	0.16	1.00	7 / 141	16 / 138		11.98
Random	1 and 3			0.59	0.41	0.85				
	1 and 4	Goldstein	1 and 4	0.77	0.17	3.43	5 / 70	3 / 33		10.14
	1 and 4	HMAQ-B	1 and 4	0.37	0.12	1.20	6 / 75	7 / 37		16.52
	1 and 4	Kasper	1 and 4	1.22	0.27	5.53	4 / 180	3 / 164		9.92
	1 and 4	Fava 2005	1 and 4	1.36	0.38	4.83	6 / 43	5 / 47		14.14
	1 and 4	Byerley	1 and 4	0.52	0.09	3.07	2 / 29	4 / 32		7.17
	1 and 4	Cohn 1985	1 and 4	0.30	0.09	0.99	4 / 57	11 / 54		15.41
	1 and 4	Cohn 1989	1 and 4	0.37	0.10	1.39	4 / 29	9 / 30		13.15
	1 and 4	Fava 1998	1 and 4	0.46	0.09	2.30	2 / 19	11 / 54		8.77
	1 and 4	Corrigan	1 and 4	0.14	0.02	1.20	1 / 34	6 / 33		4.78
Random	1 and 4			0.52	0.32	0.84				
	1 and 5	Cassano	1 and 5	0.41	0.15	1.08	6 / 149	15 / 161		27.48
	1 and 5	Claghorn	1 and 5	1.79	0.40	7.96	5 / 46	3 / 47		14.53
	1 and 5	Fabre 1996	1 and 5	0.27	0.05	1.36	2 / 44	7 / 46		12.54
	1 and 5	Itil 1983	1 and 5	0.18	0.03	0.95	2 / 22	8 / 22		11.77
	1 and 5	Feighner	1 and 5	1.27	0.25	6.39	3 / 19	4 / 31		12.69
	1 and 5	Dominguez	1 and 5	0.58	0.18	1.88	6 / 32	10 / 36		21.00
Random	1 and 5			0.54	0.29	1.01				



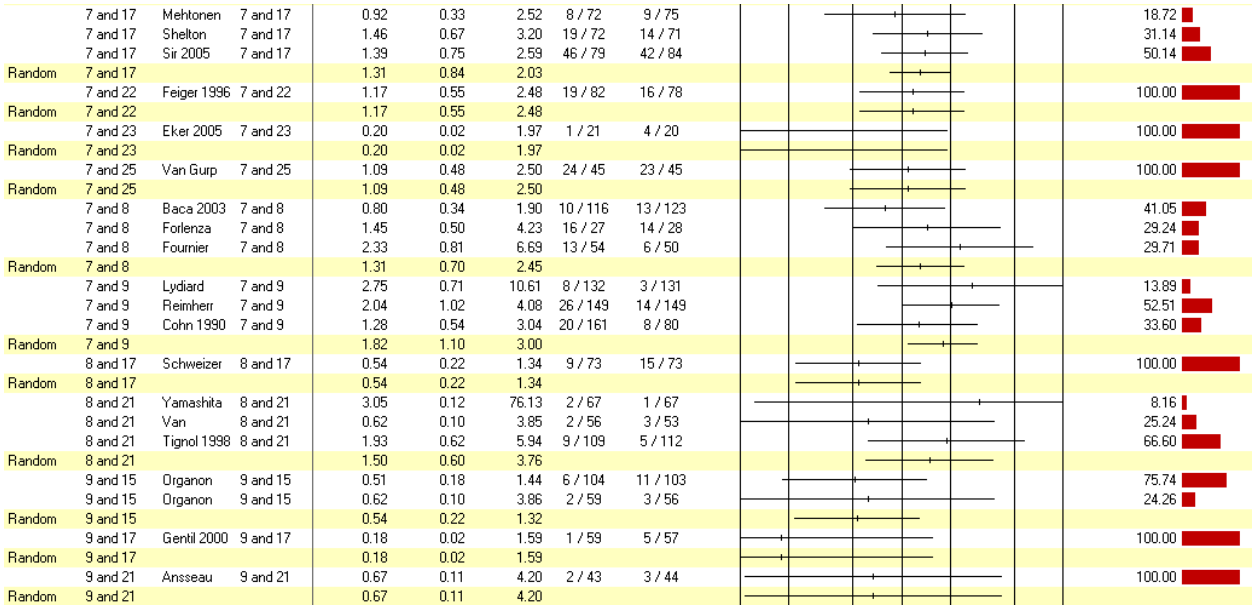
Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	1 and 6	Detke	1 and 6	2.25	0.56	9.00	7 / 93	3 / 86	10.72
	1 and 6	Goldstein	1 and 6	0.68	0.21	2.23	5 / 89	7 / 87	13.18
	1 and 6	Higuchi	1 and 6	0.62	0.22	1.74	6 / 156	10 / 164	15.53
	1 and 6	HMAT-A	1 and 6	0.60	0.19	1.90	5 / 90	8 / 89	13.61
	1 and 6	Perahia	1 and 6	0.07	0.00	1.27	1 / 100	7 / 98	3.20
	1 and 6	Fava 1998	1 and 6	0.29	0.06	1.39	2 / 19	16 / 55	8.89
	1 and 6	GSK	1 and 6	0.27	0.13	0.59	9 / 102	50 / 192	21.18
	1 and 6	Feighner	1 and 6	1.00	0.32	3.17	7 / 40	7 / 40	13.68
Random	1 and 6			0.56	0.33	0.96			
	1 and 7	SCT-MD-27	1 and 7	1.04	0.49	2.23	15 / 132	15 / 137	23.53
	1 and 7	Lydiard	1 and 7	0.37	0.10	1.42	3 / 129	8 / 132	12.03
	1 and 7	Reimherr	1 and 7	0.56	0.29	1.10	16 / 150	26 / 149	26.11
	1 and 7	Coleman	1 and 7	0.34	0.14	0.80	8 / 121	20 / 115	20.81
	1 and 7	Croft 1999	1 and 7	0.20	0.07	0.56	5 / 119	21 / 118	17.51
Random	1 and 7			0.47	0.27	0.81			
	1 and 8	Byerley	1 and 8	2.44	0.21	28.43	2 / 29	1 / 34	3.06
	1 and 8	Cohn 1985	1 and 8	0.74	0.19	2.91	4 / 57	5 / 54	9.80
	1 and 8	Cohn 1989	1 and 8	2.24	0.38	13.30	4 / 29	2 / 30	5.81
	1 and 8	Cassano	1 and 8	0.60	0.21	1.69	6 / 149	10 / 153	17.09
	1 and 8	Claghorn	1 and 8	1.25	0.31	4.99	5 / 46	4 / 45	9.62
	1 and 8	Fabre 1996	1 and 8	1.10	0.15	8.13	2 / 44	2 / 48	4.59
	1 and 8	Itil 1983	1 and 8	0.32	0.06	1.77	2 / 22	6 / 25	6.23
	1 and 8	Feighner	1 and 8	0.91	0.20	4.12	3 / 19	6 / 35	8.03
	1 and 8	Dominguez	1 and 8	14.74	0.78	278.31	6 / 32	1 / 36	2.13
	1 and 8	Feighner	1 and 8	0.94	0.30	2.99	7 / 40	7 / 38	13.77
	1 and 8	Schweizer	1 and 8	1.05	0.40	2.74	10 / 78	9 / 73	19.86
Random	1 and 8			0.96	0.63	1.48			
	1 and 9	Lydiard	1 and 9	1.02	0.20	5.13	3 / 129	3 / 131	17.90
	1 and 9	Reimherr	1 and 9	1.15	0.54	2.45	16 / 150	14 / 149	82.10
Random	1 and 9			1.13	0.57	2.23			
	10 and 21	Leinonen	10 and 21	0.18	0.04	0.88	2 / 55	9 / 52	100.00
Random	10 and 21			0.18	0.04	0.88			
	11 and 23	FCE	11 and 23	1.03	0.43	2.49	12 / 89	11 / 84	100.00
Random	11 and 23			1.03	0.43	2.49			
	13 and 14	Tourian	13 and 14	0.63	0.37	1.06	37 / 298	29 / 157	100.00
Random	13 and 14			0.63	0.37	1.06			
	14 and 17	HMCQ	14 and 17	1.22	0.71	2.12	23 / 164	40 / 340	62.76
	14 and 17	Perahia	14 and 17	0.62	0.26	1.48	9 / 166	14 / 166	37.24
Random	14 and 17			0.95	0.50	1.80			
	15 and 17	Guelfi 2001	15 and 17	0.64	0.25	1.66	8 / 78	12 / 79	100.00
Random	15 and 17			0.64	0.25	1.66			
	2 and 23	Langworth	2 and 23	0.54	0.21	1.40	7 / 164	12 / 156	100.00
Random	2 and 23			0.54	0.21	1.40			
	2 and 3	Burke 2002	2 and 3	0.94	0.47	1.84	14 / 125	29 / 244	41.94
	2 and 3	Lepola	2 and 3	0.76	0.29	1.99	8 / 160	10 / 155	21.03
	2 and 3	SCT-MD-02	2 and 3	0.82	0.38	1.74	14 / 123	17 / 125	33.72
	2 and 3	Moore 2005	2 and 3	0.46	0.04	5.17	1 / 152	2 / 142	3.31
Random	2 and 3			0.84	0.54	1.30			
	2 and 4	Patris 1996	2 and 4	0.83	0.32	2.17	8 / 153	10 / 161	62.99
	2 and 4	Bougerol	2 and 4	1.78	0.51	6.22	7 / 158	4 / 158	37.01
Random	2 and 4			1.10	0.52	2.36			
	2 and 6	GSK	2 and 6	0.48	0.29	0.79	29 / 202	50 / 192	100.00
Random	2 and 6			0.48	0.29	0.79			
	2 and 7	Hsu 2011	2 and 7	0.30	0.03	3.15	1 / 21	3 / 21	30.80
	2 and 7	Ekselius	2 and 7	1.76	0.68	4.57	12 / 200	7 / 200	69.20
Random	2 and 7			1.02	0.21	5.06			
	20 and 21	Endo 1995	20 and 21	0.88	0.05	14.34	1 / 95	1 / 84	100.00
Random	20 and 21			0.88	0.05	14.34			



Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	3 and 14	Nieremberg	3 and 14	0.81	0.46	1.43	24 / 274	29 / 273	42.86
	3 and 14	Wade 2007	3 and 14	0.36	0.15	0.88	7 / 143	19 / 151	21.53
	3 and 14	Khan 2007	3 and 14	0.49	0.25	0.93	17 / 137	30 / 133	35.61
Random	3 and 14			0.57	0.36	0.89			
	3 and 17	Bielsky	3 and 17	1.02	0.39	2.69	9 / 98	9 / 100	42.07
	3 and 17	Montgomery	3 and 17	0.75	0.33	1.71	11 / 146	14 / 143	57.93
Random	3 and 17			0.85	0.46	1.60			
	3 and 4	Kasper	3 and 4	1.27	0.28	5.76	4 / 173	3 / 164	16.18
	3 and 4	SCT-MD-16	3 and 4	0.72	0.37	1.40	20 / 98	26 / 99	83.82
Random	3 and 4			0.79	0.43	1.45			
	3 and 6	Boulenger	3 and 6	1.00	0.50	2.02	17 / 153	18 / 162	65.74
	3 and 6	Baldwin	3 and 6	1.54	0.58	4.08	11 / 165	7 / 158	34.26
Random	3 and 6			1.16	0.66	2.05			
	3 and 7	SCT-MD-27	3 and 7	1.43	0.70	2.92	20 / 134	15 / 137	52.11
	3 and 7	Ventura	3 and 7	0.78	0.36	1.66	14 / 104	18 / 108	47.89
Random	3 and 7			1.07	0.59	1.93			
	4 and 10	Noguera	4 and 10	0.49	0.04	5.57	1 / 60	2 / 60	52.84
	4 and 10	Ropert	4 and 10	14.39	0.80	260.41	7 / 72	1 / 73	47.16
Random	4 and 10			2.42	0.09	65.75			
	4 and 12	Akhondaze	4 and 12	2.20	0.36	13.34	4 / 24	2 / 24	100.00
Random	4 and 12			2.20	0.36	13.34			
	4 and 14	Goldstein	4 and 14	0.40	0.11	1.50	3 / 33	14 / 70	42.63
	4 and 14	HMAQ-B	4 and 14	1.24	0.45	3.41	7 / 37	13 / 82	57.37
Random	4 and 14			0.76	0.26	2.29			
	4 and 15	Versiani	4 and 15	1.88	0.73	4.87	13 / 149	7 / 145	100.00
Random	4 and 15			1.88	0.73	4.87			
	4 and 17	Alves 1999	4 and 17	2.26	0.41	12.35	5 / 47	2 / 40	9.25
	4 and 17	Clerc 1994	4 and 17	0.97	0.18	5.18	3 / 34	3 / 33	9.48
	4 and 17	Costa e	4 and 17	1.35	0.61	2.96	15 / 186	12 / 196	43.04
	4 and 17	Dierick	4 and 17	1.13	0.49	2.61	13 / 161	11 / 153	38.22
Random	4 and 17			1.28	0.76	2.15			
	4 and 19	Corne 1989	4 and 19	3.12	0.12	78.55	2 / 50	1 / 51	32.83
	4 and 19	Dowling	4 and 19	4.46	0.47	42.51	4 / 30	1 / 30	67.17
Random	4 and 19			3.97	0.63	25.18			
	4 and 21	Ansseau	4 and 21	1.50	0.46	4.90	7 / 93	5 / 97	39.11
	4 and 21	Guelfi 1998	4 and 21	2.89	1.06	7.84	10 / 100	7 / 189	55.08
	4 and 21	Lee 2002	4 and 21	6.69	0.31	144.74	3 / 32	1 / 40	5.81
Random	4 and 21			2.35	1.12	4.92			
	4 and 22	Berlanga	4 and 22	2.32	0.80	6.73	13 / 37	7 / 37	59.22
	4 and 22	Rush 1998	4 and 22	1.94	0.54	7.01	7 / 61	4 / 64	40.78
Random	4 and 22			2.16	0.95	4.90			
	4 and 24	Corrigan	4 and 24	1.43	0.50	4.08	6 / 33	14 / 104	100.00
Random	4 and 24			1.43	0.50	4.08			
	4 and 25	Fava 2005	4 and 25	0.65	0.19	2.21	5 / 47	7 / 45	100.00
Random	4 and 25			0.65	0.19	2.21			
	4 and 5	Rapaport	4 and 5	0.70	0.29	1.67	13 / 46	17 / 47	100.00
Random	4 and 5			0.70	0.29	1.67			
	4 and 6	Fava 1998	4 and 6	0.62	0.26	1.51	11 / 54	16 / 55	15.10
	4 and 6	Chouinard	4 and 6	0.82	0.43	1.55	23 / 101	27 / 102	28.64
	4 and 6	Gagiano	4 and 6	2.00	0.61	6.52	9 / 45	5 / 45	8.40
	4 and 6	Schone	4 and 6	1.52	0.45	5.15	7 / 52	5 / 54	7.93
	4 and 6	GSK	4 and 6	1.25	0.55	2.85	16 / 70	13 / 68	17.35
	4 and 6	Fava 2002	4 and 6	0.86	0.42	1.77	17 / 92	20 / 96	22.58
Random	4 and 6			0.97	0.69	1.37			
	4 and 7	Newhouse	4 and 7	1.05	0.50	2.20	17 / 119	16 / 117	41.85
	4 and 7	Sechter	4 and 7	0.98	0.24	4.02	4 / 120	4 / 118	11.41
	4 and 7	Fava 2002	4 and 7	0.64	0.32	1.29	17 / 92	25 / 96	46.75
Random	4 and 7			0.83	0.52	1.34			



