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A SYSTEMATIC REVIEW OF THE EFFICACY AND TOLERABILITY OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS IN THE TREATMENT OF CHINESE PATIENTS WITH DEPRESSIVE DISORDERS

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AD	Antidepressant Drug
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical Classification Index
CAM	Complementary and Alternative Medicine
CBM	China Biomedicine Database
CCMD	Chinese Classification of Mental Disorder
CDC	Centre for Disease Control and Prevention
CENTRAL	Cochrane Central Register of Controlled Trial
CGI-S	Clinical Global Impression Severity
CMA	Comprehensive Meta Analysis
CMCC	Chinese Medical Current Content
CNKI	China National Knowledge Infrastructure
CONSORT	Consolidated Standards of Reporting Trial
DDD	Defined Daily Doses
DSM	Diagnostic and Statistical Manual of Mental Disorder
EA	Electro Acupuncture
EBM	Evidence-Based Medicine
ER	Extended Release
HAMA	Hamilton Anxiety Scale
HAMD	Hamilton Rating Scale of Depression
ICD	International Statistical Classification of Disease
ICMJE	International Committee of Medical Journal Editor
ITT	Intention-To-Treat-Analysis
LOCF	Last Observation Carried Forward
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOIS	Monoamine Oxidase Inhibitor
MDD	Major Depression
MESSS	Mangled Extremity Severity Score
MH	Mantel-Haenszel
MMSE	Mini-Mental State Examination

NARI	Norepinephrine Reuptake Inhibitor
NDRI	Norepinephrine and Dopamine Reuptake Inhibitor
NDS	Neural Function Deficient Scale
NICE	National Institute for Health and Clinical Excellence
OC	Observed Case
PSD	Post-Stroke Depression
QOL	Quality of Life
RCT	Randomised Controlled Trial
RR	Risk Ratio
SARI	Serotonin Antagonist and Reuptake Inhibitor
SD	Standard Deviation
SDS	Self-rating Depression Scale
SERS	Åsberg Rating Scale for Side Effect
SMD	Standardized mean difference
SNRI	Selective Noradrenaline Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SSS	Scandinavian Stroke Scale
TCA	Tricyclic Antidepressant
TCM	Traditional Chinese Medicine
teCA	Tetracyclic Antidepressant
TESS	Treatment Emergent Symptom Scale
VIP	Chinese Scientific Journals Full-text Database
WHO	World Health Organization

1 INTRODUCTION

Depression is the most common psychiatric illness affecting about 121 million people worldwide [134] and characterized by symptoms such as depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, and suicidal ideation. The Global Burden of Disease Program of World Health Organization (WHO) indicates that depression ranks fourth among causes of disability and early death. By the year 2020, it will jump to the second place calculated for all ages and both sexes [93]. The WHO estimated that 3% of adults in the world are suffering from depression, yet prevalence estimates of depression differ among ethnic groups [95] and regions [11]. Major Depression (MDD) has a 16.2% lifetime prevalence in the U.S. [55], 16.4% in France [131], 19.9% in Thailand [122], but only 3.6% in China [63].

One explanation used to account for this cross-cultural discrepancy is that the Chinese tend to express depression somatically [97]. Another explanation is the high prevalence of neurasthenia among psychiatric diagnoses [57]. In spite of this, over 26 million patients have been diagnosed with depression and a total of 114,663 suicides (40%) were due to depression in 2000 according to the estimation of the Ministry of Health of the People's Republic of China [100]. Therefore, depression has now aroused increased attention.

Classification of psychiatric diagnoses in China

The first Chinese Classification of Mental Disorders (CCMD) was published in 1979. The current version CCMD-3 [23] is widely used by Chinese psychiatrists. It was made to be consistent with the International Classification of Diseases (ICD) taking into consideration Chinese cultural characteristics. As a result, there are still some differences between CCMD, ICD and Diagnostic and Statistical Manual of Mental Disorders (DSM). For example, depressive episode (抑郁发作) is defined in CCMD-3 in a way that different from the definition of major

depressive disorders in DSM-IV [126]. In CCMD-3, loss of interest or pleasure is not an essential feature. In addition, weight gain and increase in appetite are not included among symptoms, but decreased libido is. In spite of these differences, broad similarities between the ICD-10 [134] and CCMD-3 are still obvious [20]. A recent study showed a high concordance rate of the diagnosis of depression between CCMD-3 and DSM-IV [126].

Treatment of Depression in China

Traditional Chinese Medicine (TCM) has been widely used as an alternative method for the treatment of depression in China. It is based on yin-yang theory，the theory of five elements, and on the theory of relevant adaptation of the human body to natural environment [15]. In recent decades it has become more popular in Western medical practice and is part of Complementary and Alternative Medicine (CAM). Depression has a long history in TCM and was named as "郁证 (yu zheng), 脏躁 (zang zao), 梅核气 (mei he qi), and 百合病 (bai he bing)". TCM holds that depression is caused by emotional frustration which induces a stagnation of Qi (the fundamental energy of our body) within the liver [81]. Electrical acupuncture has been available in China for 60 years as a treatment for depression. There are many other sorts of treatment such as: Chinese herbal compounds, single TCM, and cupping. However, there is no consistent evidence of the effect of TCM treatment options. A recent review showed that the TCM treated group did not decrease in Hamilton Rating Scale of Depression (HAMD) scores and in scores of self-rating depression scales [156]. On the contrary, herbal depression treatment was found to be effective in 62.5% of patients, which was significant better than placebo (34%) [78], and electrical acupuncture was found to have faster onset than sertraline [157].

In Western countries, pharmacotherapy, herbal treatment such as St. John's wort (Hypericum perforatum), psychotherapy, and electroconvulsive therapy have been recommended for the treatment of

depressive disorders. Among these treatment options, antidepressant drugs are used most commonly in industrialized countries [36,49]. Their remission rate in the first six months is about 50%, and reaching up to 80% in the long term [53]. A total of 60 antidepressants (see Appendix 1 for a full list) are classified as antidepressants by the WHO Collaborating Center for Drug Statistics Methodology [132]. They include traditional Tricyclic antidepressants (TCAs), tetracyclics, Monoamine oxidase inhibitors (MAOIs), second-generation antidepressants, such as Selective Serotonin Reuptake Inhibitors (SSRIs), Selective Noradrenaline Reuptake Inhibitors (SNRIs), and other drugs.

In China 27 drugs (list see Appendix 1) are listed as antidepressant drugs (ADs) in the current 17th version of New Pharmacy 新编药物学 [19]. Four of them, i.e. amphetamine (苯丙胺), atomoxetine (托莫西), methylphenidate (哌甲酯), and pemoline (匹莫), were not considered to be antidepressant agents according to the WHO. Although around 20 traditional Chinese herbs exist in China's antidepressant market, none of them were mentioned in the Guidelines for the Prevention and Treatment of Depression [24] and in the Chinese book "New Pharmacy" [19]. Similar to previous publications [7,61,114,124], SSRIs constitute the dominant subcategory of antidepressants in China [152].

SSRIs were first introduced to the U.S market in 1988, and they have largely replaced TCA and MAOI in the last decade due to fewer side-effects and the ease of use [107]. They seem to be less effective for depression in which physical symptoms or pain are prominent features when compared with TCAs or SNRIs [12]. More and more studies comparing the effectiveness and safety of different ADs have been conducted, but there is no consistent evidence [24,94].

Meta-analysis

In order to make decisions about optimal patient care, meta-analysis offers a statistical approach in Evidence-Based Medicine (EBM) to

combine the results from independent trials. This method was first used in 1904 by Pearson [98], the term meta-analysis was defined by Glass in 1976 [39]. Meta-analysis usually increases statistical power and thereby can detect effects or relationships which did not reach statistical significance in the primary studies included. Meta-analyses are accepted by the Scottish Intercollegiate Guidelines Network as the strongest level of evidence to guide physicians in making decisions [1]. According to the hierarchy of evidence and recommendation grading scheme, meta-analysis of Randomised controlled trials (RCTs) provides evidence with the highest quality (Level I and Grade A).

Chinese articles boom

Currently, there are more than 1200 Chinese biomedical journals. Roughly 11.5% of the world's total articles in 2008 were published by Chinese authors [106]. Although Chinese articles have been criticized for their low quality of design and reporting, they are now available to the public through biomedical databases, such as China National Knowledge Infrastructure (CNKI), Chinese Scientific Journals Full-text Database (VIP), China Biomedicine Database (CBM), Chinese Medical Current Content (CMCC), and Wan Fang. CNKI, for example, has a total of more than eight million full-text articles from 6100 Chinese domestic core or specialty journals and over 15 million bibliographies. VIP has a collection of full-text articles from 8000 Chinese domestic journals from 1989 to present, and it increases at the rate of 1 million articles annually.

Many studies were carried out to compare the effectiveness and safety of antidepressants in Chinese patients, including comparisons between SSRI and TCM (acupuncture, Chinese herbs). Meta-analyses were also conducted and named in China as "荟萃分析 (hui cui fen xi)", "汇总分析 (hui zong fen xi", or "综合分析 (zong he fen xi)". But most meta-analyses failed to report important data, such as age, comorbid disorders, and sponsoring. RCT is the so-called "gold standard" for

treatment studies. However, Chinese meta-analyses usually used "studies published in China" as an inclusion criterion rather than RCT. The quality of primary studies was also rarely evaluated.

Chinese studies were included in only about 7% of Western meta-analyses, although most Western meta-analyses of antidepressants did not report a language restriction. A recent study investigated Chinese biomedical databases and reported that less than 6% of the 2500 journals in these databases were listed as being indexed for MEDLINE [137]. In spite of the fact that most Chinese studies are underpowered with low reporting quality [59,150], some methodologists suggested that those studies may be acceptable, because using systematic review and meta-analysis underpowered trials could ultimately be combined [40,41,48,111]. Within a co-operation with the department of psychiatry of Tongde Hospital of Zhejiang Province, the efficacy of venlafaxine was compared with any other antidepressant and/or placebo [59]. No significant difference between venlafaxine and SSRI was found. However, the results were hard to interpret because that only nine studies provided suitable data and striking similarities in both text and figures were showed in three pairs of publications [118,128], [102,159] and [80,155].