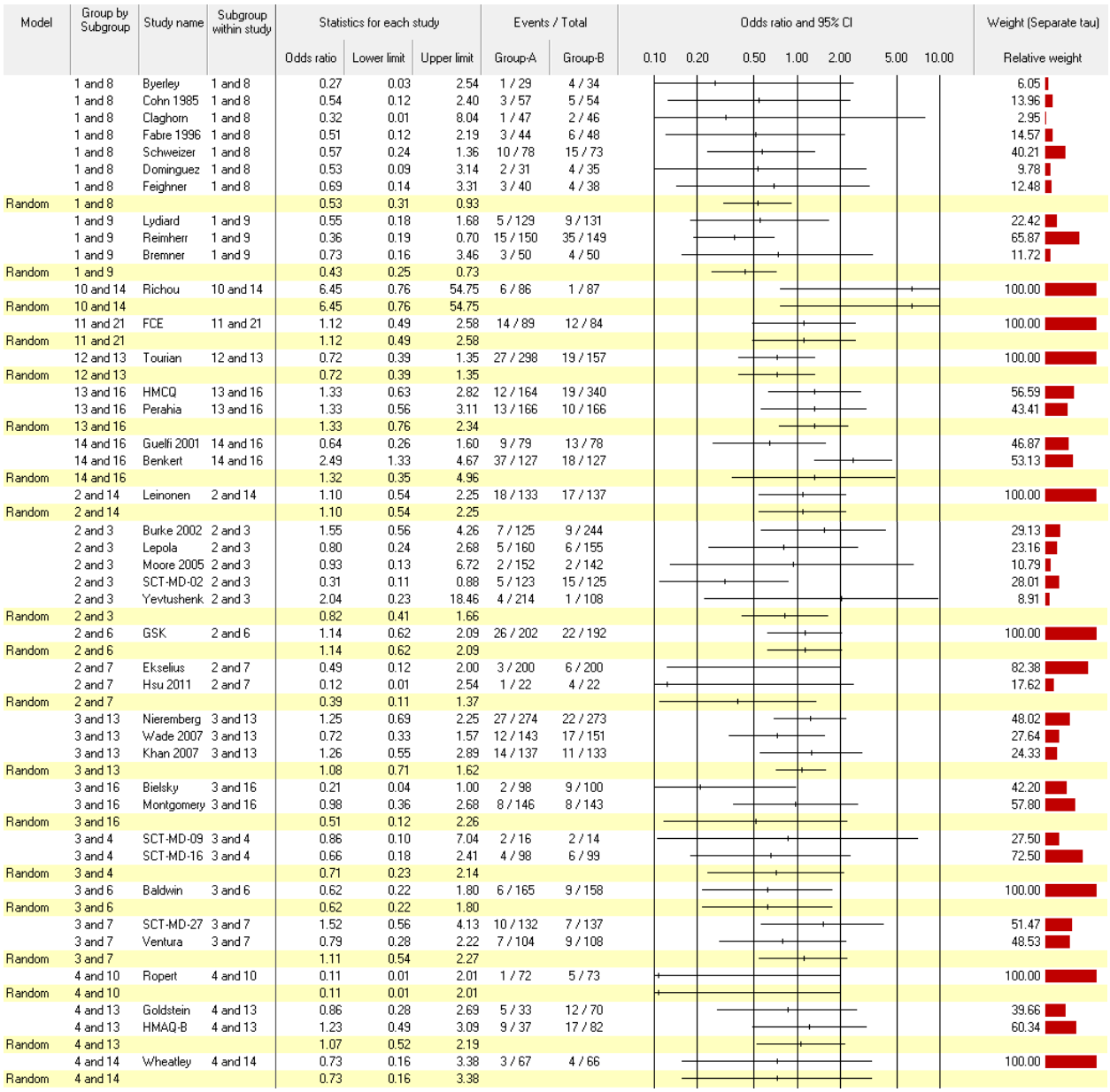
Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	4 and 8	Byerley	4 and 8	4.71	0.50	44.66	4 / 32	1 / 34	12.74
	4 and 8	Cohn 1985	4 and 8	2.51	0.81	7.79	11 / 54	5 / 54	50.09
	4 and 8	Cohn 1989	4 and 8	6.00	1.17	30.72	9 / 30	2 / 30	24.13
	4 and 8	Beasley	4 and 8	4.69	0.51	43.30	4 / 56	1 / 62	13.04
Random	4 and 8			3.64	1.63	8.12			
	4 and 9	De Ronchi	4 and 9	1.03	0.19	5.55	3 / 32	3 / 33	40.89
	4 and 9	Judd 1993	4 and 9	3.21	0.57	18.24	5 / 26	2 / 29	38.28
	4 and 9	Masco	4 and 9	3.53	0.34	37.15	3 / 20	1 / 21	20.83
Random	4 and 9			2.06	0.70	6.04			
	5 and 10	Coleman	5 and 10	0.84	0.32	2.21	10 / 50	11 / 48	67.47
	5 and 10	Dick 1983	5 and 10	0.78	0.19	3.13	8 / 17	8 / 15	32.53
Random	5 and 10			0.82	0.37	1.81			
	5 and 16	Barrelet	5 and 16	0.75	0.15	3.67	3 / 30	4 / 31	20.36
	5 and 16	Bougerol	5 and 16	0.57	0.25	1.27	13 / 61	21 / 65	79.64
Random	5 and 16			0.60	0.29	1.23			
	5 and 18	Brunner	5 and 18	0.10	0.01	0.89	13 / 20	19 / 20	100.00
Random	5 and 18			0.10	0.01	0.89			
	5 and 21	Ansseau	5 and 21	1.27	0.46	3.51	7 / 41	12 / 86	90.94
	5 and 21	Clerc 2001	5 and 21	3.11	0.12	77.93	2 / 57	1 / 58	9.06
Random	5 and 21			1.38	0.52	3.63			
	5 and 6	Kiev 1997	5 and 6	1.71	0.52	5.62	9 / 30	6 / 30	100.00
Random	5 and 6			1.71	0.52	5.62			
	5 and 7	Nemeroff	5 and 7	0.68	0.28	1.63	13 / 49	16 / 46	100.00
Random	5 and 7			0.68	0.28	1.63			
	5 and 8	Cassano	5 and 8	1.47	0.64	3.38	15 / 161	10 / 153	29.79
	5 and 8	Claghorn	5 and 8	0.70	0.15	3.31	3 / 47	4 / 45	11.65
	5 and 8	Fabre 1996	5 and 8	4.13	0.81	21.04	7 / 46	2 / 48	10.78
	5 and 8	Itil 1983	5 and 8	1.81	0.51	6.40	8 / 22	6 / 25	16.42
	5 and 8	Feighner	5 and 8	0.72	0.18	2.82	4 / 31	6 / 35	14.43
	5 and 8	Dominguez	5 and 8	25.45	1.42	457.06	10 / 36	1 / 36	3.78
	5 and 8	Amore 1989	5 and 8	1.71	0.40	7.29	8 / 15	6 / 15	13.16
Random	5 and 8			1.60	0.90	2.84			
	5 and 9	Murasaki	5 and 9	5.49	0.26	115.67	3 / 114	1 / 123	100.00
Random	5 and 9			5.49	0.26	115.67			
	6 and 14	Detke	6 and 14	0.64	0.17	2.40	3 / 86	10 / 188	10.02
	6 and 14	Goldstein	6 and 14	0.38	0.16	0.90	7 / 87	33 / 177	23.46
	6 and 14	Higuchi	6 and 14	0.65	0.28	1.47	10 / 164	16 / 175	25.78
	6 and 14	HMAT-A	6 and 14	0.62	0.27	1.45	8 / 89	24 / 175	24.34
	6 and 14	Perahia	6 and 14	1.40	0.50	3.92	7 / 98	10 / 197	16.41
Random	6 and 14			0.64	0.42	0.97			
	6 and 15	Wade 2003	6 and 15	2.62	0.89	7.75	12 / 98	5 / 99	42.87
	6 and 15	Schatzberg	6 and 15	0.94	0.43	2.04	14 / 126	15 / 128	57.13
Random	6 and 15			1.46	0.54	3.95			
	6 and 7	Fava 2002	6 and 7	0.75	0.38	1.46	20 / 96	25 / 96	43.95
	6 and 7	Aberg-Wiste	6 and 7	1.14	0.63	2.07	27 / 177	24 / 176	56.05
Random	6 and 7			0.95	0.61	1.48			
	6 and 8	Feighner	6 and 8	0.94	0.30	2.99	7 / 40	7 / 38	100.00
Random	6 and 8			0.94	0.30	2.99			
	6 and 9	BRL-02906	6 and 9	1.07	0.20	5.62	3 / 44	3 / 47	100.00
Random	6 and 9			1.07	0.20	5.62			
	7 and 15	Behnke	7 and 15	1.81	0.77	4.25	15 / 169	9 / 176	52.87
	7 and 15	Thase 2000	7 and 15	4.16	1.62	10.65	22 / 126	6 / 124	47.13
Random	7 and 15			2.68	1.18	6.05			
	7 and 16	Soogard	7 and 16	0.90	0.45	1.82	19 / 100	20 / 97	100.00
Random	7 and 16			0.90	0.45	1.82			



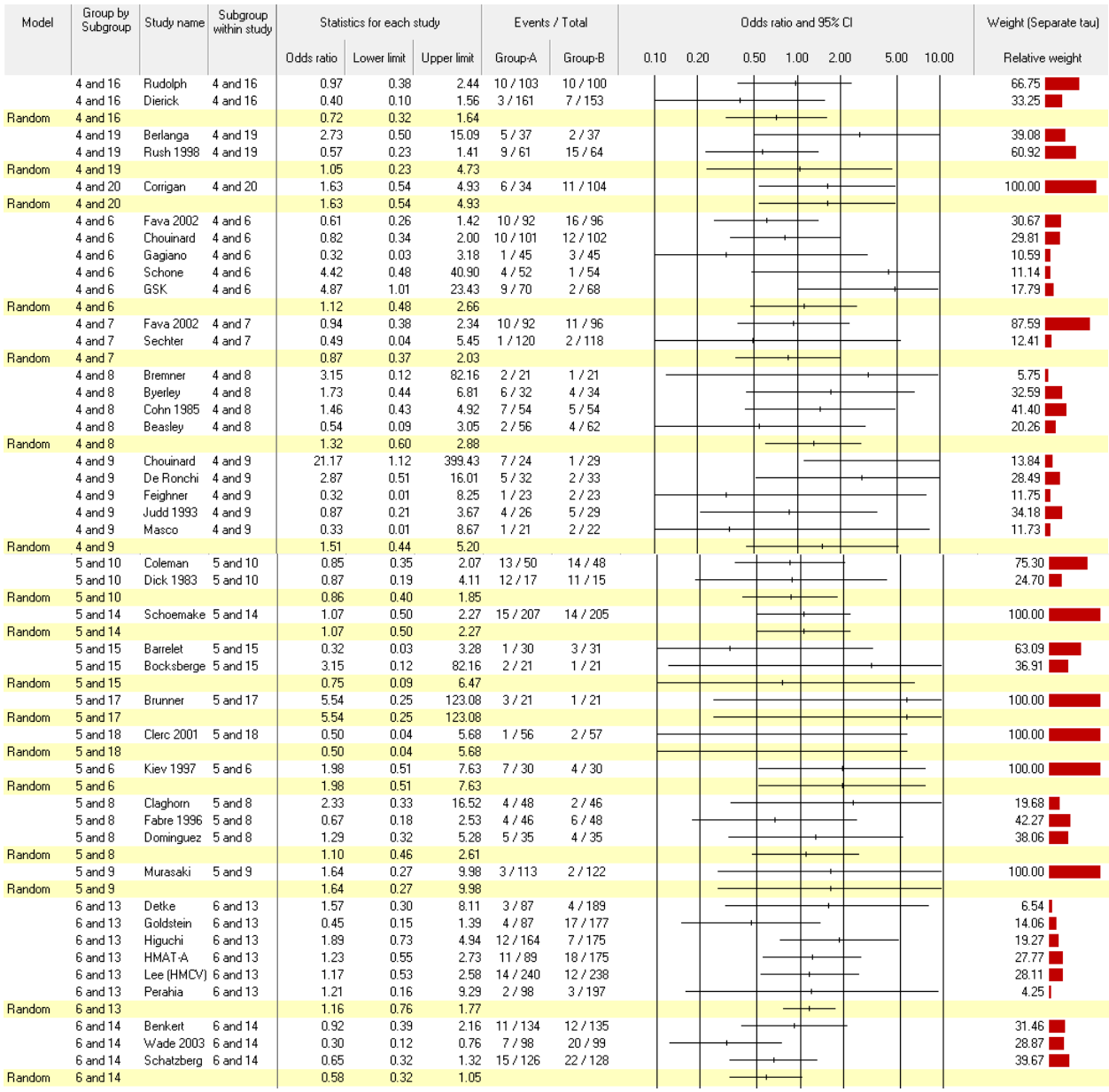
	7 and 17	Mehtonen	7 and 17	0.92	0.33	2.52	8 / 72	9 / 75	18.72
	7 and 17	Shelton	7 and 17	1.46	0.67	3.20	19 / 72	14 / 71	31.14
	7 and 17	Sir 2005	7 and 17	1.39	0.75	2.59	46 / 79	42 / 84	50.14
Random	7 and 17			1.31	0.84	2.03			
	7 and 22	Feiger 1996	7 and 22	1.17	0.55	2.48	19 / 82	16 / 78	100.00
Random	7 and 22			1.17	0.55	2.48			
	7 and 23	Eker 2005	7 and 23	0.20	0.02	1.97	1 / 21	4 / 20	100.00
Random	7 and 23			0.20	0.02	1.97			
	7 and 25	Van Gurp	7 and 25	1.09	0.48	2.50	24 / 45	23 / 45	100.00
Random	7 and 25			1.09	0.48	2.50			
	7 and 8	Baca 2003	7 and 8	0.80	0.34	1.90	10 / 116	13 / 123	41.05
	7 and 8	Forlenza	7 and 8	1.45	0.50	4.23	16 / 27	14 / 28	29.24
	7 and 8	Fournier	7 and 8	2.33	0.81	6.69	13 / 54	6 / 50	29.71
Random	7 and 8			1.31	0.70	2.45			
	7 and 9	Lydiard	7 and 9	2.75	0.71	10.61	8 / 132	3 / 131	13.89
	7 and 9	Reimherr	7 and 9	2.04	1.02	4.08	26 / 149	14 / 149	52.51
	7 and 9	Cohn 1990	7 and 9	1.28	0.54	3.04	20 / 161	8 / 80	33.60
Random	7 and 9			1.82	1.10	3.00			
	8 and 17	Schweizer	8 and 17	0.54	0.22	1.34	9 / 73	15 / 73	100.00
Random	8 and 17			0.54	0.22	1.34			
	8 and 21	Yamashita	8 and 21	3.05	0.12	76.13	2 / 67	1 / 67	8.16
	8 and 21	Van	8 and 21	0.62	0.10	3.85	2 / 56	3 / 53	25.24
	8 and 21	Tignol 1998	8 and 21	1.93	0.62	5.94	9 / 109	5 / 112	66.60
Random	8 and 21			1.50	0.60	3.76			
	9 and 15	Organon	9 and 15	0.51	0.18	1.44	6 / 104	11 / 103	75.74
	9 and 15	Organon	9 and 15	0.62	0.10	3.86	2 / 59	3 / 56	24.26
Random	9 and 15			0.54	0.22	1.32			
	9 and 17	Gentil 2000	9 and 17	0.18	0.02	1.59	1 / 59	5 / 57	100.00
Random	9 and 17			0.18	0.02	1.59			
	9 and 21	Ansseau	9 and 21	0.67	0.11	4.20	2 / 43	3 / 44	100.00
Random	9 and 21			0.67	0.11	4.20			

Fatigue

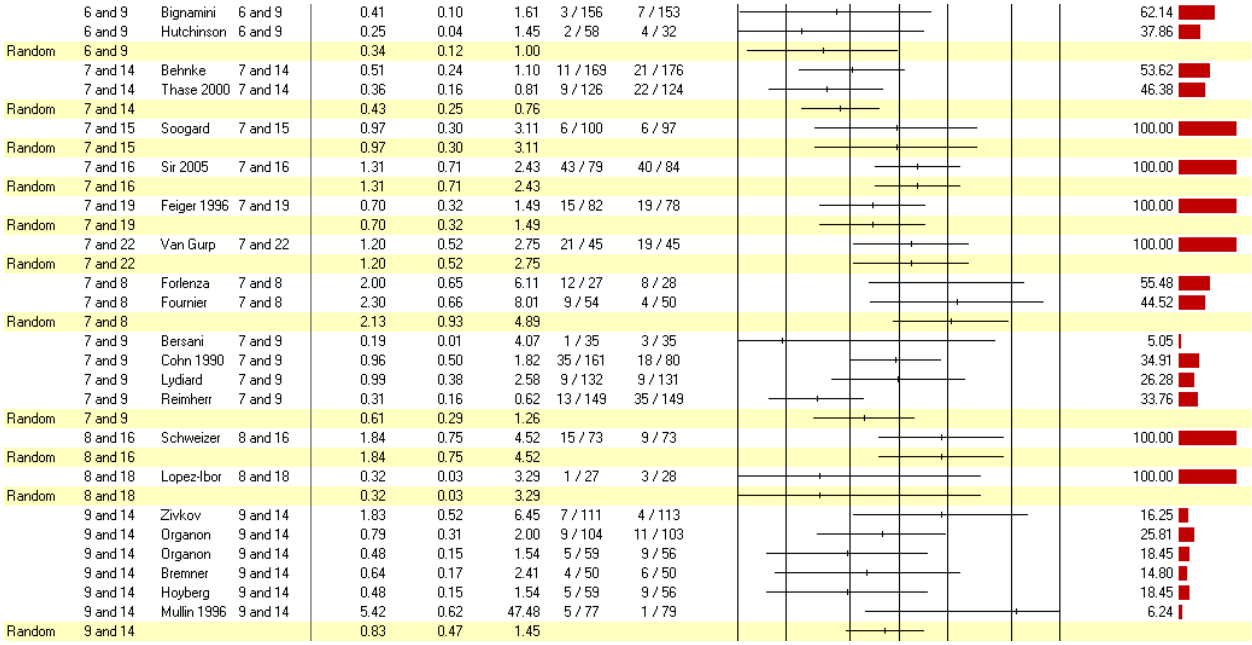
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 11	FCE	1 and 11	0.71	0.30	1.71	10 / 85	14 / 89		100.00
Random	1 and 11			0.71	0.30	1.71				
	1 and 12	Tourian	1 and 12	0.39	0.16	0.96	6 / 161	27 / 298		100.00
Random	1 and 12			0.39	0.16	0.96				
	1 and 13	Detke	1 and 13	0.28	0.01	5.54	1 / 94	4 / 189		2.50
	1 and 13	Goldstein	1 and 13	0.22	0.06	0.80	3 / 70	12 / 70		9.96
	1 and 13	Goldstein	1 and 13	0.22	0.05	0.96	2 / 89	17 / 177		8.26
	1 and 13	Higuchi	1 and 13	0.96	0.32	2.92	6 / 156	7 / 175		12.52
	1 and 13	HMAQ-B	1 and 13	0.27	0.10	0.78	5 / 75	17 / 82		13.43
	1 and 13	HMAT-A	1 and 13	0.74	0.30	1.83	7 / 90	18 / 175		15.90
	1 and 13	Nieremberg	1 and 13	1.10	0.52	2.29	12 / 137	22 / 273		19.77
	1 and 13	Perahia	1 and 13	0.39	0.02	8.22	1 / 100	3 / 197		2.39
	1 and 13	Tourian	1 and 13	0.28	0.11	0.72	6 / 161	19 / 157		15.27
Random	1 and 13			0.48	0.29	0.78				
	1 and 14	Bremner	1 and 14	0.47	0.11	1.99	3 / 50	6 / 50		100.00
Random	1 and 14			0.47	0.11	1.99				
	1 and 16	Rudolph	1 and 16	0.19	0.04	0.88	2 / 98	10 / 100		19.80
	1 and 16	Schweizer	1 and 16	1.05	0.40	2.74	10 / 78	9 / 73		35.81
	1 and 16	Hewett	1 and 16	0.85	0.40	1.82	13 / 187	16 / 198		44.39
Random	1 and 16			0.68	0.30	1.52				
	1 and 2	Burke 2002	1 and 2	0.72	0.22	2.33	5 / 122	7 / 125		25.38
	1 and 2	Lepola	1 and 2	1.04	0.30	3.67	5 / 154	5 / 160		22.11
	1 and 2	SCT-MD-02	1 and 2	0.57	0.13	2.44	3 / 127	5 / 123		16.61
	1 and 2	GSK	1 and 2	0.35	0.13	0.94	5 / 102	26 / 202		35.90
Random	1 and 2			0.58	0.32	1.05				
	1 and 20	Corrigan	1 and 20	0.12	0.01	2.14	1 / 35	11 / 104		100.00
Random	1 and 20			0.12	0.01	2.14				
	1 and 21	FCE	1 and 21	0.80	0.33	1.97	10 / 85	12 / 84		100.00
Random	1 and 21			0.80	0.33	1.97				
	1 and 3	Nieremberg	1 and 3	0.88	0.43	1.79	12 / 137	27 / 274		18.65
	1 and 3	AK130926	1 and 3	0.20	0.08	0.47	7 / 143	28 / 135		16.18
	1 and 3	AK 130927	1 and 3	0.79	0.32	1.96	9 / 141	11 / 138		15.46
	1 and 3	Burke 2002	1 and 3	1.12	0.37	3.40	5 / 122	9 / 244		12.74
	1 and 3	Lepola	1 and 3	0.83	0.25	2.79	5 / 154	6 / 155		11.66
	1 and 3	SCT-MD-02	1 and 3	0.18	0.05	0.63	3 / 127	15 / 125		11.04
	1 and 3	SCT-MD-27	1 and 3	0.68	0.25	1.85	7 / 132	10 / 132		14.27
Random	1 and 3			0.56	0.33	0.97				
	1 and 4	Goldstein	1 and 4	0.25	0.06	1.12	3 / 70	5 / 33		18.45
	1 and 4	HMAQ-B	1 and 4	0.22	0.07	0.72	5 / 75	9 / 37		29.84
	1 and 4	Byerley	1 and 4	0.15	0.02	1.37	1 / 29	6 / 32		8.68
	1 and 4	Cohn 1985	1 and 4	0.37	0.09	1.52	3 / 57	7 / 54		20.88
	1 and 4	Corrigan	1 and 4	0.08	0.00	1.42	1 / 35	6 / 34		4.80
	1 and 4	Rudolph	1 and 4	0.19	0.04	0.91	2 / 98	10 / 103		17.35
Random	1 and 4			0.23	0.12	0.43				
	1 and 5	Claghorn	1 and 5	0.14	0.01	2.72	1 / 47	4 / 48		12.95
	1 and 5	Fabre 1996	1 and 5	0.77	0.16	3.65	3 / 44	4 / 46		47.76
	1 and 5	Dominguez	1 and 5	0.41	0.07	2.30	2 / 31	5 / 35		39.29
Random	1 and 5			0.48	0.16	1.41				
	1 and 6	Detke	1 and 6	0.18	0.01	3.82	1 / 94	3 / 87		2.67
	1 and 6	Goldstein	1 and 6	0.48	0.09	2.67	2 / 89	4 / 87		8.37
	1 and 6	Higuchi	1 and 6	0.51	0.19	1.39	6 / 156	12 / 164		24.60
	1 and 6	HMAT-A	1 and 6	0.60	0.22	1.62	7 / 90	11 / 89		25.04
	1 and 6	Perahia	1 and 6	0.32	0.01	8.03	1 / 100	2 / 98		2.41
	1 and 6	GSK	1 and 6	0.40	0.15	1.09	5 / 102	22 / 192		24.75
	1 and 6	Feighner	1 and 6	0.38	0.09	1.60	3 / 40	7 / 40		12.14
Random	1 and 6			0.46	0.28	0.76				
	1 and 7	SCT-MD-27	1 and 7	1.04	0.35	3.05	7 / 132	7 / 137		26.15
	1 and 7	Lydiard	1 and 7	0.55	0.18	1.69	5 / 129	9 / 132		24.08
	1 and 7	Reimherr	1 and 7	1.16	0.53	2.54	15 / 150	13 / 149		49.77
Random	1 and 7			0.94	0.54	1.64				