Not only in Chinese meta-analyses [37,52,73,145] but also in Western meta-analyses [3,26,54,84,91,92,101,108,116,117], there is no consistent evidence that SSRI have an advantage over other antidepressants. Within the SSRI class there are also conflicting results.

These considerations indicate a need to do this systematic review and meta-analysis investigating the efficacy and tolerability of SSRI in the treatment of Chinese patients suffering from depression.

Objectives

The aims of the present study are:

1. To determine the efficacy and tolerability of SSRI in comparison with other anti-depressive agents, TCM and placebo in the treatment of Chinese adult patients with depression.
2. To evaluate the quality of Chinese double-blind RCTs.

2 MATERIALS AND METHODS

This study and the statistical analysis were conducted according to an a priori defined protocol. A comprehensive search strategy was developed to identify all available studies that met the a priori defined inclusion and exclusion criteria. After abstract and fulltext screening, data were extracted from primary studies included and were analyzed using a random-effects model.

2.1 Criteria for considering studies for this review

Types of studies

This review included double-blind RCTs only. Quasi-randomised trials, such as those allocating by using alternate days of the week, were included if they were reported as "randomised". Trials were not excluded on the basis of quality assessment.

Types of participants

Study participants had to be Chinese adult patients (including Taiwanese patients) of both sexes with a primary diagnosis of depression. Studies adopting any standardised criteria such as DSM, ICD and/or CCMD to define patients suffering from depression were included. Trials were excluded if diagnosic criteria were not reported. This review included patients suffering from post-stroke depression (PSD), other mental illnesses and/or concomitant physical illness. In line with the treatment guideline for depression of the National Institute for Health and Clinical Excellence (NICE) [94], studies were excluded if more than 20% of the participants had a primary diagnosis of dysthymia or if more than 15% had a primary diagnosis of bipolar disorder. Trials were excluded if reports suggested that dysthymia and/or bipolar disorders were included but proportions of patients remained unclear. Trials that included children and/or adolescents were excluded.

Types of intervention

Included trials compared SSRI (fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline) with other antidepressants (SSRI, SNRI, TCA etc.), TCM (acupuncture or Chinese herbs) and/or placebo as monotherapy. No restrictions on dose, frequency, intensity and duration were applied. Head to head trials of SSRIs were also included. Studies using SSRI as an augmentation strategy were excluded. If the trial had three (or more) treatment arms, data was only extracted from antidepressants, TCM and placebo arms, but not from study arms exposed to other types of psychotropic agents such as anxiolytics, anticonvulsants, antipsychotics or mood-stabilisers. Both trials that randomised patients into receiving more than one treatment (antidepressant medications or TCM) simultaneously and cross-over trials were excluded. Venlafaxine and venlafaxine extended release (ER) were combined as venlafaxine. To combine the data from arms with different doses of one substance, dichotomous data were analyzed using sums, e.g. the sum of the numbers of patients responding to treatment with the same substance; and continuous data were analyzed with the average of data from all arms, e.g. the average of the mean total HAMD scores at endpoint.

2.2 Search methods for study identification

The literature search was based on a systematic search in the two largest Chinese biomedical databases CNKI and VIP with English and Chinese search terms for depression combined with substance and trade names for SSRIs (fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline). Furthermore, Western databases MEDLINE and EMBASE were searched using the terms "depression" combined with "China" or "Taiwan". There was no limit on language, publication type or publication date. Literature search was last updated in January 2011 (see Appendix 4 for the search strategies).

In addition, reference lists of studies included were hand searched for further published and unpublished research.

2.3 Data collection and analysis

Selection of studies

The title and abstracts of the articles identified by the literature search were screened for potentially relevant articles. All articles rated as "potentially relevant" were then retrieved to see if they met the inclusion criteria. The inclusion of the studies was independently verified by another Chinese researcher (Yongchun Ma). Reasons for exclusion were recorded. If the raters disagreed the final rating was consented by discussion.

Data extraction and management

Dichotomous and continuous data were extracted from each study if available. Dichotomous data included response, remission, and dropout rates. Continuous data included the Total Treatment Emergent Symptom Scale (TESS) score and the mean total HAMD scores at endpoint. In Western studies, response is usually defined as 50% reduction on the HAMD-17 total score at endpoint and remission is defined as a HAMD-17 total score of 7 or below at study endpoint. In Chinese studies, response and remission rates are usually reported according to the following four levels defined by the Chinese Medical Association: "remission" as a HAMD reduction of more than 75%, "significant progress" as a HAMD reduction of 50-74%, "progress" as HAMD reduction of 25-49%, and "ineffective" as HAMD reduction of less than 25%. As a proxy, remission was defined a priori in this present meta-analysis as a HAMD reduction of more than 75% or HAMD ≤ either 7 or 8 and response was defined as a HAMD reduction of at least 50% in accordance with a previous meta-analysis [59].

As primary outcomes were defined:

1) response rates

2) remission rates

3) dropout rates due to side effects

As secondary outcomes were defined:

1) mean total HAMD scores at endpoint

2) overall dropouts rates

3) total TESS score

Data concerning participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, study setting etc.), intervention details (intended dose range, mean daily dose actually prescribed, SSRI as investigational drug or as control drug, sponsorship etc.) and outcome measures of interest were extracted from each included study using a pre-designed form. Data were entered into Microsoft excel and subsequently into Comprehensive Meta Analysis (CMA) 2 [8].

Unit of analysis issues

If a trial used different doses of the same substance in different treatment arms, raw data were counted across treatment arms in case of dichotomous data before they were entered in CMA 2, whilst continuous data were analyzed in CMA 2 with the average of their means. Three-arm trials with different interventions were considered as independent comparisons and were analysed separately.

Dealing with missing data

In case of missing data, the attempt was made to contact trial authors in order to obtain further information. As mentioned previously, responses and remissions were recalculated according to the a priori definitions if possible with response defined as a HAMD reduction of at least 50% and remission defined as a HAMD reduction of more than 75% or HAMD endpoint score of not more than 8. To prevent bias associated

with non-random loss of participants [62,64,65], recalculation was performed according to the intention-to-treat (ITT) principle. Reported last observation carried forward (LOCF) data were used and dropouts were considered as non-responders. If only HAMD change scores and baseline scores were reported, the mean total HAMD scores at endpoint were calculated and the reported baseline standard deviation (SD) was used.

Assessment of heterogeneity

Heterogeneity of treatment effect between studies was investigated using the I^2 parameter [44] and by visual inspection of the forest plots. I^2 values of more than 50% were considered to indicate heterogeneity [129].

Assessment of reporting biases

Publication bias was assessed with funnel plots, Beggs rank correlation test, and regression tests. Furthermore, using Fail-Safe-N-test of Rosenthal [105], calculations were made of how many unpublished studies with null results (of similar size) must exist to nullify the observed effect.

Assessment of risk of bias in included studies

The risk of bias of included studies was accessed using risk of bias instruments of the Cochrane Collaboration [123]. This instrument consists of six items, assessing (i) adequacy of sequence generation, (ii) allocation concealment, (iii) blinding of participants, personnel and outcome assessors, (iv) likelihood of incomplete outcome data, (v) selective outcome reporting, and (vi) other sources of bias. These items were rated as yes, no, or unclear according to defined criteria.

Assessment of reporting quality

Additionally, the percentage of fulfilled Consolidated Standards of Reporting Trials (CONSORT) Items [109] was used to assess the

reporting quality. The checklist of the current version of the CONSORT statement is presented in Table 14.

Assessment of other aspects of quality

Other criteria which are not explicitly mentioned in CONSORT, for example obtaining informed consent from participants and contact details for the corresponding author, were also assessed.

Data synthesis

Effect size Hedges' g was used for continuous outcomes, whilst Mantel-Haenszel Risk Ratio (MH RR) was used for dichotomous outcomes, both with 95% confidence intervals. Given the variety of studies it seemed unlikely that all the studies estimate a common effect size. Therefore, data were extracted and combined with a random effects model with the assumption that true effects are heterogeneous and normally distributed. The weights assigned here are more balanced so that small studies have more of an impact than in a fixed effect model. Furthermore, a random effects model considers differences between studies, it is more conservative than a fixed effect model and findings can be generalized to a range of populations, although the random effects model has less statistical power than a fixed effects model. In case of no heterogeneity, fixed and random effects models converge and will provide the same estimates.

Subgroup analysis

Subgroup analyses were planned for different control groups (SSRI, SNRI, TCA, TCM etc.) and for geriatric vs. non-geriatric patients.

Sensitivity analysis

To control for any "Wish-Bias" [6] sensitivity analyses were planned for SSRI as control substance vs. investigational substance.