Model	Group by Subgroup	Study name	Subgroup within study	Odds ratio	Lower limit	Upper limit	Group-A	Group-B	Relative weight
	1 and 8	Byerley	1 and 8	0.27	0.03	2.54	1 / 29	4 / 34	6.05
	1 and 8	Cohn 1985	1 and 8	0.54	0.12	2.40	3 / 57	5 / 54	13.96
	1 and 8	Claghorn	1 and 8	0.32	0.01	8.04	1 / 47	2 / 46	2.95
	1 and 8	Fabre 1996	1 and 8	0.51	0.12	2.19	3 / 44	6 / 48	14.57
	1 and 8	Schweizer	1 and 8	0.57	0.24	1.36	10 / 78	15 / 73	40.21
	1 and 8	Dominguez	1 and 8	0.53	0.09	3.14	2 / 31	4 / 35	9.78
	1 and 8	Feighner	1 and 8	0.69	0.14	3.31	3 / 40	4 / 38	12.48
Random	1 and 8			0.53	0.31	0.93			
	1 and 9	Lydiard	1 and 9	0.55	0.18	1.68	5 / 129	9 / 131	22.42
	1 and 9	Reimherr	1 and 9	0.36	0.19	0.70	15 / 150	35 / 149	65.87
	1 and 9	Bremner	1 and 9	0.73	0.16	3.46	3 / 50	4 / 50	11.72
Random	1 and 9			0.43	0.25	0.73			
	10 and 14	Richou	10 and 14	6.45	0.76	54.75	6 / 86	1 / 87	100.00
Random	10 and 14			6.45	0.76	54.75			
	11 and 21	FCE	11 and 21	1.12	0.49	2.58	14 / 89	12 / 84	100.00
Random	11 and 21			1.12	0.49	2.58			
	12 and 13	Tourian	12 and 13	0.72	0.39	1.35	27 / 298	19 / 157	100.00
Random	12 and 13			0.72	0.39	1.35			
	13 and 16	HMCQ	13 and 16	1.33	0.63	2.82	12 / 164	19 / 340	56.59
	13 and 16	Perahia	13 and 16	1.33	0.56	3.11	13 / 166	10 / 166	43.41
Random	13 and 16			1.33	0.76	2.34			
	14 and 16	Guelfi 2001	14 and 16	0.64	0.26	1.60	9 / 79	13 / 78	46.87
	14 and 16	Benkert	14 and 16	2.49	1.33	4.67	37 / 127	18 / 127	53.13
Random	14 and 16			1.32	0.35	4.96			
	2 and 14	Leinonen	2 and 14	1.10	0.54	2.25	18 / 133	17 / 137	100.00
Random	2 and 14			1.10	0.54	2.25			
	2 and 3	Burke 2002	2 and 3	1.55	0.56	4.26	7 / 125	9 / 244	29.13
	2 and 3	Lepola	2 and 3	0.80	0.24	2.68	5 / 160	6 / 155	23.16
	2 and 3	Moore 2005	2 and 3	0.93	0.13	6.72	2 / 152	2 / 142	10.79
	2 and 3	SCT-MD-02	2 and 3	0.31	0.11	0.88	5 / 123	15 / 125	28.01
	2 and 3	Yevtushenk	2 and 3	2.04	0.23	18.46	4 / 214	1 / 108	8.91
Random	2 and 3			0.82	0.41	1.66			
	2 and 6	GSK	2 and 6	1.14	0.62	2.09	26 / 202	22 / 192	100.00
Random	2 and 6			1.14	0.62	2.09			
	2 and 7	Ekselius	2 and 7	0.49	0.12	2.00	3 / 200	6 / 200	82.38
	2 and 7	Hsu 2011	2 and 7	0.12	0.01	2.54	1 / 22	4 / 22	17.62
Random	2 and 7			0.39	0.11	1.37			
	3 and 13	Nieremberg	3 and 13	1.25	0.69	2.25	27 / 274	22 / 273	48.02
	3 and 13	Wade 2007	3 and 13	0.72	0.33	1.57	12 / 143	17 / 151	27.64
	3 and 13	Khan 2007	3 and 13	1.26	0.55	2.89	14 / 137	11 / 133	24.33
Random	3 and 13			1.08	0.71	1.62			
	3 and 16	Bielsky	3 and 16	0.21	0.04	1.00	2 / 98	9 / 100	42.20
	3 and 16	Montgomery	3 and 16	0.98	0.36	2.68	8 / 146	8 / 143	57.80
Random	3 and 16			0.51	0.12	2.26			
	3 and 4	SCT-MD-09	3 and 4	0.86	0.10	7.04	2 / 16	2 / 14	27.50
	3 and 4	SCT-MD-16	3 and 4	0.66	0.18	2.41	4 / 98	6 / 99	72.50
Random	3 and 4			0.71	0.23	2.14			
	3 and 6	Baldwin	3 and 6	0.62	0.22	1.80	6 / 165	9 / 158	100.00
Random	3 and 6			0.62	0.22	1.80			
	3 and 7	SCT-MD-27	3 and 7	1.52	0.56	4.13	10 / 132	7 / 137	51.47
	3 and 7	Ventura	3 and 7	0.79	0.28	2.22	7 / 104	9 / 108	48.53
Random	3 and 7			1.11	0.54	2.27			
	4 and 10	Ropert	4 and 10	0.11	0.01	2.01	1 / 72	5 / 73	100.00
Random	4 and 10			0.11	0.01	2.01			
	4 and 13	Goldstein	4 and 13	0.86	0.28	2.69	5 / 33	12 / 70	39.66
	4 and 13	HMAQ-B	4 and 13	1.23	0.49	3.09	9 / 37	17 / 82	60.34
Random	4 and 13			1.07	0.52	2.19			
	4 and 14	Wheatley	4 and 14	0.73	0.16	3.38	3 / 67	4 / 66	100.00
Random	4 and 14			0.73	0.16	3.38			

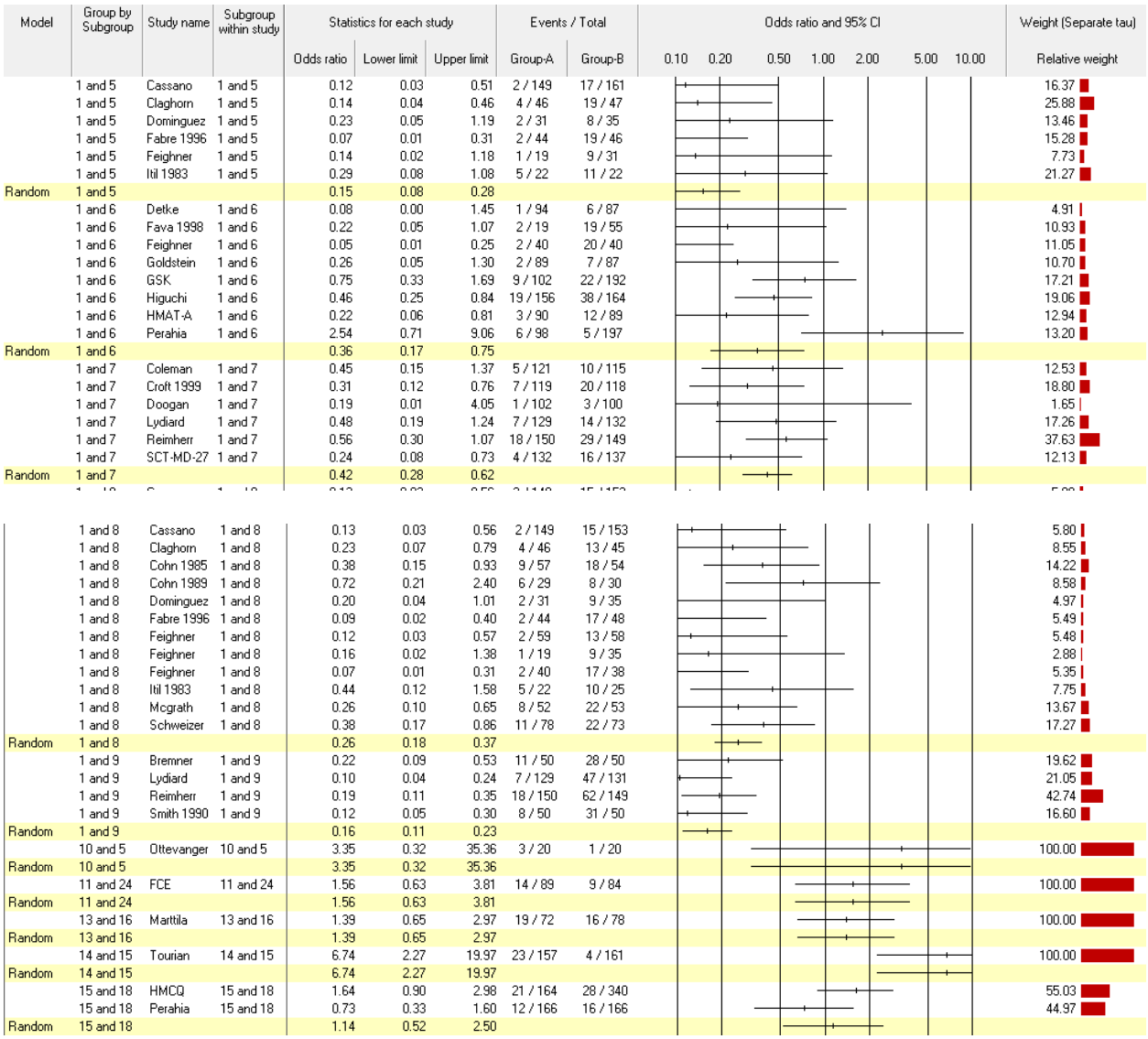


Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	4 and 16	Rudolph	4 and 16	0.97	0.38	2.44	10 / 103	10 / 100		66.75
	4 and 16	Dierick	4 and 16	0.40	0.10	1.56	3 / 161	7 / 153		33.25
Random	4 and 16			0.72	0.32	1.64				
	4 and 19	Berlanga	4 and 19	2.73	0.50	15.09	5 / 37	2 / 37		39.08
	4 and 19	Rush 1998	4 and 19	0.57	0.23	1.41	9 / 61	15 / 64		60.92
Random	4 and 19			1.05	0.23	4.73				
	4 and 20	Corrigan	4 and 20	1.63	0.54	4.93	6 / 34	11 / 104		100.00
Random	4 and 20			1.63	0.54	4.93				
	4 and 6	Fava 2002	4 and 6	0.61	0.26	1.42	10 / 92	16 / 96		30.67
	4 and 6	Chouinard	4 and 6	0.82	0.34	2.00	10 / 101	12 / 102		29.81
	4 and 6	Gagiano	4 and 6	0.32	0.03	3.18	1 / 45	3 / 45		10.59
	4 and 6	Schone	4 and 6	4.42	0.48	40.90	4 / 52	1 / 54		11.14
	4 and 6	GSK	4 and 6	4.87	1.01	23.43	9 / 70	2 / 68		17.79
Random	4 and 6			1.12	0.48	2.66				
	4 and 7	Fava 2002	4 and 7	0.94	0.38	2.34	10 / 92	11 / 96		87.59
	4 and 7	Sechter	4 and 7	0.49	0.04	5.45	1 / 120	2 / 118		12.41
Random	4 and 7			0.87	0.37	2.03				
	4 and 8	Bremner	4 and 8	3.15	0.12	82.16	2 / 21	1 / 21		5.75
	4 and 8	Byerley	4 and 8	1.73	0.44	6.81	6 / 32	4 / 34		32.59
	4 and 8	Cohn 1985	4 and 8	1.46	0.43	4.92	7 / 54	5 / 54		41.40
	4 and 8	Beasley	4 and 8	0.54	0.09	3.05	2 / 56	4 / 62		20.26
Random	4 and 8			1.32	0.60	2.88				
	4 and 9	Chouinard	4 and 9	21.17	1.12	399.43	7 / 24	1 / 29		13.84
	4 and 9	De Ronchi	4 and 9	2.87	0.51	16.01	5 / 32	2 / 33		28.49
	4 and 9	Feighner	4 and 9	0.32	0.01	8.25	1 / 23	2 / 23		11.75
	4 and 9	Judd 1993	4 and 9	0.87	0.21	3.67	4 / 26	5 / 29		34.18
	4 and 9	Masco	4 and 9	0.33	0.01	8.67	1 / 21	2 / 22		11.73
Random	4 and 9			1.51	0.44	5.20				
	5 and 10	Coleman	5 and 10	0.85	0.35	2.07	13 / 50	14 / 48		75.30
	5 and 10	Dick 1983	5 and 10	0.87	0.19	4.11	12 / 17	11 / 15		24.70
Random	5 and 10			0.86	0.40	1.85				
	5 and 14	Schoemake	5 and 14	1.07	0.50	2.27	15 / 207	14 / 205		100.00
Random	5 and 14			1.07	0.50	2.27				
	5 and 15	Barrelet	5 and 15	0.32	0.03	3.28	1 / 30	3 / 31		63.09
	5 and 15	Bocksberge	5 and 15	3.15	0.12	82.16	2 / 21	1 / 21		36.91
Random	5 and 15			0.75	0.09	6.47				
	5 and 17	Brunner	5 and 17	5.54	0.25	123.08	3 / 21	1 / 21		100.00
Random	5 and 17			5.54	0.25	123.08				
	5 and 18	Clerc 2001	5 and 18	0.50	0.04	5.68	1 / 56	2 / 57		100.00
Random	5 and 18			0.50	0.04	5.68				
	5 and 6	Kiev 1997	5 and 6	1.98	0.51	7.63	7 / 30	4 / 30		100.00
Random	5 and 6			1.98	0.51	7.63				
	5 and 8	Claghorn	5 and 8	2.33	0.33	16.52	4 / 48	2 / 46		19.68
	5 and 8	Fabre 1996	5 and 8	0.67	0.18	2.53	4 / 46	6 / 48		42.27
	5 and 8	Dominguez	5 and 8	1.29	0.32	5.28	5 / 35	4 / 35		38.06
Random	5 and 8			1.10	0.46	2.61				
	5 and 9	Murasaki	5 and 9	1.64	0.27	9.98	3 / 113	2 / 122		100.00
Random	5 and 9			1.64	0.27	9.98				
	6 and 13	Detke	6 and 13	1.57	0.30	8.11	3 / 87	4 / 189		6.54
	6 and 13	Goldstein	6 and 13	0.45	0.15	1.39	4 / 87	17 / 177		14.06
	6 and 13	Higuchi	6 and 13	1.89	0.73	4.94	12 / 164	7 / 175		19.27
	6 and 13	HMAT-A	6 and 13	1.23	0.55	2.73	11 / 89	18 / 175		27.77
	6 and 13	Lee (HMCV)	6 and 13	1.17	0.53	2.58	14 / 240	12 / 238		28.11
	6 and 13	Perahia	6 and 13	1.21	0.16	9.29	2 / 98	3 / 197		4.25
Random	6 and 13			1.16	0.76	1.77				
	6 and 14	Benkert	6 and 14	0.92	0.39	2.16	11 / 134	12 / 135		31.46
	6 and 14	Wade 2003	6 and 14	0.30	0.12	0.76	7 / 98	20 / 99		28.87
	6 and 14	Schatzberg	6 and 14	0.65	0.32	1.32	15 / 126	22 / 128		39.67
Random	6 and 14			0.58	0.32	1.05				


6 and 9 Bignamini 6 and 9 0.41 0.10 1.61 3 / 156 7 / 153 62.14
6 and 9 Hutchinson 6 and 9 0.25 0.04 1.45 2 / 58 4 / 32 37.86
Random 6 and 9 0.34 0.12 1.00
7 and 14 Behnke 7 and 14 0.51 0.24 1.10 11 / 169 21 / 176 53.62
7 and 14 Thase 2000 7 and 14 0.36 0.16 0.81 9 / 126 22 / 124 46.38
Random 7 and 14 0.43 0.25 0.76
7 and 15 Soogard 7 and 15 0.97 0.30 3.11 6 / 100 6 / 97 100.00
Random 7 and 15 0.97 0.30 3.11
7 and 16 Sir 2005 7 and 16 1.31 0.71 2.43 43 / 79 40 / 84 100.00
Random 7 and 16 1.31 0.71 2.43
7 and 19 Feiger 1996 7 and 19 0.70 0.32 1.49 15 / 82 19 / 78 100.00
Random 7 and 19 0.70 0.32 1.49
7 and 22 Van Gurp 7 and 22 1.20 0.52 2.75 21 / 45 19 / 45 100.00
Random 7 and 22 1.20 0.52 2.75
7 and 8 Forlenza 7 and 8 2.00 0.65 6.11 12 / 27 8 / 28 55.48
7 and 8 Fournier 7 and 8 2.30 0.66 8.01 9 / 54 4 / 50 44.52
Random 7 and 8 2.13 0.93 4.89
7 and 9 Bersani 7 and 9 0.19 0.01 4.07 1 / 35 3 / 35 5.05
7 and 9 Cohn 1990 7 and 9 0.96 0.50 1.82 35 / 161 18 / 80 34.91
7 and 9 Lydiard 7 and 9 0.99 0.38 2.58 9 / 132 9 / 131 26.28
7 and 9 Reimherr 7 and 9 0.31 0.16 0.62 13 / 149 35 / 149 33.76
Random 7 and 9 0.61 0.29 1.26
8 and 16 Schweizer 8 and 16 1.84 0.75 4.52 15 / 73 9 / 73 100.00
Random 8 and 16 1.84 0.75 4.52
8 and 18 Lopez-Ibor 8 and 18 0.32 0.03 3.29 1 / 27 3 / 28 100.00
Random 8 and 18 0.32 0.03 3.29
9 and 14 Zivkov 9 and 14 1.83 0.52 6.45 7 / 111 4 / 113 16.25
9 and 14 Organon 9 and 14 0.79 0.31 2.00 9 / 104 11 / 103 25.81
9 and 14 Organon 9 and 14 0.48 0.15 1.54 5 / 59 9 / 56 18.45
9 and 14 Bremner 9 and 14 0.64 0.17 2.41 4 / 50 6 / 50 14.80
9 and 14 Hoyberg 9 and 14 0.48 0.15 1.54 5 / 59 9 / 56 18.45
9 and 14 Mullin 1996 9 and 14 5.42 0.62 47.48 5 / 77 1 / 79 6.24
Random 9 and 14 0.83 0.47 1.45

Drowsiness

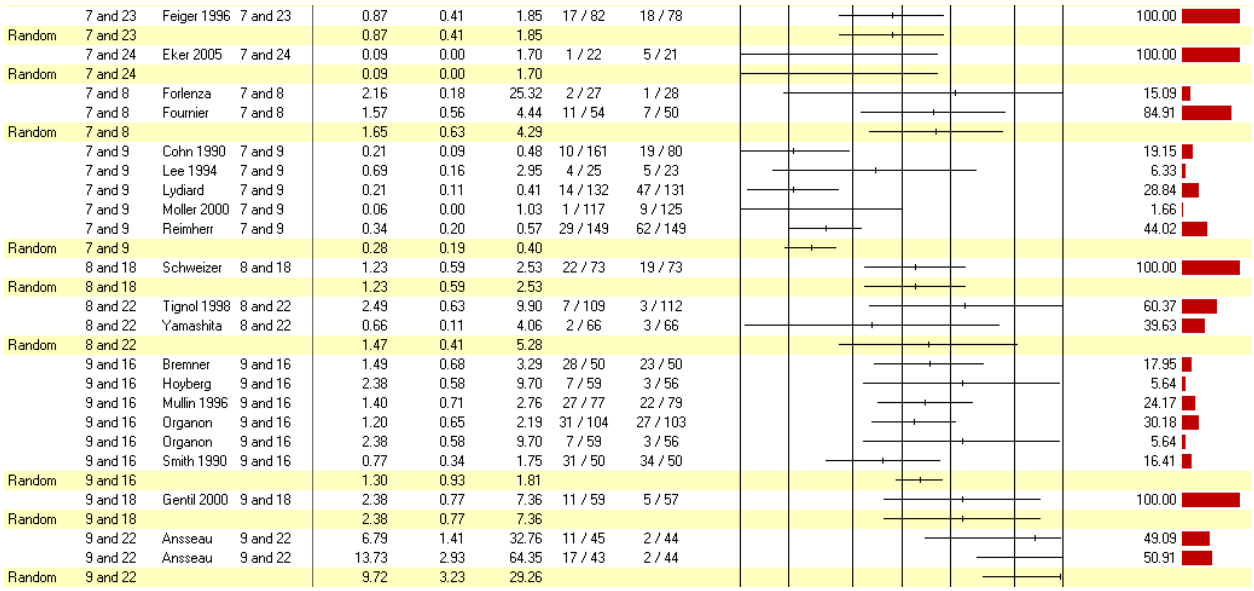
Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	1 and 11	FCE	1 and 11	0.71	0.30	1.71	10 / 85	14 / 89		100.00
Random	1 and 11			0.71	0.30	1.71				
	1 and 14	Tourian	1 and 14	0.56	0.31	1.01	26 / 298	23 / 157		100.00
Random	1 and 14			0.56	0.31	1.01				
	1 and 15	Detke	1 and 15	0.10	0.01	1.76	1 / 94	10 / 189		4.91
	1 and 15	Goldstein	1 and 15	0.49	0.18	1.31	7 / 70	13 / 70		13.81
	1 and 15	Goldstein	1 and 15	0.14	0.03	0.60	2 / 89	25 / 177		10.66
	1 and 15	Higuchi	1 and 15	0.47	0.26	0.85	19 / 156	40 / 175		16.36
	1 and 15	HMAQ-B	1 and 15	2.43	0.51	11.69	10 / 82	2 / 37		10.02
	1 and 15	HMAT-A	1 and 15	0.27	0.08	0.92	3 / 90	20 / 175		12.08
	1 and 15	Nieremberg	1 and 15	0.58	0.23	1.48	6 / 137	20 / 273		14.15
	1 and 15	Perahia	1 and 15	11.83	0.65	216.96	6 / 98	1 / 100		4.78
	1 and 15	Tourian	1 and 15	3.75	1.29	10.95	26 / 298	4 / 161		13.23
Random	1 and 15			0.67	0.32	1.40				
	1 and 16	Bremner	1 and 16	0.33	0.14	0.79	11 / 50	23 / 50		34.41
	1 and 16	Halikas	1 and 16	0.24	0.10	0.57	11 / 50	27 / 50		34.41
	1 and 16	Smith 1990	1 and 16	0.09	0.03	0.23	8 / 50	34 / 50		31.18
Random	1 and 16			0.20	0.09	0.42				
	1 and 18	Hewett	1 and 18	1.06	0.41	2.74	9 / 187	9 / 198		32.67
	1 and 18	Rudolph	1 and 18	0.75	0.25	2.25	6 / 98	8 / 100		24.30
	1 and 18	Schweizer	1 and 18	0.47	0.20	1.06	11 / 78	19 / 73		43.03
Random	1 and 18			0.69	0.40	1.18				
	1 and 2	Burke 2002	1 and 2	0.61	0.14	2.59	3 / 122	5 / 125		13.98
	1 and 2	GSK	1 and 2	0.46	0.21	1.00	9 / 102	35 / 202		49.16
	1 and 2	Lepola	1 and 2	0.41	0.08	2.13	2 / 154	5 / 160		10.78
	1 and 2	SCT-MD-02	1 and 2	0.63	0.22	1.82	6 / 127	9 / 123		26.08
Random	1 and 2			0.51	0.30	0.88				
	1 and 20	Doogan	1 and 20	0.11	0.01	2.15	1 / 102	5 / 109		100.00
Random	1 and 20			0.11	0.01	2.15				
	1 and 24	FCE	1 and 24	1.11	0.43	2.89	10 / 85	9 / 84		100.00
Random	1 and 24			1.11	0.43	2.89				
	1 and 26	Corrigan	1 and 26	0.23	0.05	1.05	2 / 34	22 / 104		100.00
Random	1 and 26			0.23	0.05	1.05				
	1 and 27	Fava 2005	1 and 27	0.35	0.09	1.41	3 / 43	8 / 45		100.00
Random	1 and 27			0.35	0.09	1.41				
	1 and 3	AK 130927	1 and 3	0.51	0.18	1.43	6 / 141	11 / 138		15.05
	1 and 3	AK130926	1 and 3	0.67	0.26	1.71	8 / 143	11 / 135		17.75
	1 and 3	Burke 2002	1 and 3	0.30	0.09	1.03	3 / 122	19 / 244		10.30
	1 and 3	Kasper	1 and 3	0.31	0.05	2.02	2 / 181	5 / 174		4.56
	1 and 3	Lepola	1 and 3	0.24	0.05	1.16	2 / 154	8 / 155		6.43
	1 and 3	Nieremberg	1 and 3	0.58	0.23	1.48	6 / 137	20 / 274		17.99
	1 and 3	SCT-MD-02	1 and 3	0.43	0.16	1.16	6 / 127	13 / 125		15.75
	1 and 3	SCT-MD-27	1 and 3	0.27	0.09	0.84	4 / 132	14 / 134		12.17
Random	1 and 3			0.44	0.29	0.65				
	1 and 4	Cohn 1985	1 and 4	0.32	0.13	0.78	9 / 57	20 / 54		17.59
	1 and 4	Cohn 1989	1 and 4	0.45	0.14	1.45	6 / 29	11 / 30		10.51
	1 and 4	Corrigan	1 and 4	0.63	0.10	4.00	2 / 34	3 / 33		4.14
	1 and 4	Fava 1998	1 and 4	0.34	0.07	1.64	2 / 19	14 / 54		5.68
	1 and 4	Fava 2005	1 and 4	0.51	0.12	2.19	3 / 43	6 / 47		6.77
	1 and 4	Feighner	1 and 4	0.39	0.07	2.11	2 / 59	5 / 61		5.06
	1 and 4	Goldstein	1 and 4	0.41	0.13	1.29	7 / 70	7 / 33		10.94
	1 and 4	HMAQ-B	1 and 4	2.47	0.74	8.23	10 / 82	4 / 75		9.84
	1 and 4	Kasper	1 and 4	2.75	0.11	67.96	2 / 181	1 / 165		1.39
	1 and 4	Mcgrath	1 and 4	0.56	0.21	1.52	8 / 52	12 / 49		14.41
	1 and 4	Rudolph	1 and 4	0.49	0.18	1.37	6 / 98	12 / 103		13.68
Random	1 and 4			0.53	0.36	0.78				


Model
Group by Subgroup
Study name
Subgroup within study
Statistics for each study
Odds ratio
Lower limit
Upper limit
Events / Total
Group-A
Group-B
Odds ratio and 95% CI
0.10
0.20
0.50
1.00
2.00
5.00
10.00
Weight (Separate tau)
Relative weight
1 and 5 Cassano 1 and 5 0.12 0.03 0.51 2 / 149 17 / 161 16.37
1 and 5 Claghorn 1 and 5 0.14 0.04 0.46 4 / 46 19 / 47 25.88
1 and 5 Dominguez 1 and 5 0.23 0.05 1.19 2 / 31 8 / 35 13.46
1 and 5 Fabre 1996 1 and 5 0.07 0.01 0.31 2 / 44 19 / 46 15.28
1 and 5 Feighner 1 and 5 0.14 0.02 1.18 1 / 19 9 / 31 7.73
1 and 5 Itil 1983 1 and 5 0.29 0.08 1.08 5 / 22 11 / 22 21.27
Random 1 and 5 0.15 0.08 0.28
1 and 6 Detke 1 and 6 0.08 0.00 1.45 1 / 94 6 / 87 4.91
1 and 6 Fava 1998 1 and 6 0.22 0.05 1.07 2 / 19 19 / 55 10.93
1 and 6 Feighner 1 and 6 0.05 0.01 0.25 2 / 40 20 / 40 11.05
1 and 6 Goldstein 1 and 6 0.26 0.05 1.30 2 / 89 7 / 87 10.70
1 and 6 GSK 1 and 6 0.75 0.33 1.69 9 / 102 22 / 192 17.21
1 and 6 Higuchi 1 and 6 0.46 0.25 0.84 19 / 156 38 / 164 19.06
1 and 6 HMAT-A 1 and 6 0.22 0.06 0.81 3 / 90 12 / 89 12.94
1 and 6 Perahia 1 and 6 2.54 0.71 9.06 6 / 98 5 / 197 13.20
Random 1 and 6 0.36 0.17 0.75
1 and 7 Coleman 1 and 7 0.45 0.15 1.37 5 / 121 10 / 115 12.53
1 and 7 Croft 1999 1 and 7 0.31 0.12 0.76 7 / 119 20 / 118 18.80
1 and 7 Doogan 1 and 7 0.19 0.01 4.05 1 / 102 3 / 100 1.65
1 and 7 Lydiard 1 and 7 0.48 0.19 1.24 7 / 129 14 / 132 17.26
1 and 7 Reimherr 1 and 7 0.56 0.30 1.07 18 / 150 29 / 149 37.63
1 and 7 SCT-MD-27 1 and 7 0.24 0.08 0.73 4 / 132 16 / 137 12.13
Random 1 and 7 0.42 0.28 0.62
1 and 8 Cassano 1 and 8 0.13 0.03 0.56 2 / 149 15 / 153 5.80
1 and 8 Claghorn 1 and 8 0.23 0.07 0.79 4 / 46 13 / 45 8.55
1 and 8 Cohn 1985 1 and 8 0.38 0.15 0.93 9 / 57 18 / 54 14.22
1 and 8 Cohn 1989 1 and 8 0.72 0.21 2.40 6 / 29 8 / 30 8.58
1 and 8 Dominguez 1 and 8 0.20 0.04 1.01 2 / 31 9 / 35 4.97
1 and 8 Fabre 1996 1 and 8 0.09 0.02 0.40 2 / 44 17 / 48 5.49
1 and 8 Feighner 1 and 8 0.12 0.03 0.57 2 / 59 13 / 58 5.48
1 and 8 Feighner 1 and 8 0.16 0.02 1.38 1 / 19 9 / 35 2.88
1 and 8 Feighner 1 and 8 0.07 0.01 0.31 2 / 40 17 / 38 5.35
1 and 8 Itil 1983 1 and 8 0.44 0.12 1.58 5 / 22 10 / 25 7.75
1 and 8 Mcgrath 1 and 8 0.26 0.10 0.65 8 / 52 22 / 53 13.67
1 and 8 Schweizer 1 and 8 0.38 0.17 0.86 11 / 78 22 / 73 17.27
Random 1 and 8 0.26 0.18 0.37
1 and 9 Bremner 1 and 9 0.22 0.09 0.53 11 / 50 28 / 50 19.62
1 and 9 Lydiard 1 and 9 0.10 0.04 0.24 7 / 129 47 / 131 21.05
1 and 9 Reimherr 1 and 9 0.19 0.11 0.35 18 / 150 62 / 149 42.74
1 and 9 Smith 1990 1 and 9 0.12 0.05 0.30 8 / 50 31 / 50 16.60
Random 1 and 9 0.16 0.11 0.23
10 and 5 Ottevanger 10 and 5 3.35 0.32 35.36 3 / 20 1 / 20 100.00
Random 10 and 5 3.35 0.32 35.36
11 and 24 FCE 11 and 24 1.56 0.63 3.81 14 / 89 9 / 84 100.00
Random 11 and 24 1.56 0.63 3.81
13 and 16 Marttila 13 and 16 1.39 0.65 2.97 19 / 72 16 / 78 100.00
Random 13 and 16 1.39 0.65 2.97
14 and 15 Tourian 14 and 15 6.74 2.27 19.97 23 / 157 4 / 161 100.00
Random 14 and 15 6.74 2.27 19.97
15 and 18 HMCQ 15 and 18 1.64 0.90 2.98 21 / 164 28 / 340 55.03
15 and 18 Perahia 15 and 18 0.73 0.33 1.60 12 / 166 16 / 166 44.97
Random 15 and 18 1.14 0.52 2.50