Meta-regression analysis

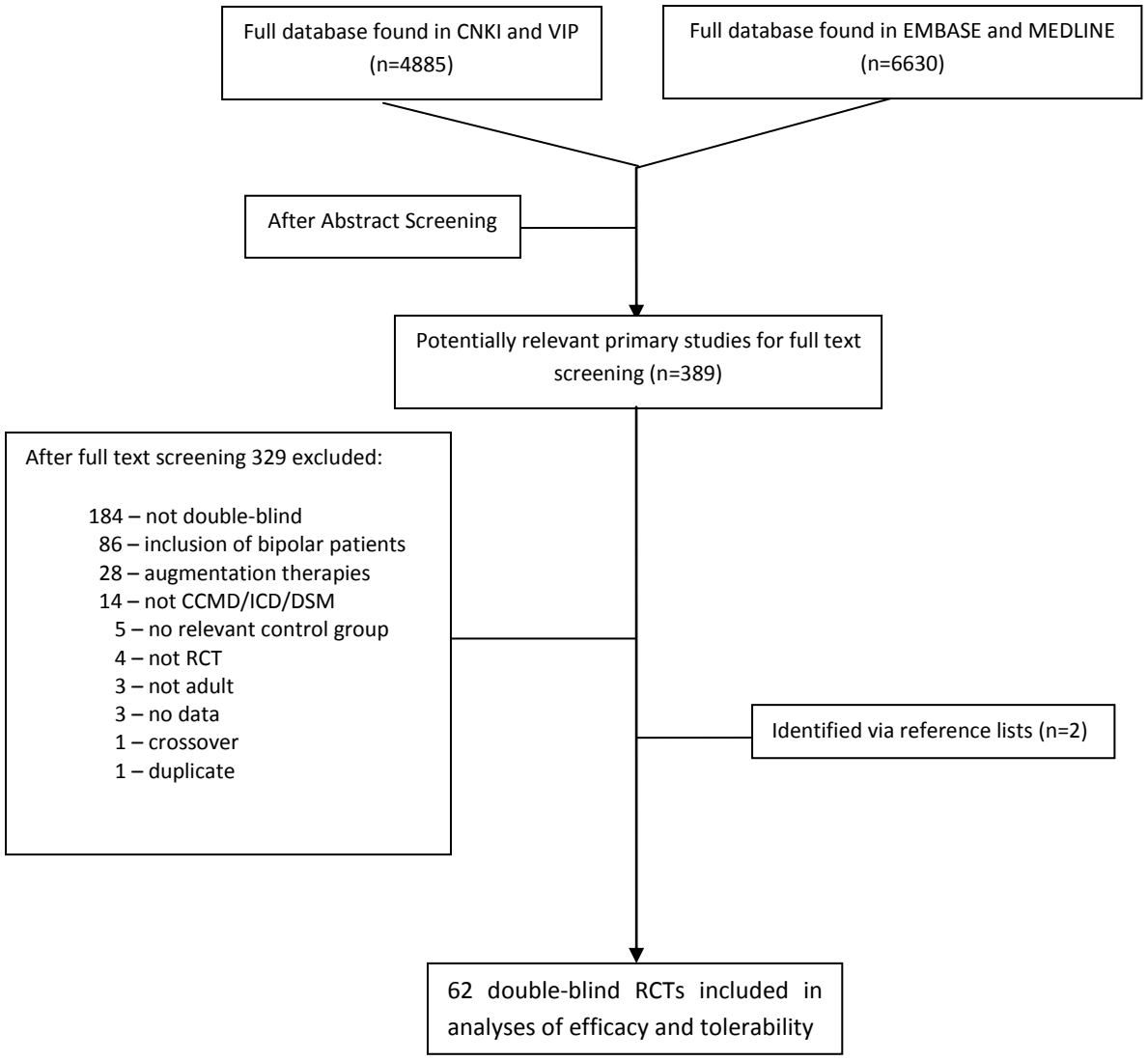
Meta-regression analyses were planned to examine the impact of trial quality on efficacy effect sizes.

3 RESULTS

3.1 Description of studies

Results of the literature search

A total of 11615 citations were identified by the systematic literature search from the VIP, CNKI, EMBASE and MEDLINE databases. Of these, 389 full papers were obtained and read to assess for inclusion (Flowchart of study selection see Figure 1).



RCT: Randomised controlled trials
CCMD: Chinese classification of mental disorders
ICD: International classification of diseases
DSM: Diagnostic and statistical manual of mental disorders
TCM: Traditional Chinese medicine
CNKI: China national knowledge infrastructure
VIP: Chinese scientific journals full-text database

Figure 1. Flowchart of study selection.

Included studies

62 relevant double-blind RCTs [13,14,16-18,21,29-32,34,35,38,42, 43,45-47,50,51,60,67-72,74-77,80,82,83,85-87,96,99,103,112,113, 119-121,125,127,135,138-141,143,144,146-148,151,153,154,158, 160] were identified that met the inclusion criteria and provided suitable data for analysis. The characteristics of the studies included are described in detail in Appendix 5. All studies were conducted by authors based in Chinese hospitals. Only one [45] of these studies could not be found by CNKI and VIP. Two studies were published in English [45,86] and listed in MEDLINE and EMBASE. The 329 studies excluded from the review are listed with reasons for exclusion in Appendix 3. In total, the included studies randomised 6141 patients. Data from 6078 patients were analyzed in the primary studies. Efficacy data from 62 RCT (6078 patients) and tolerability data from 41 RCT (4659 patients) were pooled.

Trial Design

According to the inclusion criteria, all studies were double-blind RCTs. 12 studies (19%) reported the use of a double-dummy design to ensure allocation concealment. The median of number of patients per study was 64 (range: 25-480). Details are described in Table 1. Five three-arm studies were included, and data from all treatment arms were used from four studies [43,82,120,125]. From the fifth three-arm study [42], data were only extracted from two arms, because patients in the third arm received a combination of treatments (fluoxetine and TCM).

Table 1. Frequency and Percentage of Study Characteristics.

Characteristics	Frequency	Percentage
Year of publication		
1996-1999	7	11.3
2000-2003	9	14.5
2004-2007	29	46.8
2008-2011	17	27.4
Duration		
8 weeks	11	17.7
6 weeks	47	75.8
4 weeks	3	4.8
2 weeks	1	1.6
Study design		
Sample size 10-29/group	14	22.6
Sample size 30-49/group	34	54.8
Sample size 50-79/group	4	6.5
Sample size 80-99/group	2	3.2
Sample size 100-360/group	8	12.9
Inpatients	21	33.9
Outpatients	6	9.7
In- and outpatients	26	41.9
Not reported	9	14.5
Three-arm	5	8.1
Placebo controlled	1	1.6
PSD	11	17.7

PSD: Post-stroke depression

Four studies were published in the Journal of Clinical Psychological Medicine, four in the Chinese Journal of New Drugs, three each in the Journal of clinical Psychiatry and in the Medical Journal of Chinese People's Health, two each in Modern Medicine Health, Shandong Archives of Psychiatry, Journal of Qiqihar Medical College, Shanghai Archives of Psychiatry and the Chinese Journal of New Drugs and Clinical Remedies. The others were published in different journals.

Age Range

The mean age range of the included studies was 30-70 years. Ten studies (16.13%) included only elderly patients of age 55 years and over.

Diagnoses

Most studies used CCMD to verify the diagnosis (see Table. 2). Nine studies [35,45,67,71,82,85,86,113,125] used Western classifications only. Seven studies [18,112,139,140,143,147] used both Chinese and Western diagnostic systems.

Table 2. Frequency and percentage of diagnosis systems used in the 62 included studies.

Diagnosis	Frequency	Percentage
CCMD (all versions)	53	85.5
CCMD-3	39	62.9
CCMD-2-R	11	17.7
CCMD-2	2	3.2
DSM (all versions)	10	16.1
DSM-IV	6	9.7
DSM-III-R	4	6.5
ICD-10	6	9.7

CCMD: Chinese Classification of Mental Disorders

ICD: International Statistical Classification of Diseases

DSM: Diagnostic and Statistical Manual of Mental Disorders

Assessment Measures

All studies used the HAMD to assess efficacy and most of studies used TESS to assess side-effects. Details of measurement used are listed in Table 3.

Table 3. Frequency and percentage of measurement used in the 62 included studies.

Measurement	Frequency	Percentage
HAMD	62	100
HAMA	18	29.0
CGI	34	54.8
TESS	45	72.6
MESSS	2	3.2
ADL	3	4.8
QOL	1	1.6
MMSE	1	1.6
NDS	1	1.6
AE	1	1.6
SERS	2	3.2
SDS	2	3.2
MADRS	1	1.6
SSS	1	1.6

HAMD: Hamilton rating scale of depression, HAMA: Hamilton anxiety scale, CGI: Clinical global impression TESS: Treatment emergent symptom scale, MESSS: Mangled extremity severity score, ADL: Activities of daily living, QOL: Quality of life, MMSE: Mini mental state examination, NDS: Neural function deficient scale, AE: Adverse event, SERS: Åsberg rating scale for side effect, SDS: Self-rating depression scale, MADRS: Montgomery-Åsberg depression rating scale, SSS: Scandinavian stroke scale

Symptom severity

Most studies included only patients with a HAMD above 18 points. In five studies the Hamilton Anxiety Scale (HAMA) ≥14 and 17, Clinical Global Impression Severity (CGI-S) ≥4 as well as Self-rating Depression Scale (SDS) ≥53 were also used as inclusion criteria.

Types of intervention

A total of 16 trials (17 comparisons) compared two SSRIs (fluoxetine, citalopram, escitalopram, fluvoxamine, paroxetine, or sertraline). 47 trials (50 comparisons) compared SSRI with 12 other antidepressants from different classes (SNRI, TCA, teCA etc.), or with eight types of TCM (acupuncture and Chinese herbs) as monotherapy. Only one trial compared SSRI with placebo [82]. Numbers of comparisons for each antidepressant are listed in Table 4; numbers of studies and references for each comparison are presented in tables 5-13.

Table 4. Antidepressants investigated in the included studies.

SSRI	TCA	SNRI	teCA	NARI	NDRI	SARI
Fluoxetine (k=35)	Amitriptyline (k=20)	Venlafaxine ER (k=1)	Mirtazapine (k=2)	Reboxetine (k=4)	Bupropion (k=4)	Nefazodone (k=1)
Citalopram (k=17)	Doxepin (k=1)	Venlafaxine (k=2)	Maprotiline (k=2)			
Paroxetine (k=14)	Imipramine (k=1)	Duloxetine (k=1)	Mianserin (k=1)			
Sertraline (k=12)						
Escitalopram (k=7)						
Fluvoxamine (k=1)						

K=number of treatment arms, SSRI: Selective serotonin reuptake inhibitors, TCA: Tricyclic antidepressant
SNRI: Selective noradrenaline reuptake inhibitor, teCA: tetracyclic antidepressant
NARI: Norepinephrine reuptake inhibitor, NDRI: Norepinephrine and dopamine reuptake inhibitors
SARI: Serotonin antagonist and reuptake inhibitors, TCM: Traditional Chinese medicine

Table 5. SSRI versus SSRI.

Comparison	No. of studies	References of studies
citalopram vs. fluoxetine	5	[31,35,47,146,153]
citalopram vs. escitalopram	5	[46,51,72,77,144]
citalopram vs. sertraline	1	[30]
fluoxetine vs. sertraline	1	[141]
fluoxetine vs. escitalopram	1	[85]
fluvoxamine vs. sertraline	1	[34]
sertraline vs. fluoxetine vs. paroxetine	1	[43]
paroxetine vs. sertraline vs. amitriptyline	1	[120]

Table 6. SSRI versus teCA.

Comparison	No. of studies	References of studies
fluoxetine vs. mirtazapine	1	[45]
paroxetine vs. mirtazapine	1	[71]
sertraline vs. maprotiline	1	[16]
citalopram vs. maprotiline	1	[160]
escitalopram vs. mianserin	1	[21]

Table 7. SSRI versus TCA.

Comparison	No. of studies	References of studies
fluoxetine vs. amitriptyline	5	[32,38,42,99,147]
paroxetine vs. amitriptyline	5	[112,113,138,140,151]
citalopram vs. amitriptyline	4	[60,121,127,148]
sertraline vs. amitriptyline	4	[67,87,143,154]
fluoxetine vs. doxepin	1	[119]
paroxetine vs. imipramine	1	[158]
paroxetine vs. sertraline vs. amitriptyline	1	[120]

Table 8. SSRI versus TCM.

Comparison	No. of studies	References of studies
fluoxetine vs. Shu Yu Capsule (舒郁胶囊)	1	[74]
fluoxetine vs. recipe of TCM	1	[83]
fluoxetine vs. Pei Yuan Jie You Decoction	1	[103]
fluoxetine vs. Areca catechu (槟榔)	1	[139]
fluoxetine vs. Anjiaxin capsules (安佳欣胶囊)	1	[29]
fluoxetine vs. EA (电针) vs. placebo	1	[82]
fluoxetine vs. Morinda officinalis oligose capsule (巴戟天寡糖胶囊) (in the higher dosage range) vs. Morinda officinalis oligose capsule (within the standard therapeutic range)	1	[125]
paroxetine vs. AN SHEN ER HAO ("安神二号"胶囊)	1	[18]

Table 9. SSRI versus SNRI.

Comparison	No. of studies	References of studies
paroxetine vs. venlafaxine ER	2	[17,80]
fluoxetine vs. venlafaxine	1	[96]
fluoxetine vs. duloxetine	1	[76]

Table 10. SSRI versus NARI.

Comparison	No. of studies	References of studies
fluxoetine vs. reboxetine	3	[69,75,85]
citalopram vs. reboxetine	1	[13]

Table 11. SSRI versus NDRI.

Comparison	No. of studies	References of studies
fluxoetine vs. bupropion	4	[14,68,70,135]

Table 12. SSRI versus SARI.

Comparison	No. of studies	References of studies
fluxoetine vs. nefazodone	1	[50]

Table 13. SSRI versus Placebo.

Comparison	No. of studies	References of studies
fluxoetine vs. placebo vs. TCM	1	[82]

3.2 Quality of Studies

Assessment of risk of bias in included studies

Risk of bias of the studies included, measured by the Cochrane risk of bias tool [123], is presented in Figure 2 and 3. In 13 (21%) studies adequate methods of sequence generation were described, such as: a random number table, a computer random number generator, coin tossing, or drawing of lots. In ten articles "random" was used inappropriately in which systematic, non-random approaches were reported, such as hospital number or date of admission. 13 (21%) studies described adequate allocation concealment mechanism, such as central allocation, sequentially numbered bottles of identical appearance, or sequentially numbered, sealed, opaque envelopes. Due to insufficient information, it is unclear for most studies whether they resulted in comparable groups or whether intervention allocation could have been foreseen in advance of, or during, enrolment. The possibility of selective outcome reporting and other bias was also difficult to judge.

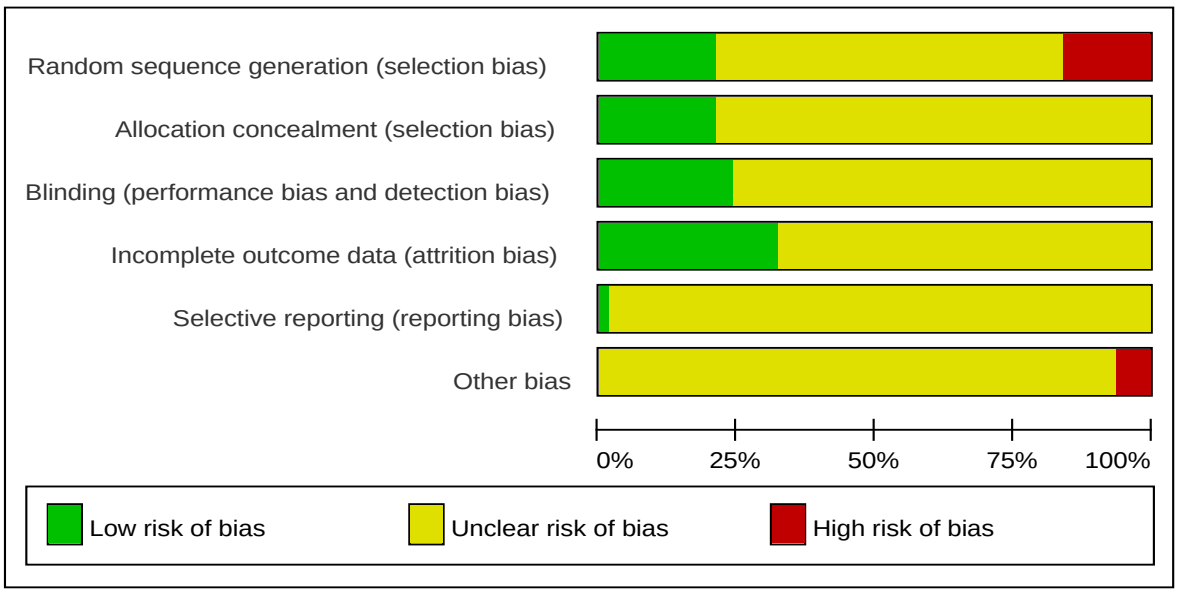


Figure 2. Methodological quality graph: judgements about each methodological quality item presented as percentages across all included studies.

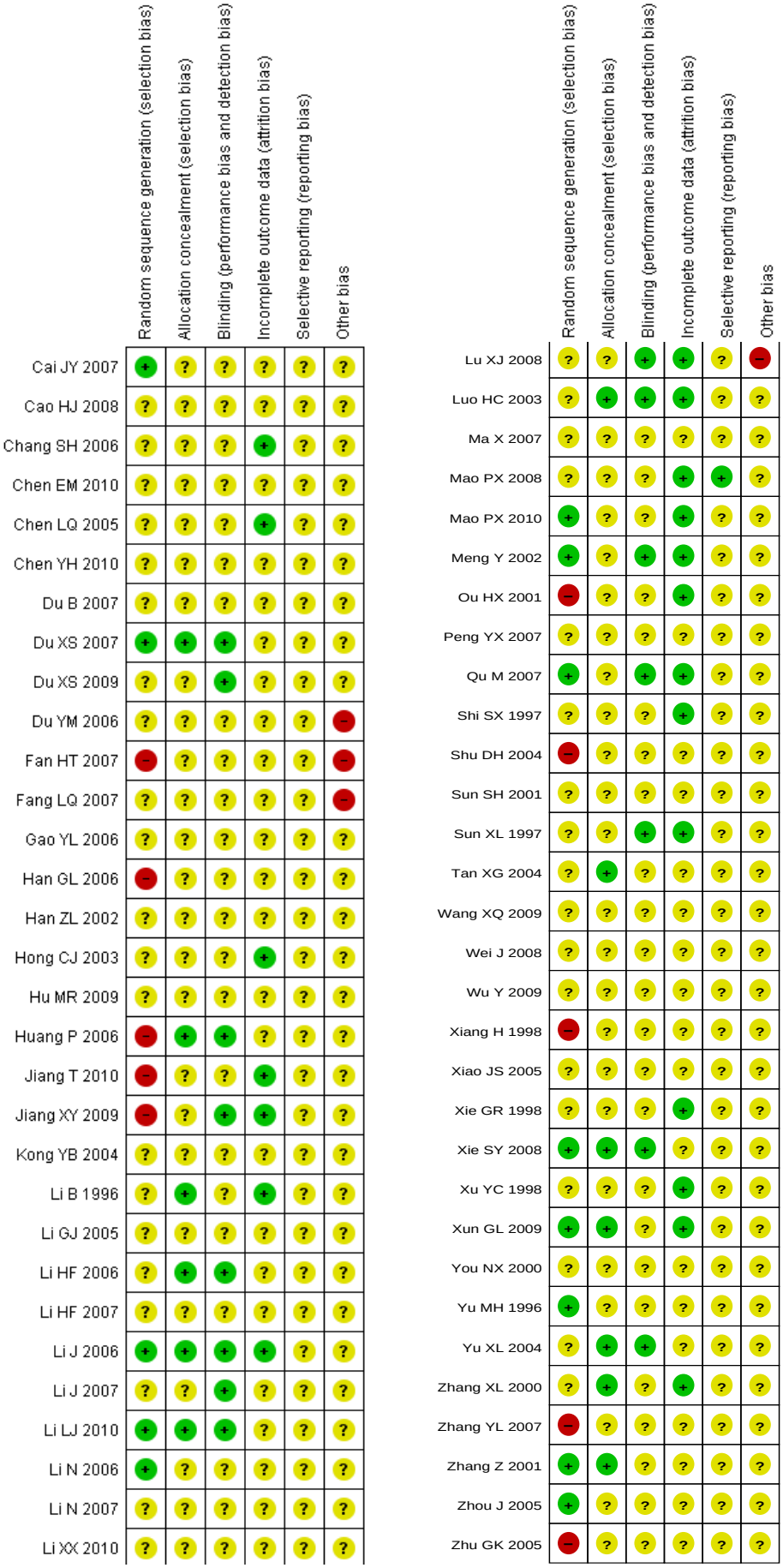


Figure 3. Methodological quality summary: judgements about each methodological quality item for all studies included.