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	16 and 18	Guelfi 2000	16 and 18	1.56	0.42	5.77	6 / 78	4 / 79		74.20
	16 and 18	Guelfi 2001	16 and 18	4.22	0.46	38.60	4 / 78	1 / 79		25.80
Random	16 and 18			2.02	0.66	6.22				
	2 and 16	Leinonen	2 and 16	0.73	0.29	1.88	8 / 133	11 / 137		100.00
Random	2 and 16			0.73	0.29	1.88				
	2 and 3	Burke 2002	2 and 3	0.49	0.18	1.35	5 / 125	19 / 244		30.30
	2 and 3	Lepola	2 and 3	0.59	0.19	1.85	5 / 160	8 / 155		23.78
	2 and 3	Moore 2005	2 and 3	6.67	0.34	130.32	4 / 153	1 / 143		3.50
	2 and 3	SCT-MD-02	2 and 3	0.68	0.28	1.65	9 / 123	13 / 125		39.09
	2 and 3	Yevtushenk	2 and 3	2.55	0.12	53.65	3 / 215	1 / 109		3.33
Random	2 and 3			0.68	0.39	1.18				
	2 and 4	Bougerol	2 and 4	1.42	0.44	4.57	7 / 158	5 / 158		100.00
Random	2 and 4			1.42	0.44	4.57				
	2 and 6	GSK	2 and 6	1.62	0.91	2.88	35 / 202	22 / 192		100.00
Random	2 and 6			1.62	0.91	2.88				
	2 and 7	Ekselius	2 and 7	0.90	0.36	2.25	9 / 200	10 / 200		86.65
	2 and 7	Hsu 2011	2 and 7	0.30	0.03	3.15	1 / 21	3 / 21		13.35
Random	2 and 7			0.77	0.33	1.83				
	21 and 22	Endo 1995	21 and 22	4.76	1.71	13.23	22 / 95	5 / 84		100.00
Random	21 and 22			4.76	1.71	13.23				
	3 and 15	Khan 2007	3 and 15	1.79	0.81	3.91	19 / 137	11 / 133		38.52
	3 and 15	Nieremberg	3 and 15	1.00	0.52	1.90	20 / 274	20 / 273		46.14
	3 and 15	Wade 2007	3 and 15	4.41	0.92	21.15	8 / 143	2 / 151		15.34
Random	3 and 15			1.57	0.79	3.11				
	3 and 18	Bielsky	3 and 18	0.49	0.21	1.17	9 / 98	17 / 100		53.89
	3 and 18	Montgomery	3 and 18	2.28	0.69	7.59	9 / 146	4 / 143		46.11
Random	3 and 18			1.00	0.22	4.47				
	3 and 4	Kasper	3 and 4	8.73	0.47	163.51	5 / 174	1 / 165		6.05
	3 and 4	Mao 2008	3 and 4	1.09	0.38	3.12	8 / 123	7 / 117		47.32
	3 and 4	SCT-MD-16	3 and 4	1.17	0.41	3.36	8 / 98	7 / 99		46.63
Random	3 and 4			1.28	0.62	2.63				
	3 and 6	Baldwin	3 and 6	0.95	0.39	2.36	10 / 165	10 / 158		34.49
	3 and 6	Boulenger	3 and 6	1.13	0.59	2.18	21 / 153	20 / 162		65.51
Random	3 and 6			1.07	0.63	1.81				
	3 and 7	SCT-MD-27	3 and 7	0.88	0.41	1.89	14 / 134	16 / 137		57.07
	3 and 7	Ventura	3 and 7	2.22	0.80	6.15	12 / 104	6 / 108		42.93
Random	3 and 7			1.31	0.54	3.20				
	4 and 10	Ginestet	4 and 10	0.40	0.09	1.80	3 / 28	6 / 26		44.03
	4 and 10	Ropert	4 and 10	0.27	0.07	1.04	3 / 71	10 / 72		55.97
Random	4 and 10			0.32	0.12	0.88				
	4 and 12	Akhondaze	4 and 12	0.82	0.24	2.80	7 / 24	8 / 24		100.00
Random	4 and 12			0.82	0.24	2.80				
	4 and 15	Goldstein	4 and 15	1.18	0.42	3.30	7 / 33	13 / 70		74.19
	4 and 15	HMAQ-B	4 and 15	0.99	0.17	5.65	4 / 75	2 / 37		25.81
Random	4 and 15			1.13	0.46	2.73				
	4 and 16	Amini 2005	4 and 16	0.26	0.04	1.55	2 / 15	6 / 16		8.99
	4 and 16	Hong 2003	4 and 16	0.35	0.09	1.36	3 / 66	8 / 66		15.43
	4 and 16	Versiani	4 and 16	0.65	0.31	1.34	14 / 149	20 / 145		55.41
	4 and 16	Wheatley	4 and 16	0.68	0.20	2.26	5 / 67	7 / 66		20.17
Random	4 and 16			0.55	0.32	0.94				
	4 and 18	Costa e	4 and 18	0.18	0.05	0.64	3 / 186	16 / 196		48.01
	4 and 18	Rudolph	4 and 18	1.52	0.59	3.88	12 / 103	8 / 100		51.99
Random	4 and 18			0.55	0.07	4.34				
	4 and 20	Corne 1989	4 and 20	0.13	0.02	1.11	1 / 49	7 / 51		39.53
	4 and 20	Dowling	4 and 20	0.36	0.06	2.01	2 / 30	5 / 30		60.47
Random	4 and 20			0.24	0.06	0.92				
	4 and 22	Ansseau	4 and 22	1.04	0.14	7.57	2 / 93	2 / 97		66.85
	4 and 22	Lee 2002	4 and 22	1.27	0.08	21.10	1 / 31	1 / 39		33.15
Random	4 and 22			1.11	0.22	5.62				

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	4 and 23	Berlanga	4 and 23	1.24	0.34	4.48	6 / 37	5 / 37		30.55
	4 and 23	Rush 1998	4 and 23	0.97	0.41	2.27	13 / 61	14 / 64		69.45
Random	4 and 23			1.04	0.51	2.12				
	4 and 25	Albi 1993	4 and 25	0.98	0.27	3.49	5 / 104	5 / 102		100.00
Random	4 and 25			0.98	0.27	3.49				
	4 and 26	Corrigan	4 and 26	0.37	0.10	1.34	3 / 33	22 / 104		100.00
Random	4 and 26			0.37	0.10	1.34				
	4 and 27	Fava 2005	4 and 27	0.68	0.21	2.13	6 / 47	8 / 45		100.00
Random	4 and 27			0.68	0.21	2.13				
	4 and 6	Chouinard	4 and 6	0.88	0.43	1.82	17 / 101	19 / 102		29.60
	4 and 6	Fava 1998	4 and 6	0.66	0.29	1.51	14 / 54	19 / 55		22.66
	4 and 6	Fava 2002	4 and 6	0.83	0.38	1.81	14 / 92	17 / 96		25.73
	4 and 6	Gagiano	4 and 6	0.23	0.02	2.17	1 / 45	4 / 45		3.09
	4 and 6	GSK	4 and 6	0.79	0.23	2.74	5 / 70	6 / 68		10.06
	4 and 6	Ontiveros	4 and 6	0.63	0.17	2.36	4 / 61	6 / 60		8.85
Random	4 and 6			0.75	0.51	1.11				
	4 and 7	Aguglia	4 and 7	0.22	0.02	2.02	1 / 56	4 / 52		6.90
	4 and 7	Bennie	4 and 7	0.99	0.31	3.13	6 / 144	6 / 142		25.57
	4 and 7	Fava 2002	4 and 7	1.15	0.51	2.59	14 / 92	13 / 96		51.37
	4 and 7	Sechter	4 and 7	1.67	0.39	7.14	5 / 120	3 / 118		16.16
Random	4 and 7			1.04	0.58	1.87				
	4 and 8	Beasley	4 and 8	1.47	0.53	4.03	10 / 56	8 / 62		18.39
	4 and 8	Bremner	4 and 8	0.32	0.01	8.26	1 / 21	2 / 21		2.93
	4 and 8	Cohn 1985	4 and 8	1.18	0.53	2.59	20 / 54	18 / 54		23.46
	4 and 8	Cohn 1989	4 and 8	1.59	0.53	4.77	11 / 30	8 / 30		16.68
	4 and 8	Feighner	4 and 8	0.31	0.10	0.93	5 / 61	13 / 58		16.58
	4 and 8	Mcgrath	4 and 8	0.46	0.20	1.07	12 / 49	22 / 53		21.96
Random	4 and 8			0.81	0.45	1.44				
	4 and 9	Altamura	4 and 9	0.13	0.01	2.83	1 / 14	4 / 16		5.27
	4 and 9	Chouinard	4 and 9	0.88	0.26	3.05	6 / 23	8 / 28		21.64
	4 and 9	De Ronchi	4 and 9	1.45	0.47	4.53	9 / 32	7 / 33		24.00
	4 and 9	Feighner	4 and 9	0.48	0.12	1.94	4 / 22	7 / 22		18.42
	4 and 9	Judd 1993	4 and 9	0.14	0.03	0.57	3 / 26	14 / 29		18.43
	4 and 9	Marchesi	4 and 9	1.10	0.07	18.01	1 / 68	1 / 75		6.22
	4 and 9	Masco	4 and 9	1.05	0.06	18.05	1 / 20	1 / 21		6.02
Random	4 and 9			0.59	0.28	1.23				
	5 and 10	Dick 1983	5 and 10	1.09	0.25	4.71	6 / 17	5 / 15		100.00
Random	5 and 10			1.09	0.25	4.71				
	5 and 12	Otsubo	5 and 12	0.56	0.22	1.42	12 / 36	18 / 38		100.00
Random	5 and 12			0.56	0.22	1.42				
	5 and 16	Schoemake	5 and 16	0.47	0.29	0.76	33 / 207	59 / 205		100.00
Random	5 and 16			0.47	0.29	0.76				
	5 and 17	Bougerol	5 and 17	1.70	0.57	5.10	9 / 61	6 / 65		100.00
Random	5 and 17			1.70	0.57	5.10				
	5 and 19	Brunner	5 and 19	6.33	0.67	60.16	5 / 20	1 / 20		100.00
Random	5 and 19			6.33	0.67	60.16				
	5 and 20	Mullin 1988	5 and 20	1.55	0.40	6.02	6 / 37	4 / 36		100.00
Random	5 and 20			1.55	0.40	6.02				
	5 and 22	Ansseau	5 and 22	1.40	0.50	3.93	7 / 41	11 / 86		68.92
	5 and 22	Clerc 2001	5 and 22	6.72	0.78	57.75	6 / 56	1 / 57		31.08
Random	5 and 22			2.28	0.55	9.45				
	5 and 6	Ansseau	5 and 6	0.07	0.00	1.34	1 / 65	6 / 57		39.78
	5 and 6	Kiev 1997	5 and 6	1.56	0.53	4.53	12 / 30	9 / 30		60.22
Random	5 and 6			0.46	0.02	8.69				

Model	Group by Subgroup	Study name	Subgroup within study	Statistics for each study			Events / Total		Odds ratio and 95% CI	Weight (Separate tau)
				Odds ratio	Lower limit	Upper limit	Group-A	Group-B	0.10 0.20 0.50 1.00 2.00 5.00 10.00	Relative weight
	5 and 7	Nemeroff	5 and 7	1.54	0.57	4.20	12 / 49	8 / 46		100.00
Random	5 and 7			1.54	0.57	4.20				
	5 and 8	Amore 1989	5 and 8	2.36	0.36	15.45	4 / 15	2 / 15		2.38
	5 and 8	Asakura	5 and 8	0.72	0.44	1.18	40 / 152	52 / 157		34.80
	5 and 8	Cassano	5 and 8	1.09	0.52	2.26	17 / 161	15 / 153		15.62
	5 and 8	Claghorn	5 and 8	1.67	0.70	3.98	19 / 47	13 / 45		11.10
	5 and 8	Dominguez	5 and 8	0.86	0.29	2.56	8 / 35	9 / 35		7.00
	5 and 8	Fabre 1996	5 and 8	1.28	0.56	2.95	19 / 46	17 / 48		12.07
	5 and 8	Feighner	5 and 8	1.18	0.40	3.50	9 / 31	9 / 35		7.13
	5 and 8	Guy 1984	5 and 8	0.86	0.19	3.92	4 / 17	5 / 19		3.65
	5 and 8	Itil 1983	5 and 8	1.50	0.47	4.77	11 / 22	10 / 25		6.26
Random	5 and 8			1.03	0.77	1.37				
	5 and 9	Barge-Scha	5 and 9	0.04	0.00	0.79	1 / 14	6 / 11		18.34
	5 and 9	Harris 1991	5 and 9	0.18	0.01	3.96	1 / 36	3 / 35		18.27
	5 and 9	Kostiukova	5 and 9	0.07	0.02	0.32	3 / 25	15 / 23		29.21
	5 and 9	Murasaki	5 and 9	1.02	0.53	1.96	23 / 122	21 / 113		34.18
Random	5 and 9			0.19	0.03	1.23				
	6 and 15	Detke	6 and 15	1.28	0.43	3.76	6 / 87	10 / 189		7.77
	6 and 15	Goldstein	6 and 15	0.53	0.22	1.28	7 / 87	25 / 177		11.73
	6 and 15	Higuchi	6 and 15	1.02	0.61	1.69	38 / 164	40 / 175		35.55
	6 and 15	HMAT-A	6 and 15	1.21	0.56	2.60	12 / 89	20 / 175		15.51
	6 and 15	Lee (HMCV)	6 and 15	0.99	0.56	1.75	27 / 240	27 / 238		28.38
	6 and 15	Perahia	6 and 15	4.65	0.25	87.27	5 / 197	1 / 100		1.06
Random	6 and 15			0.99	0.74	1.34				
	6 and 16	Benkert	6 and 16	0.65	0.28	1.49	10 / 134	15 / 135		21.71
	6 and 16	Schatzberg	6 and 16	0.95	0.55	1.62	37 / 126	39 / 128		52.90
	6 and 16	Wade 2003	6 and 16	0.69	0.32	1.49	13 / 98	18 / 99		25.38
Random	6 and 16			0.80	0.54	1.19				
	6 and 7	Aberg-Wiste	6 and 7	2.57	0.79	8.37	10 / 177	4 / 176		30.72
	6 and 7	Fava 2002	6 and 7	1.37	0.63	3.01	17 / 96	13 / 96		69.28
Random	6 and 7			1.67	0.87	3.20				
	6 and 8	Feighner	6 and 8	1.24	0.51	3.01	20 / 40	17 / 38		100.00
Random	6 and 8			1.24	0.51	3.01				
	6 and 9	Bignamini	6 and 9	0.88	0.36	2.15	10 / 156	11 / 153		43.33
	6 and 9	GSK	6 and 9	0.52	0.22	1.23	9 / 109	16 / 108		45.63
	6 and 9	Hutchinson	6 and 9	0.25	0.04	1.45	2 / 58	4 / 32		11.04
Random	6 and 9			0.60	0.34	1.08				
	7 and 10	Edwards	7 and 10	1.67	0.32	8.59	5 / 17	3 / 15		100.00
Random	7 and 10			1.67	0.32	8.59				
	7 and 12	Bondareff	7 and 12	1.26	0.33	4.84	5 / 104	4 / 104		100.00
Random	7 and 12			1.26	0.33	4.84				
	7 and 16	Behnke	7 and 16	0.34	0.17	0.66	13 / 169	35 / 176		51.64
	7 and 16	Thase 2000	7 and 16	0.32	0.16	0.64	13 / 126	33 / 124		48.36
Random	7 and 16			0.33	0.20	0.53				
	7 and 17	Soogard	7 and 17	0.54	0.15	1.89	4 / 100	7 / 97		100.00
Random	7 and 17			0.54	0.15	1.89				
	7 and 18	Mehtonen	7 and 18	1.75	0.54	5.63	8 / 72	5 / 75		100.00
Random	7 and 18			1.75	0.54	5.63				
	7 and 20	Doogan	7 and 20	0.60	0.12	2.86	3 / 100	5 / 109		100.00
Random	7 and 20			0.60	0.12	2.86				
	7 and 23	Feiger 1996	7 and 23	0.87	0.41	1.85	17 / 82	18 / 78		100.00
Random	7 and 23			0.87	0.41	1.85				



	7 and 23	Feiger 1996	7 and 23	0.87	0.41	1.85	17 / 82	18 / 78		100.00
Random	7 and 23			0.87	0.41	1.85				
	7 and 24	Eker 2005	7 and 24	0.09	0.00	1.70	1 / 22	5 / 21		100.00
Random	7 and 24			0.09	0.00	1.70				
	7 and 8	Forlenza	7 and 8	2.16	0.18	25.32	2 / 27	1 / 28		15.09
	7 and 8	Fournier	7 and 8	1.57	0.56	4.44	11 / 54	7 / 50		84.91
Random	7 and 8			1.65	0.63	4.29				
	7 and 9	Cohn 1990	7 and 9	0.21	0.09	0.48	10 / 161	19 / 80		19.15
	7 and 9	Lee 1994	7 and 9	0.69	0.16	2.95	4 / 25	5 / 23		6.33
	7 and 9	Lydiard	7 and 9	0.21	0.11	0.41	14 / 132	47 / 131		28.84
	7 and 9	Moller 2000	7 and 9	0.06	0.00	1.03	1 / 117	9 / 125		1.66
	7 and 9	Reimherr	7 and 9	0.34	0.20	0.57	29 / 149	62 / 149		44.02
Random	7 and 9			0.28	0.19	0.40				
	8 and 18	Schweizer	8 and 18	1.23	0.59	2.53	22 / 73	19 / 73		100.00
Random	8 and 18			1.23	0.59	2.53				
	8 and 22	Tignol 1998	8 and 22	2.49	0.63	9.90	7 / 109	3 / 112		60.37
	8 and 22	Yamashita	8 and 22	0.66	0.11	4.06	2 / 66	3 / 66		39.63
Random	8 and 22			1.47	0.41	5.28				
	9 and 16	Bremner	9 and 16	1.49	0.68	3.29	28 / 50	23 / 50		17.95
	9 and 16	Hoyberg	9 and 16	2.38	0.58	9.70	7 / 59	3 / 56		5.64
	9 and 16	Mullin 1996	9 and 16	1.40	0.71	2.76	27 / 77	22 / 79		24.17
	9 and 16	Organon	9 and 16	1.20	0.65	2.19	31 / 104	27 / 103		30.18
	9 and 16	Organon	9 and 16	2.38	0.58	9.70	7 / 59	3 / 56		5.64
	9 and 16	Smith 1990	9 and 16	0.77	0.34	1.75	31 / 50	34 / 50		16.41
Random	9 and 16			1.30	0.93	1.81				
	9 and 18	Gentil 2000	9 and 18	2.38	0.77	7.36	11 / 59	5 / 57		100.00
Random	9 and 18			2.38	0.77	7.36				
	9 and 22	Ansseau	9 and 22	6.79	1.41	32.76	11 / 45	2 / 44		49.09
	9 and 22	Ansseau	9 and 22	13.73	2.93	64.35	17 / 43	2 / 44		50.91
Random	9 and 22			9.72	3.23	29.26				

Appendix 3:
Summary of Model Fit from Network Meta-Analyses

The adequacy of statistical fit for a given model can be established by comparing the number of data points in the data set to the residual deviance for the corresponding analysis; approximately a 1-1 ratio should be present. To compare the fit of competing models, their deviance information criteria values can be compared. We consistenly used random effects consistency models over fixed effects consistency models based on our findings given that they were consistently associated with similar or improved DIC values and random effects models are more justifiable. Comparison of DIC inconsistency and control rate meta-regression models with the unadjusted primary analysis did not show improvement in model fit for any of our clinical outcomes.

Outcome	# data points in data set of RCTs	Model fit statistics (residual deviance; deviance information criteria)			
		FE consistency	RE consistency	RE inconsistency	RE control rate metareg
Vision Problems	140	157.5; 648.6	137.3; 653.4	143.6; 661.5	143.9; 662.2
Dizziness	328	356.7; 1621.2	315.2; 1623.3	307.4; 1646.7	316.2; 1633.4
Hypotension	98	91.1; 427.0	89.5; 428.7	89.8; 429.6	90.9; 431.5
Insomnia	271	284.3; 1416.6	271.0; 1416.0	276.3; 1455.3	270.9; 1427.6
Fatigue	224	253.1; 1153.9	216.1; 1144.3	222.8; 1172.6	217.5; 1154.5
Drowsiness	328	410.3;1767.9	343.0; 1745.3	344.4; 1773.1	339.8; 1751.8

Appendix 4:
Summary of Findings from Control Group Risk Network Meta-Analyses

The following tables provide a comparison of comparisons of each of the active treatments against placebo obtained from both the primary analyses based on random effects network meta-analysis modeling as well as an additional random effects meta-regression model for network meta-analysis adjusting for control group risk as a sensitivity analysis. For brevity not all possible pairwise comparisons are reported. The tables include summary estimates for all treatments included in our treatment networks, including those not discussed in the main text which are not currently on Canadian provincial drug benefit plans for treatment of depression. All estimates are reported as summary odds ratios with corresponding 95% credible intervals. Model fit statistics for all models are provided in the preceding Appendix.

Insomnia: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	1.65 (1.17-2.33)	1.8 (1.3-2.48)
escitalopram	1.79 (1.4-2.31)	1.83 (1.46-2.28)
fluoxetine	2.13 (1.66-2.73)	2.31 (1.83-2.92)
fluvoxamine	1.79 (1.25-2.58)	2.05 (1.46-2.86)
paroxetine	1.91 (1.47-2.47)	2.03 (1.59-2.57)
sertraline	2.05 (1.62-2.6)	2.24 (1.79-2.8)
imipramine	1.11 (0.8-1.55)	1.3 (0.94-1.76)
amitriptyline	0.89 (0.58-1.38)	0.97 (0.64-1.51)
clomipramine	1.02 (0.51-2.13)	1.16 (0.58-2.35)
desipramine	2.41 (0.9-6.47)	2.34 (0.96-5.61)
nortriptyline	0.93 (0.11-5.92)	0.92 (0.09-6.33)
desvenlafaxine	2.18 (1.15-4.19)	2.33 (1.23-4.32)
duloxetine	2.73 (2.11-3.58)	2.7 (2.13-3.44)
mirtazapine	1.14 (0.74-1.7)	1.23 (0.8-1.87)
moclobemide	2.62 (1.45-4.88)	2.91 (1.55-5.49)
venlafaxine	1.93 (1.45-2.6)	2.04 (1.53-2.72)
amineptine	30.1 (3.06-1460)	29.44 (3.64-811)
dothiepine	0.43 (0.03-2.67)	0.47 (0.03-2.81)
mianserin	1.04 (0.02-38.69)	1.09 (0.02-48.77)
milnacipran	1.16 (0.68-1.93)	1.29 (0.75-2.14)
nefazodone	1.31 (0.69-2.49)	1.44 (0.74-2.7)
reboxetine	2.78 (1.38-5.87)	2.88 (1.49-5.7)
pramipexole	2.15 (0.76-6.6)	2.55 (0.98-6.88)
hypericum	1.98 (0.94-4)	2.1 (1-4.25)

Dizziness: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	1.31 (0.82-2.06)	1.38 (0.87-2.21)
escitalopram	1.77 (1.29-2.45)	1.8 (1.31-2.44)
fluoxetine	1.53 (1.19-1.98)	1.72 (1.33-2.2)
fluvoxamine	1.06 (0.74-1.5)	1.17 (0.82-1.66)
paroxetine	2.04 (1.55-2.71)	2.2 (1.67-2.86)
sertraline	1.77 (1.34-2.37)	1.92 (1.46-2.52)
imipramine	4.26 (3.21-5.72)	4.89 (3.68-6.43)
amitriptyline	2.9 (2.17-3.91)	3.2 (2.39-4.29)
clomipramine	4.19 (2.55-7.09)	4.69 (2.8-8.14)
desipramine	2.82 (1.38-5.78)	3.23 (1.58-6.63)
nortriptyline	2.46 (1.22-4.94)	2.67 (1.33-5.51)
doxepin	4.72 (1.08-27.42)	5 (1.1-28.17)
duloxetine	2.79 (2.07-3.77)	2.82 (2.11-3.73)
maprotiline	9.18 (1.97-54.06)	11.06 (2.33-65.86)
mirtazapine	1.9 (1.41-2.6)	2.1 (1.55-2.86)
moclobemide	3.04 (1.08-8.78)	3.37 (1.15-10.36)
venlafaxine	2.97 (2.22-4.09)	3.22 (2.4-4.4)
amineptine	0.43 (0.04-3.1)	0.43 (0.04-3.23)
dothiepine	0.83 (0.3-2.1)	0.86 (0.32-2.12)
mianserin	9.45 (0.98-315.7)	10.88 (1.17-397.3)
milnacipran	1.75 (1.09-2.85)	1.96 (1.2-3.21)
nefazodone	6.61 (3.27-13.93)	7.3 (3.5-15.43)
reboxetine	1.33 (0.84-2.12)	1.52 (0.94-2.42)
pramipexole	3.21 (1.18-10.26)	3.46 (1.37-9.76)
hypericum	1 (0.41-2.42)	1.15 (0.46-2.72)