Assessment of fulfillment of CONSORT 2010

On average 41% of 37 CONSORT checklist items (range: 16-73%) were reported. Details are listed in Table 14 and in the characteristics of the included studies (Appendix 5). All authors failed to report trial registration. Informed consent of study participants was reported in 20 (32%) studies. Seven studies discussed results considering trial limitations or addressing sources of potential bias, and six studies reported sources of funding. One trial [86] reported pharmaceutical company funding, it was also the only one reporting protocol and sample size calculation. This study was one of the two studies [45,86] published in English language journals. According to this CONSORT assessment, these two studies had the highest reporting quality with 62% and 73% of the CONSORT items reported respectively. In general, reporting of articles published in Chinese journals was incomplete and inaccurate.

Table 14. CONSORT checklist items reported in the 62 included Chinese double-blind RCTs.

Item No	Description	Frequency of articles reporting the item
1a	Identification as a randomised trial in the title	13
1b	Structured summary of trial design, methods, results, and conclusions	52
2a	Scientific background and explanation of rationale	52
2b	Specific objectives or hypotheses	62
3a	Description of trial design (such as parallel, factorial) including allocation ratio	36
3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	0
4a	Eligibility criteria for participants	62
4b	Settings and locations where the data were collected	55
5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	61
6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
6b	Any changes to trial outcomes after the trial commenced, with reasons	0
7a	How sample size was determined	1
7b	When applicable, explanation of any interim analyses and stopping guidelines	0
8a	Method used to generate the random allocation sequence	24
8b	Type of randomisation; details of any restriction (such as blocking and block size)	15
9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	0
11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, care providers, those assessing outcomes) and how	14
11b	If relevant, description of the similarity of interventions	27
12a	Statistical methods used to compare groups for primary and secondary outcomes	48
12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	2
13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	42
13b	For each group, losses and exclusions after randomisation, together with reasons	25
14a	Dates defining the periods of recruitment and follow-up	11
14b	Why the trial ended or was stopped	0
15	A table showing baseline demographic and clinical characteristics for each group	7
16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	49
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	61
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	46
18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	2
19	All important harms or unintended effects in each group	57
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	7
21	Generalisability (external validity, applicability) of the trial findings	1
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	56
23	Registration number and name of trial registry	0
24	Where the full trial protocol can be accessed, if available	0
25	Sources of funding and other support (such as supply of drugs), role of funders	6

Assessment of other aspects of quality

Abstract quality was also moderate at best. "Randomised" and "double-blinding" were written only in titles and abstracts of 34 studies. Seven studies had no abstract. 27 studies (44%) had no English abstract. 29 Studies (46.8%) failed to report Dropout rates. An overview of other items, which are not explicitly evaluated in CONSORT, is presented in Table 15.

Table 15. Frequency and percentage of items related to reporting quality reported in the 62 included Chinese double-blind RCTs.

Information reported	Frequency	Percentage
Informed consent	20	32.3
Financial support	5	8.1
ITT	11	17.7
Dropout due to side effects	19	30.7
No dropout	1	1.6
Dropout rate of 0-5%	13	21.0
Dropout rate of 6-10%	13	21.0
Dropout rate of more than 11%	6	9.7
Email address of corresponding author	14	22.6

ITT: intention-to-treat

Furthermore, three pairs of publications [32] and [67], [35] and [60], [47] and [34] showed striking similarities in both text and figures. In addition, another study [80] was found to have similarities with a study [155] which was excluded because of single-blinded design. All pairs were conducted in different groups and regions. Contact details for the corresponding author were only provided for one study, thus further exploration was not possible.

3.3 Efficacy and tolerability measures

The forest plots of the analyses are presented in Appendix 6 (Analyses 1.1-14.4). MH RR of response rate and remission rate lower than one indicate a difference in favor of the control group; whilst MH RR of dropout rate lower than one indicates a difference in favor of the

investigational group. Negative Hedges' g (falling to the left of the midline) indicates a difference favoring the control group.

3.3.1 COMPARISON 1: SSRIs VERSUS SSRIs

Primary outcome

I. Response rates

Response rates were obtained from 14 head-to-head trials each comparing two SSRIs. There was no evidence of heterogeneity (I^2=0%, p=0.590), indicating that the effect sizes from the individual trials could be combined. No significant differences were observed between fluoxetine and all other SSRIs on the response rate (MH RR=0.97, 95% CI -0.88 to 1.06) (see Analysis 1.1). No significant differences were observed between citalopram and all other SSRIs (MH RR=1.01, 95% CI 0.94 to 1.09, I^2=0%, p=0.911) (see Analysis 2.1). There was also no evidence of differences between any individual SSRIs (Table 16).

Table 16. Estimates of response rates of fluoxetine/citalopram/sertraline in comparison with other SSRIs: MH RR (95% CI), random effects model.

Control \ Investigational	Fluoxetine	Citalopram	Sertraline
Citalopram	0.94 (0.81-1.08) K=5		
Escitalopram	1.00 (0.86-1.15) K=1	1.01 (0.93-1.09) K=5	
Sertraline	0.97 (0.78-1.20) K=1	1.05 (0.74-1.49) K=1	
Fluvoxamine	-	-	1.06 (0.82-1.37) K=1

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio

MH RR (95% CI)<1 favours control group; MH RR (95% CI)>1 favours investigational group

II. Remission rates

There were 13 studies included in this analysis of remission rates. In accordance with the analyses of response rates, no significant

differences were observed between fluoxetine and all other SSRIs on the remission rates (MH RR=0.98, 95% CI 0.83 to 1.17) (Analysis 1.2 in the Appendix). No heterogeneity between studies was found (I^2=0%, p=0.986). No substantial effect was found for citalopram compared to all other SSRIs (MH RR=0.89, 95% CI 0.75 to 1.06, I^2=0%, p=0.603) (Analysis 2.2). There was also no evidence of significant differences between any individual SSRIs (Table 17).

Table 17. Estimates of remission rates of fluoxetine/citalopram/sertraline in comparison with other SSRIs: MH RR (95% CI), random effects model.

Control \ Investigational	Fluoxetine	Citalopram	Sertraline
Citalopram	0.97 (0.74-1.29) K=4		
Escitalopram	1.02 (0.80-1.30) K=1	0.88 (0.73-1.05) K=5	
Sertraline	0.89 (0.96-1.42) K=1	1.10 (0.96-2.17) K=1	
Paroxetine	-	-	0.93 (0.71-1.24) K=1

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio
MH RR (95% CI)<1 favours control group; MH RR (95% CI)>1 favours investigational group

III. Dropout rates due to side effects

Four head-to-head trials provided suitable data for analysis. There was no evidence of heterogeneity (I^2=0%, p=0.524). No significant differences were observed in the comparisons (Table 18).

Table 18. Estimates of dropout rates due to side effects of fluoxetine/citalopram in comparison with other SSRIs: MH RR (95% CI), random effects model.

Control \ Investigational	Fluoxetine	Citalopram
Escitalopram	0.88 (0.27-2.79) K=1	1.38 (0.42-4.56) K=3

K=number of comparisons, CI=confidence Interval, MH RR= Mantel-Haenszel Risk Ratio
MH RR (95% CI)<1 favours investigational group; MH RR (95% CI)>1 favours control group

Secondary outcomes

The mean total HAMD scores at endpoint, dropout rates, and Total TESS scores are presented in tables 19-21. There was one significant difference favoring sertraline over fluoxetine in terms of Total TESS scores. However, only one trial provided suitable data for this analysis. No significant differences were observed in other comparisons.

Table 19. Estimates of the mean total HAMD scores at endpoint of fluoxetine/citalopram/sertraline in comparison with other SSRIs: Hedges' g (95% CI), random effects model.

Control \ Investigational	Fluoxetine	Citalopram	Sertraline
Citalopram	-0.19 (-0.42-0.04) K=4		
Escitalopram	-0.07 (-0.32-0.18) K=1	-0.06 (-0.31- 0.18) K=5	
Sertraline	-0.06 (-0.41-0.30) K=2	0.28 (-0.24- 0.80) K=1	
Paroxetine	-0.27 (-0.84-0.31) K=1	-	-0.15 (-0.57-0.28) K=2

K=number of comparisons, CI=confidence interval

Hedges'g (95% CI)<0 favours control group; Hedges'g (95% CI) >0 favours investigational group

Table 20. Estimates of Dropout rates overall of fluoxetine/citalopram in comparison with other SSRIs: MH RR (95% CI), random effects model.

Control \ Investigational	Fluoxetine	Citalopram
Escitalopram	0.88 (0.27-2.79) K=1	1.01 (0.58-1.74) K=4
Sertraline	1.50 (0.46-4.87) K=1	0.50 (0.05-5.20) K=1

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio

MH RR (95% CI)<1 favours investigational group; MH RR (95% CI)>1 favours control group

Table 21. Estimates of Total TESS scores of fluoxetine in comparison with other SSRIs: Hedges' g (95% CI), random effects model.

Control \ Investigational	Fluoxetine
Citalopram	-1.16 (-3.21-0.89) K=2
Sertraline	-0.77 (-1.24- -0.30) K=1

K=number of comparisons, CI=confidence interval

Hedges' g (95% CI)<0 favours control group; Hedges' g (95% CI) >0 favours investigational group

3.3.2 COMPARISON 2: SSRIs VERSUS non-SSRIs

Primary outcome

1. Response rates

A total of 37 head-to-head trials provided suitable data for the analysis of response rates (see Table 22 and analysis 4.1 in the Appendix). 19 studies contributed to the analysis of SSRIs vs. TCAs. There was no evidence of heterogeneity (I^2=0%, p=0.997), indicating that the effect sizes from individual trials could be combined. None of the studies reported significant differences between SSRIs and TCAs. However, meta-analysis demonstrated that there was a significant difference favoring SSRIs over TCAs in terms of response rate (MH RR=1.09, 95% CI 1.03 to 1.16). Response rates were significantly higher in patients receiving sertraline than in those receiving TCA (MH RR=1.17, 95% CI 1.01 to 1.37). This meta-analysis also showed significant differences favoring paroxetine over TCA (MH RR=1.09, 95% CI 1.02 to 1.16). No significant differences were found between SSRIs and other classes.