Hypotension: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	0.48 (0.08-2.19)	0.43 (0.07-2.13)
escitalopram	1.73 (0.24-13.69)	1.14 (0.15-7.44)
fluoxetine	0.54 (0.21-1.38)	0.56 (0.2-1.33)
fluvoxamine	0.61 (0.25-1.41)	0.67 (0.26-1.5)
paroxetine	0.3 (0.11-0.78)	0.33 (0.11-0.81)
sertraline	0.45 (0.07-2.27)	0.41 (0.06-2.25)
amitriptyline	2.25 (0.96-5.73)	2.61 (0.99-5.89)
imipramine	3.57 (1.61-8.18)	4 (1.7-8.63)
clomipramine	1.12 (0.41-3.12)	1.22 (0.42-3.38)
desipramine	10.9 (0.57-8976)	11.43 (0.52-5840)
nortriptyline	1.56 (0.28-10.33)	1.79 (0.28-11.99)
duloxetine	0.27 (0.03-1.31)	0.32 (0.04-1.55)
mirtazapine	0.93 (0.31-2.58)	0.99 (0.33-2.71)
venlafaxine	5.87 (0.88-55.33)	6.18 (0.96-67.27)
mianserin	0.18 (0-8.23)	0.22 (0-8.76)
milnacipran	1.11 (0.44-2.85)	1.19 (0.44-2.88)
reboxetine	1.39 (0.34-5.25)	1.38 (0.31-5.3)

Fatigue: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	1.8 (1.11-2.86)	1.87 (1.19-2.89)
escitalopram	1.88 (1.33-2.65)	2.08 (1.51-2.81)
fluoxetine	2.4 (1.64-3.54)	2.95 (2.07-4.2)
fluvoxamine	3.21 (1.82-5.78)	3.7 (2.15-6.33)
paroxetine	2.25 (1.59-3.17)	2.52 (1.83-3.43)
sertraline	1.74 (1.21-2.55)	2.04 (1.46-2.88)
imipramine	1.77 (1.1-2.85)	2.27 (1.45-3.49)
amitriptyline	2.78 (1.82-4.29)	3.25 (2.19-4.82)
clomipramine	6.16 (2.52-15.86)	7.23 (2.97-18.3)
desipramine	1.42 (0.46-4.54)	2.72 (0.94-7.56)
desvenlafaxine	1.87 (0.8-4.52)	2.12 (0.91-4.99)
duloxetine	2.14 (1.52-3.01)	2.43 (1.78-3.29)
mirtazapine	3.08 (2.08-4.62)	3.53 (2.42-5.12)
moclobemide	2.51 (0.78-8.09)	2.99 (0.92-9.64)
venlafaxine	1.9 (1.29-2.85)	2.3 (1.59-3.37)
amineptine	0.13 (0-1.08)	0.17 (0.01-1.38)
milnacipran	6.77 (1.11-60.42)	8.37 (1.4-77.47)
nefazodone	2.6 (1.2-5.68)	3.09 (1.42-6.78)
pramipexole	2.21 (0.66-8.27)	2.93 (0.93-9.56)
reboxetine	1.25 (0.4-4.05)	2.41 (0.81-6.87)
hypericum	1.45 (0.46-4.68)	1.69 (0.51-5.59)

Vision Problems: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	2.55 (1-6.56)	3.12 (1.17-8.09)
escitalopram	1.2 (0.43-3.11)	1.29 (0.47-2.98)
fluoxetine	1.54 (0.96-2.53)	1.96 (1.1-3.04)
paroxetine	2.93 (1.51-5.46)	3.25 (1.83-5.67)
sertraline	2.76 (1.57-5.09)	3.31 (1.94-5.52)
amitriptyline	4.5 (2.75-7.9)	5.58 (3.14-8.88)
imipramine	1.86 (1-3.35)	2.81 (1.47-5.13)
desipramine	6.18 (1.61-29.47)	7.19 (2.33-20.88)
desvenlafaxine	8.92 (2.35-46.14)	5.95 (1.72-22.14)
duloxetine	2.31 (1.28-4.07)	2.38 (1.46-3.7)
mirtazapine	3.13 (1.74-5.82)	3.8 (2.23-6.62)
moclobemide	0.92 (0.23-3.18)	1.07 (0.27-3.9)
venlafaxine	2.35 (1.11-4.89)	2.72 (1.32-5.36)
dothiepine	3.31 (0.95-11.93)	2.93 (0.93-10.6)
milnacipran	1 (0.45-2.34)	1.32 (0.52-2.99)
nefazodone	4.92 (2.1-11.88)	6.21 (2.52-14.62)
reboxetine	1.03 (0.16-6.32)	1.26 (0.23-4.65)
hypericum	2.28 (0.53-9.26)	2.7 (0.66-13.69)

Drowsiness: Summary of comparisons versus placebo from primary analysis and control group risk meta-regression from network meta-analyses (OR, 95% CrI)		
Treatment vs placebo	**Unadjusted model**	**Adjusted for control group risk**
citalopram	2.48 (1.61-3.83)	2.5 (1.62-3.87)
escitalopram	2.68 (1.97-3.68)	2.67 (1.95-3.65)
fluoxetine	2 (1.54-2.6)	2.17 (1.64-2.86)
fluvoxamine	2.97 (2.16-4.14)	3.37 (2.36-4.78)
paroxetine	2.91 (2.19-3.87)	3.13 (2.33-4.2)
sertraline	2.03 (1.52-2.73)	2.18 (1.6-2.96)
imipramine	2.83 (2.09-3.86)	3.24 (2.29-4.52)
amitriptyline	6.47 (4.82-8.81)	7.28 (5.22-10.18)
clomipramine	3.73 (1.63-8.61)	4.01 (1.73-9.71)
desipramine	2.31 (0.81-6.74)	2.46 (0.84-7.13)
nortriptyline	2.17 (1.2-4.02)	2.32 (1.25-4.37)
doxepin	6.54 (2.23-19.35)	7.27 (2.32-23.01)
desvenlafaxine	3.55 (1.51-8.39)	3.58 (1.49-8.92)
duloxetine	2.01 (1.46-2.75)	2.05 (1.48-2.81)
mirtazapine	4.67 (3.44-6.35)	5.23 (3.72-7.39)
moclobemide	2.49 (0.92-6.86)	2.74 (0.99-7.83)
venlafaxine	2.11 (1.46-3.06)	2.2 (1.5-3.23)
amineptine	0.34 (0.01-3.22)	0.39 (0.01-4)
dothiepine	4.67 (1.94-11.28)	4.95 (2.09-12.01)
mianserin	6.22 (1.56-26.84)	6.91 (1.64-32.02)
milnacipran	1.21 (0.63-2.3)	1.35 (0.69-2.63)
nefazodone	2.08 (1.02-4.27)	2.23 (1.06-4.69)
reboxetine	2.28 (1.07-4.91)	2.54 (1.19-5.46)
tianeptine	2.02 (0.44-9.32)	2.22 (0.45-10.79)
pramipexole	5.32 (1.65-19.53)	5.38 (1.68-19.1)
hypericum	2.93 (0.86-10.06)	3.15 (0.92-10.64)

Appendix 5:
Summary of Observational Studies

Summary of Study and Population Characteristics							
Study ID/ Study Design Publication year	**Study Objective**	**Population Summary (sample size)**	**Age in years**	**Depression Status**	**Co-morbidities (%)**	**Concomitant medication use (%)**	**History of psychiatric related hospitalizations, ECT, and/or suicide attempts (%)**
Coupland et al[18] (2011) prospective cohort study 560 tertiary care sites (US)	Association of antidepressants and risk of adverse outcomes in older people with depression, by class, duration, and dose.	Men (33.3%) and women between diagnosed with depression between age of 65 to 100 years (n=60746)	Mean (SD) 75.0 (7.6) [age groups 65-75: 51.6%; 75-84: 35.4%; > 80: 13%]	Severity: 70% mild, 26% moderate; 5% severe	55% non-smokers; 40% hypertension; history of stroke 10%; history of CHD 20%; DM 10%, hypothyroidism 6.5%; dementia 2% OCD 0.2; psychoses 0; Attempted suicide/self harm 496/59,536 (<1%); Excluded patients with schizophrenia, bipolar disorder, or other types of psychoses	Benzodiazepine: Hypnotics/anxiolytics 23.7 Lithium 0.2 NSAIDs 57.0 Anticonvulsants 2.8 Antihypertension 50.0 Aspirin 29.4 Statins 16.9 Anti-epileptic drugs 2.8 Antipsychotics 8.8	Attempted suicide/self harm: Total 496; No ADs 150; TCAs 89; SSRIs 178; other ADs 79; (out of 59,536 patients)
Gagnee et al[17] (2011) Cohort Single community site (US)	Secondary analysis of DEPS-GP Project - Compare fracture rates across patients receiving treatment with different antidepressant medication classes and explore whether the variation in fracture rates can be explained by affinity for the serotonin transport receptor (5-HTT) and whether short- vs. long-term effects are evident	Men (16.0%) and women (92% White) enrolled in pharmaceutical assistance programs in New Jersey and Pennsylvania (n=10844)	Mean (SD) 77.0 (NR)	Diagnosed with depression using ICD-9 Severity: NR	Prior fracture: 5%; prior falls: < 1%; sleeping/anxiety disorders: 11%; Parkinson's 3%; Alzheimer's: 3%; mania: 2%; psychotic disorder: 5%; osteoporosis: 16%; substance abuse: 3%	Benzodiazepine 40.4 Steroids 5.7 (oral glucocorticoids) Osteoporosis medication 5.8 Hormone therapy (Estrogen, Progestin, Testosterone) 5.2 Anticonvulsants 7.8 Proton pump inhibitors 15.0 Antidiabetic 0.7 (Thiazolidinedione) Anti-epileptic drugs 7.8 (same thing as anticonvulsants?)	800/10844 (7.4%) psychiatric hospitalizations

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Thapa et al[223] (1998) Cohort 80 nursing home sites (US)	Compare rate of falls between new TCA users and new SSRI users.	Frail and highly impaired nursing home residents at least 65 years old with depression as primary indication for starting antidepressant therapy (n=NR)*	NR for relevant subgroup	Chronically depressed Severity: NR	NR for relevant subgroup	NR for relevant subgroup	Admitted in previous 90 days: NR for depressed subgroup; ECT NR; Suicide attempts NR
Winterhalder[224] (2012) Cohort Single tertiary care site (Switzerland)	Longitudinal changes in trabecular volumetric BMD in young depressive patients under therapy with either SSRI vs. other antidepressants (TCAs, nonSSRI/nonTCAs--unspecified)	Young (25-45 years) men (5%) and women with new depression (n=40)	Mean (SD) 37 (NR)	Newly diagnosed with severe or moderate depression measured by 21 item BDI***	Excluded patients with hyper/ hypothyroidism and metabolic or chronic kidney disorders; some patients had sleep disorders and they were more likely to have been taking TCAs	Steroids 0 Osteoporosis medication 0	No
Choi et al[225] (2011) (abstract) Cohort Setting not reported	Association of SSRI use with the decrease of BMD	Depressed postmenopausal women (n=81)	Mean (SD) 65.8 (4.5)	Chronically depressed (mean (SD) 15.7 (5.7) months duration) Severity: NR	NR	Hormone therapy: same in both groups Calcium agents in about 90% of pts	No

*Number of person with depression taking antidepressants was not reported. Person-Year for various outcomes was calculated and served as sample size

#: Demographic data for relevant subgroup (patients with depression taking eligible anti-depressants) were not reported

^ Demographics were not reported for the relevant subgroup (female age 80 or older with depression and taking SSRIs)

^^ Patient Health Questionnaire: no depressive symptoms if score lower than 5; questionable if score between 5 and 14; significant if score greater than 14—proportion of participants within either of the mentioned categories were not reported for the relevant population

**Hamilton Depression Rating Scale

*** Beck Depression Inventory

Summary of Risk of Bias Assessment Assessments of Included Observational Studies, Downs and Black Scale, Items 1-10										
Author (Year)	**1. Is the hypothesis/ aim/ objective of the study clearly described?**	**2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?**	**3. Are the characteristics of the patients included in the study clearly described ?**	**4. Are the interventions of interest clearly described?**	**5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?**	**6. Are the main findings of the study clearly described?**	**7. Does the study provide estimates of the random variability in the data for the main outcomes?**	**8. Have all important adverse events that may be a consequence of the intervention been reported?**	**9. Have the characteristics of patients lost to follow-up been described?**	**10. Have actual probability values been reported for the main outcomes except where the probability value is less than 0.001?**
Coupland[18]	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes
Gagne[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Thapa[223]	Yes	Yes	No	Yes	Partially	Yes	Yes	No	No	Yes
Winterhalder[224]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Choi[225]	Not evaulable; abstract									

UAD=unable to determine

Table X: Summary of Risk of Bias Assessment Assessments of Included Observational Studies, Downs and Black Scale, Items 11-19									
Author (Year)	**11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?**	**12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?**	**13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?**	**14. Was an attempt made to blind study subjects to the intervention they have received ?**	**15. Was an attempt made to blind those measuring the main outcomes of the intervention?**	**16. If any of the results of the study were based on *"data dredging"*, was this made clear?**	**17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?**	**18. Were the statistical tests used to assess the main outcomes appropriate?**	**19. Was compliance with the intervention/s reliable?**
Coupland[18]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	0
Gagne[17]	No	No	Yes	No	No	Yes	Yes	Yes	1
Thapa[223]	Yes	UAD	Yes	No	No	No	Yes	Yes	0
Winterhalder[224]	UAD	UAD	UAD	No	No	Yes	UAD	Yes	0
Choi[225]	Not evaluable; abstract								

UAD=unable to determine

Table X: Summary of Risk of Bias Assessment Assessments of Included Observational Studies, Downs and Black Scale, Items 20-27								
Author (Year)	**20. Were the main outcome measures used accurate (valid and reliable)?**	**21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?**	**22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?**	**23. Were study subjects randomised to intervention groups?**	**24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?**	**25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?**	**26. Were losses of patients to follow-up taken into account?**	**27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?**
Coupland[18]	1	Yes	Yes	No	No	Yes	0	
Gagne[17]	1	Yes	Yes	No	No	Yes	1	
Thapa[223]	1	UAD	UAD	No	No	Yes	0	
Winterhalder[224]	1	Yes	Yes	No	No	No	0	
Choi[225]	Not evaluable; abstract							

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