Table 22. Estimates of response rates of SSRIs in comparison with other treatment: MH RR(95% CI), random effects model.

other \ SSRI	Fluoxetine	Citalopram	Paroxetine	Sertraline	Escitalopram	SSRI
Amitriptyline	1.03 (0.90-1.17) K=4	1.07 (0.93-1.23) K=4	1.11 (1.00-1.23) K=5	1.17 (1.01-1.37) K=4	-	1.09 (1.02-1.16) K=17
Doxepin	1.16 (0.82-1.64) K=1	-	-	-	-	1.16 (0.82-1.64) K=1
Imipramine	-	-	1.09 (0.83-1.42) K=1	-	-	1.09 (0.83-1.42) K=1
TCA	1.04 (0.93-1.17) K=5	1.07 (0.93-1.23) K=4	1.11 (1.01-1.22) K=6	1.17 (1.01-1.37) K=4	-	1.09 (1.03-1.16) K=19
Venlafaxine	-	-	0.97 (0.86-1.09) K=2	-	-	0.97 (0.86-1.09) K=2
Duloxetine	0.93 (0.75-1.16) K=1	-	-	-	-	0.93 (0.75-1.16) K=1
SNRI	0.93 (0.75-1.16) K=1	-	0.97 (0.86-1.09) K=2	-	-	0.97 (0.89-1.05) K=3
Reboxetine	1.07 (0.92-1.23) K=2	-	-	-	-	1.07 (0.92-1.23) K=2
NARI	1.07 (0.92-1.23) K=2	-	-	-	-	1.07 (0.92-1.23) K=2
Bupropion	1.03 (0.89-1.18) K=3	-	-	-	-	1.03 (0.89-1.18) K=3
NDRI	1.03 (0.89-1.18) K=3	-	-	-	-	1.03 (0.89-1.18) K=3
Mirtazapine	1.21 (0.84-1.75) K=1	-	0.65 (0.43-1.00) K=1	-	-	0.90 (0.49-1.65) K=2
Maprotiline	-	1.25 (0.82-1.90) K=1	-	1.00 (0.73-1.37) K=1	-	1.08 (0.84-1.40) K=2
Mianserin	-	-	-	-	1.06 (0.83-1.35) K=1	1.06 (0.83-1.35) K=1
teCA	1.21 (0.84-1.75) K=1	1.25 (0.82-1.90) K=1	0.65 (0.43-1.00) K=1	1.00 (0.73-1.37) K=1	1.06 (0.83-1.35) K=1	1.02 (0.85-1.24) K=5
Nefazodone	1.03 (0.90-1.19) K=1	-	-	-	-	1.03 (0.90-1.19) K=1
SARI	1.03 (0.90-1.19) K=1	-	-	-	-	1.03 (0.90-1.19) K=1
TCM	1.07 (0.99-1.16) K=4	-	-	-	-	1.07 (0.99-1.16) K=4

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio, TCA: Tricyclic antidepressant
teCA: tetracyclic antidepressant, TCM: traditional Chinese medicine, SARI: Serotonin antagonist and reuptake inhibitors
SSRI: Selective serotonin reuptake inhibitors, NDRI: Norepinephrine and dopamine reuptake inhibitors
SNRI: Selective noradrenaline reuptake inhibitor, NARI: Norepinephrine reuptake inhibitor
MH RR (95% CI)<1 favours other; MH RR (95% CI)>1 favours SSRIs

2. Remission rates

36 studies were included in this analysis (see Table 23 and analysis in the Appendix). In the analysis of SSRIs vs. TCAs, there was no evidence of heterogeneity (I^2=0%, p=0.880), indicating that effect sizes from the individual trials could be combined. Based on remission, a significant difference favoring SSRIs over TCAs was observed (MH RR=1.25, 95% CI 1.12 to 1.40). Significant differences favoring SSRIs over amitriptyline (MH RR=1.27, 95% CI 1.12 to 1.43), favoring paroxetine over TCA (MH RR=1.35, 95% CI 1.12 to 1.63), favoring paroxetine over amitriptyline (MH RR=1.41, 95% CI 1.14 to 1.74), favoring sertraline over TCA (MH RR=1.28, 95% CI 1.04 to 1.59) and over amitriptyline were also observed (MH RR=1.28, 95% CI 1.04 to 1.59). However, no significant differences were found between remission rates in patients receiving SSRIs and in patients receiving other classes.

Table 23. Estimates of remission rates of SSRIs in comparison with other: MH RR (95% CI).

other \ SSRI	Fluoxetine	Citalopram	Paroxetine	Sertraline	Escitalopram	SSRI
Amitriptyline	1.07 (0.79-1.46) K=3	1.19 (0.89-1.59) K=4	1.41 (1.14-1.74) K=6	1.28 (1.04-1.59) K=5	-	1.27 (1.12-1.43) K=18
Doxepin	1.20 (0.76-1.90) K=1	-	-	-	-	1.20 (0.76-1.90) K=1
Imipramine	-	-	1.12 (0.73-1.71) K=1	-	-	1.12 (0.73-1.71) K=1
TCA	1.11 (0.86-1.43) K=4	1.19 (0.89-1.59) K=4	1.35 (1.12-1.63) K=7	1.28 (1.04-1.59) K=5	-	1.25 (1.12-1.40) K=20
Venlafaxine	-	-	0.97 (0.85-1.10) K=2	-	-	0.97 (0.85-1.10) K=2
Duloxetine	0.95 (0.65-1.40) K=1	-	-	-	-	0.95 (0.65-1.40) K=1
SNRI	0.95 (0.65-1.40) K=1	-	0.97 (0.85-1.10) K=2	-	-	0.96 (0.85-1.09) K=3
Reboxetine	1.07 (0.75-1.52) K=2	0.98 (0.68-1.41) K=1	-	-	-	1.03 (0.80-1.32) K=3
NARI	1.07 (0.75-1.52) K=2	0.98 (0.68-1.41) K=1	-	-	-	1.03 (0.80-1.32) K=3
Bupropion	1.39 (0.79-2.47) K=2	-	-	-	-	1.39 (0.79-2.47) K=2
NDRI	1.39 (0.79-2.47) K=2	-	-	-	-	1.39 (0.79-2.47) K=2
Mirtazapine	0.78 (0.47-1.31) K=1	-	0.62 (0.29-1.32) K=1	-	-	0.73 (0.47-1.11) K=2
Maprotiline	-	1.25 (0.57-2.73) K=1	-	1.08 (0.61-1.90) K=1	-	1.13 (0.72-1.79) K=2
Mianserin	-	-	-	-	1.17 (0.81-1.71) K=1	1.17 (0.81-1.71) K=1
teCA	0.78 (0.47-1.31) K=1	1.25 (0.57-2.73) K=1	0.62 (0.29-1.32) K=1	1.08 (0.61-1.90) K=1	1.17 (0.81-1.71) K=1	1.00 (0.78-1.27) K=5
Nefazodone	1.06 (0.80-1.39) K=1	-	-	-	-	1.06 (0.80-1.39) K=1
SARI	1.06 (0.80-1.39) K=1	-	-	-	-	1.06 (0.80-1.39) K=1
TCM	0.99 (0.79-1.23) K=3	-	-	-	-	0.99 (0.79-1.23) K=3

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio, TCA: Tricyclic antidepressant teCA: tetracyclic antidepressant, TCM: Traditional Chinese medicine, SARI: Serotonin antagonist and reuptake inhibitors SSRI: Selective serotonin reuptake inhibitors, NDRI: Norepinephrine and dopamine reuptake inhibitors SNRI: Selective noradrenaline reuptake Inhibitor, NARI: Norepinephrine reuptake inhibitor, MH RR (95% CI)>1 favours SSRIs

3. Dropout rates due to side effects

A total of 14 head-to-head trials provided suitable data for analysis (see Table 24). Eight studies comparing SSRIs with TCAs reported dropout rates due to side effects. There was no evidence of heterogeneity (I^2=0%, p=0.984), indicating that the effect sizes from the individual trials could be combined. No significant differences between SSRIs and other classes on dropout rates due to side effects were observed.

Table 24. Estimates of dropout rates due to side effects of SSRIs in comparison with other treatments: MH RR (95% CI), random effects model.

other \ SSRI	Fluoxetine	Paroxetine	Sertraline	SSRI
Amitriptyline	0.11 (0.01-1.98) K=1	0.58 (0.20-1.72) K=4	0.55 (0.20-1.51) K=4	0.51 (0.25-1.05) K=9
TCA	0.11 (0.01-1.98) K=1	0.58 (0.20-1.72) K=4	0.55 (0.20-1.51) K=4	0.51 (0.25-1.05) K=9
Venlafaxine	1.00 (0.07-14.55) K=1	-	-	1.00 (0.07-14.55) K=1
SNRI	1.00 (0.07-14.55) K=1	-	-	1.00 (0.07-14.55) K=1
Reboxetine	0.25 (0.03-2.20) K=1	-	-	0.25 (0.03-2.20) K=1
NARI	0.25 (0.03-2.20) K=1	-	-	0.25 (0.03-2.20) K=1
Mirtazapine	0.62 (0.27-1.39) K=1	-	-	0.62 (0.27-1.39) K=1
Maprotiline	-	-	0.50 (0.05-5.23) K=1	0.50 (0.05-5.23) K=1
teCA	0.62 (0.27-1.39) K=1	-	0.50 (0.05-5.23) K=1	0.60 (0.28-1.30) K=2
Placebo	3.00 (0.13-71.00) K=1	-	-	3.00 (0.13-71.00) K=1
TCM	0.97 (0.06-14.82) K=1	0.67 (0.11-3.91) K=1	-	0.74 (0.17-3.29) K=2

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio

TCA: Tricyclic antidepressant, teCA: tetracyclic antidepressant, TCM: Traditional Chinese medicine

SSRI: Selective serotonin reuptake inhibitors, SNRI: Selective noradrenaline reuptake inhibitor

NARI: Norepinephrine reuptake inhibitor, MH RR (95% CI)<1 favours SSRIs; MH RR (95% CI)>1 favours other

Secondary outcomes

The results of the meta-analyses of the mean total HAMD scores at endpoint, dropout rates overall, and Total TESS scores are presented in tables 25-27. Based on dropout rates overall and total TESS scores, significant differences favoring SSRIs over TCAs were observed.

Table 25. Estimates of the mean total HAMD scores at endpoint of SSRIs in comparison with other treatments: Hedges' g (95% CI), random effects model.

other \ SSRI	Fluoxetine	Citalopram	Paroxetine	Sertraline	Escitalopram	SSRI
Amitriptyline	0.04 (-0.22-0.30) K=4	0.24 (-0.07-0.56) K=3	-0.04 (-0.26-0.19) K=6	0.12 (-0.09-0.33) K=5	-	0.07 (-0.05-0.19) K=18
Doxepin	-0.18 (-0.68-0.32) K=1	-	-	-	-	-0.18 (-0.68-0.32) K=1
Imipramine	-	-	0.06 (-0.43-0.55) K=1	-	-	0.06 (-0.43-0.55) K=1
TCA	-0.01 (-0.23-0.22) K=5	0.24 (-0.07-0.56) K=3	-0.02 (-0.21-0.17) K=7	0.12 (-0.09-0.33) K=5	-	0.06 (-0.05-0.17) K=20
Venlafaxine	0.27 (-0.43-0.97) K=1	-	-0.12 (-0.48-0.25) K=2	-	-	-0.05 (-0.35-0.25) K=3
Duloxetine	-0.10 (-0.57-0.37) K=1	-	-	-	-	-0.10 (-0.57-0.37) K=1
SNRI	0.02 (-0.38-0.41) K=2	-	-0.12 (-0.48-0.25) K=2	-	-	-0.05 (-0.26-0.16) K=4
Reboxetine	-0.01 (-0.19-0.18) K=3	-0.04 (-0.53-0.44) K=1	-	-	-	-0.01 (-0.19-0.16) K=4
NARI	-0.01 (-0.19-0.18) K=3	-0.04 (-0.53-0.44) K=1	-	-	-	-0.01 (-0.19-0.16) K=4
Bupropion	0.03 (-0.14-0.20) K=4	-	-	-	-	0.03 (-0.14-0.20) K=4
NDRI	0.03 (-0.14-0.20) K=4	-	-	-	-	0.03 (-0.14-0.20) K=4
Mirtazapine	-0.46 (-0.81- -0.12) K=1	-	-0.39 (-0.82-0.05) K=1	-	-	-0.43 (-0.70- -0.16) K=2
Maprotiline	-	-0.09 (-0.59-0.41) K=1	-	0.38 (-0.12-0.87) K=1	-	0.15 (-0.31-0.60) K=2
Mianserin	-	-	-	-	0.09 (-0.31-0.50) K=1	0.09 (-0.31-0.50) K=1
teCA	-0.46 (-0.81- -0.12) K=1	-0.09 (-0.59-0.41) K=1	-0.39 (-0.82-0.05) K=1	0.38 (-0.12-0.87) K=1	0.09 (-0.31-0.50) K=1	-0.11 (-0.42-0.19) K=5
Nefazodone	0.97 (0.70-1.23) K=1	-	-	-	-	0.97 (0.70-1.23) K=1
SARI	0.97 (0.70-1.23) K=1	-	-	-	-	0.97 (0.70-1.23) K=1
Placebo	0.33 (-0.15-0.82) K=1	-	-	-	-	0.33 (-0.15-0.82) K=1
TCM	-0.01 (-0.13-0.12) K=8	-	0.01 (-0.25-0.27) K=1	-	-	0.00 (-0.10-0.10) K=9

K=number of comparisons, CI=confidence Interval, Hedges'g (95% CI)>0 favours SSRIs

teCA: tetracyclic antidepressant, TCM: Traditional Chinese medicine, TCA: Tricyclic antidepressant

SARI: Serotonin antagonist and reuptake inhibitors, SSRI: Selective serotonin reuptake inhibitors

NDRI: Norepinephrine and dopamine reuptake inhibitors, SNRI: Selective noradrenaline reuptake inhibitor

NARI: Norepinephrine reuptake inhibitor

Table 26. Estimates of overall dropout rates of SSRIs in comparison with other treatments: MH RR (95% CI), random effects model.

other \ SSRI	Fluoxetine	Citalopram	Paroxetine	Sertraline	Escitalopram	SSRI
Amitriptyline	0.23 (0.03-1.52) K=2	0.15 (0.01-2.73) K=1	0.49 (0.17-1.38) K=4	0.52 (0.19-1.41) K=4	-	0.43 (0.22-0.82) K=11
TCA	0.23 (0.03-1.52) K=2	0.15 (0.01-2.73) K=1	0.49 (0.17-1.38) K=4	0.52 (0.19-1.41) K=4	-	0.43 (0.22-0.82) K=11
Venlafaxine	1.00 (0.07-14.55) K=1	-	-	-	-	1.00 (0.07-14.55) K=1
SNRI	1.00 (0.07-14.55) K=1	-	-	-	-	1.00 (0.07-14.55) K=1
Reboxetine	1.08 (0.52-2.23) K=2	-	-	-	-	1.08 (0.52-2.23) K=2
NARI	1.08 (0.52-2.23) K=2	-	-	-	-	1.08 (0.52-2.23) K=2
Bupropion	0.75 (0.26-2.12) K=3	-	-	-	-	0.75 (0.26-2.12) K=3
NDRI	0.75 (0.26-2.12) K=3	-	-	-	-	0.75 (0.26-2.12) K=3
Mirtazapine	0.73 (0.48-1.13) K=1	-	-	-	-	0.73 (0.48-1.13) K=1
Maprotiline	-	-	-	0.50 (0.05-5.23) K=1	-	0.50 (0.05-5.23) K=1
Mianserin	-	-	-	-	0.67 (0.12-3.81) K=1	0.67 (0.12-3.81) K=1
teCA	0.73 (0.48-1.13) K=1	-	-	0.50 (0.05-5.23) K=1	0.67 (0.12-3.81) K=1	0.72 (0.48-1.09) K=3
Nefazodone	0.77 (0.35-1.69) K=1	-	-	-	-	0.77 (0.35-1.69) K=1
SARI	0.77 (0.35-1.69) K=1	-	-	-	-	0.77 (0.35-1.69) K=1
Placebo	0.33 (0.04-3.04) K=1	-	-	-	-	0.33 (0.04-3.04) K=1
TCM	0.99 (0.57-1.73) K=4	-	1.08 (0.53-2.18) K=1	-	-	1.02 (0.66-1.58) K=5

K=number of comparisons, CI=confidence interval, MH RR= Mantel-Haenszel risk ratio

TCA: Tricyclic antidepressant , teCA: tetracyclic antidepressant, TCM: Traditional Chinese medicine

SARI: Serotonin antagonist and reuptake inhibitors, SSRI: Selective serotonin reuptake inhibitors

SNRI: Selective noradrenaline reuptake inhibitor, NARI: Norepinephrine reuptake inhibitor

NDRI: Norepinephrine and dopamine reuptake inhibitors, MH RR (95% CI)<1 favours SSRIs

Table 27. Estimates of Total TESS scores of SSRIs in comparison with other treatments: Hedges' g (95% CI), random effects model.

other \ SSRI	Fluoxetine	Citalopram	Paroxetine	SSRI
Amitriptyline	1.59 (1.20-1.99) K=3	2.28 (1.55-3.02) K=2	0.69 (0.37-1.02) K=2	1.48 (0.93-2.03) K=7
Imipramine	-	-	0.61 (0.11-1.11) K=1	0.61 (0.11-1.11) K=1
TCA	1.59 (1.20-1.99) K=3	2.28 (1.55-3.02) K=2	0.67 (0.39-0.94) K=3	1.36 (0.86-1.86) K=8
Reboxetine	-	-0.07 (-0.56-0.42) K=1	-	-0.07 (-0.56-0.42) K=1
NARI	-	-0.07 (-0.56-0.42) K=1	-	-0.07 (-0.56-0.42) K=1

K=number of comparisons, CI=confidence interval, Hedges'g (95% CI) >0 favours SSRIs

TCA: Tricyclic antidepressant, SSRI: Selective serotonin reuptake inhibitors

NARI: Norepinephrine reuptake inhibitor

Summary of findings and outcomes

There were 16 studies with head-to-head comparisons of SSRIs (a total of 17 comparisons). Meta-analyses showed no significant differences between different SSRIs on any outcomes. A total of 47 studies (50 comparisons) were included comparing SSRIs with TCM, placebo, and/or other antidepressants. Based on response rates, remission rates, dropout rates overall and total TESS scores, significant differences favoring SSRIs over TCAs were observed. No significant differences were observed on dropout rates due to side effects and HAMD end-point. Finally, no significant differences were observed on any outcome between SSRIs and other antidepressant interventions such as SNRI, teCA, NARI, NDRI, SARI, and TCM. However, except for TCA, only a few trials within each class of interventions could be identified. Furthermore, 47% of included studies did not mention dropout.

3.4 Additional Analyses

Subgroup analysis

The effect of age was examined using pre-planned subgroup analysis in included studies comparing SSRIs with TCAs or teCAs. The significant differences favoring SSRIs over TCAs in terms of response rate and remission rate were not found in studies included only elderly patients (see table 28). In studies comparing SSRIs with teCAs no significant differences were found (see table 29).

Table 28. Results of subgroup analyses in included studies comparing SSRIs with TCAs: MH RR (95% CI), random effect model.

Subgroups	Response	Remission	Dropout rate due to side effects
Non-geriatric	1.09	1.25	0.57
	(1.02-1.17)	(1.11-1.41)	(0.26-1.23)
	K=15	K=16	K=7
Geriatric	1.09	1.25	0.29
	(0.92-1.29)	(0.89-1.75)	(0.05-1.79)
	K=4	K=4	K=2

K=number of comparisons, MH RR= Mantel-Haenszel risk ratio, CI=confidence interval

TCA: Tricyclic antidepressant SSRI: Selective serotonin reuptake inhibitors

Table 29. Results of subgroup analyses in included studies comparing SSRIs with teCAs: MH RR (95% CI), random effects model.

Subgroups	Response	Remission	Dropout rate due to side effects
Non-geriatric	0.90	0.73	0.62
	(0.49-1.65)	(0.47-1.11)	(0.27-1.39)
	K=2	K=2	K=1
Geriatric	1.07	1.16	0.50
	(0.90-1.28)	(0.87-1.55)	(0.05-5.23)
	K=3	K=3	K=1

K=number of comparisons, MH RR= Mantel-Haenszel risk ratio, CI=confidence interval

teCA: tetracyclic antidepressant SSRI: Selective serotonin reuptake inhibitors

Sensitivity analysis

Sensitivity analysis was pre-planned to investigate the "wish-bias" (SSRI as control substance vs. investigational substance). As investigational substance and trial sponsoring were unclear in most studies this analysis could not be conducted.

Due to the striking similarities in both figures and text of three pairs of publications [32,67], [35,60], and [34,47] and another included study [80], which showed similarities with a study [155] included in the previous work [59], these were excluded in sensitivity analyses. However, results did not substantially affect the main findings.

Meta-regression analyses

Pre-planned meta-regression analyses were carried out to investigate whether the quality of reporting of primary studies as measured with CONSORT was associated with efficacy and tolerability outcomes. Primary efficacy and tolerability outcomes were used as dependent variables, whilst reported CONSORT items were used as continuous predictive variables. The number of reported CONSORT items was not correlated with efficacy (r=0.006, P=0.330, see Figure 4) and not correlated with tolerability (r=-0.001, p=0.987).

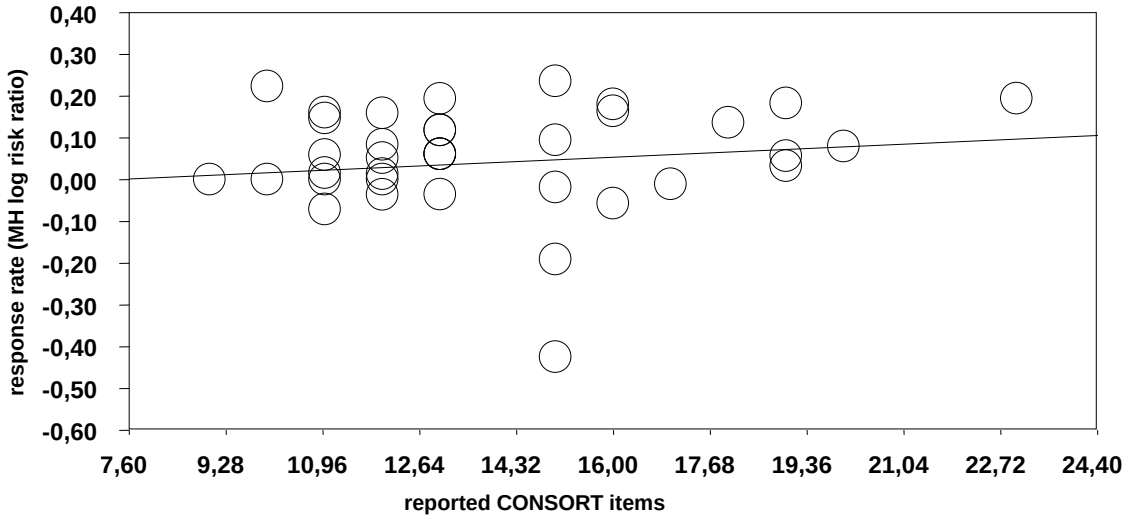


Figure 4. Meta-regression of CONSORT on response rate (MH log risk ratio)
CONSORT: Consolidated Standards of Reporting Trials

Publication bias

The funnel plots for the analysis of primary efficacy and tolerability outcomes in SSRIs versus TCAs were roughly symmetrical and resemble inverted funnels. The Begg adjusted rank correlation test (Kendall τ=-

0.012; p=0.944) and the Egger regression approach (r=0.408 [95% CI, -0.533 to 1.348], p=0.374) showed no sign of a significant publication bias for response (see Figure 5).

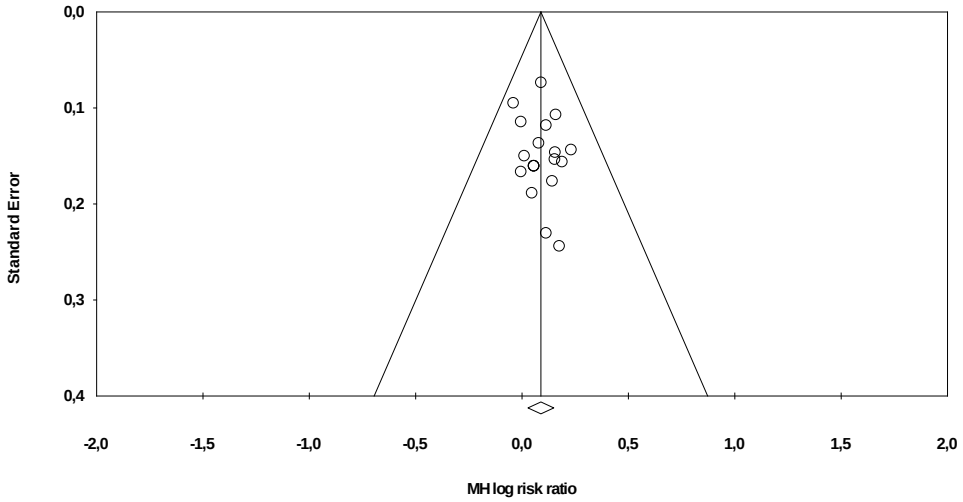


Figure 5. Funnel plot for the responder analysis in RCTs of Selective Serotonin Reuptake Inhibitors versus Tricyclic antidepressants.

For the studies included in the analysis of remission, the Kendall's τ was found to be 0.016 (p=0.922) and the r was 0.265 [95% CI, -0.889 to 1.420] (p=0.635), and was therefore not indicative of major publication bias. For the studies included in the analysis of dropout rates due to side effects, the Begg adjusted rank correlation test (Kendall τ=-0.371; p=0.175) and the Egger regression approach (r=-0.995 [95% CI, -2.252 to 0.262], p=0.103) showed no sign of a significant publication bias.

4 DISCUSSION

Summary of main results

The present study is the first systematic review and meta-analysis of the efficacy and tolerability of SSRIs against TCM, placebo, and/or other antidepressants such as TCAs, SNRIs etc. in Chinese (including Taiwanese) adult patients with a primary diagnosis of depression. A total of 62 studies involving 6078 participants were included. All studies were conducted solely in China, two of them were published in English. 11 (18%) trials included only patients suffering from PSD. Ten (16%) trials were limited to elderly patients over 55 years.

There were 16 studies with head-to-head comparisons of SSRIs (a total of 17 comparisons). Meta-analyses showed no significant differences between different SSRIs. A total of 47 studies (50 comparisons) were included comparing SSRIs with TCM, placebo, and/or other antidepressants. The findings provided evidence that SSRIs are statistically more effective than TCA (response rate: MH RR=1.09, 95% CI 1.03 to 1.16; remission rate: MH RR=1.25, 95% CI 1.12 to 1.40), significant differences were not found in studies that included only elderly patients. No significant differences were observed on dropout rates due to side effects. Finally, no significant differences were observed on any outcome between SSRIs and other antidepressant interventions such as SNRI, teCA, NARI, NDRI, SARI, and TCM.

Quantity and quality of the evidence

The median number of patients per study was 64 (range: 25-480). With the exception of TCA, only a few trials could be identified within each class of interventions (five trials with teCA, four with SNRI, four with NARI, four with NDRI, and one with SARI). Only one placebo-controlled study was retrieved.

In sum, reporting quality was low. On average, 41% (range: 16-73%) of the CONSORT 2010 items were reported. All authors failed to report trial registration data. Informed consent, sources of funding, limitations

of trials, publication of protocol, and email address were also not mentioned in a substantial proportion of studies. In 47% of all studies included the proportion of patients who dropped out of the allocated treatment was not provided. According to the Cochrane risk of bias tool, only 13 (21%) studies described adequate methods to generate the random sequence. In ten (16%) articles reporting treatment allocation in which approaches such as hospital number or date of admission the term "random" was used inappropriately. In addition, three pairs of publications showed striking similarities in both text and figures. They were excluded in the sensitivity analysis; however, results did not materially change the main findings.

Due to insufficient information, the possibility of selective outcome reporting and other bias is unknown. In most articles it is unclear whether groups were comparable or whether intervention allocation could have been foreseen in advance of, or during, enrolment. In sum, the poor reporting quality made the methodological quality, the reliability and validity of trial findings difficult to judge. Therefore, a cautious approach is mandatory in interpreting the results of this meta-analysis correctly.

Comparisons with other reviews on SSRIs

The finding of a significant advantage of SSRI over TCA in terms of response and remission rates is inconsistent with a range of Western meta-analyses which indicated comparable efficacy between SSRI and TCA [4,91,92,117], or showed that TCA were more effective than SSRI [3,84]. However, this significant advantage was not found in the four studies including elderly patients only. In contrast to previous studies [26,54,101], no significant advantage of escitalopram and sertraline over other SSRIs was found in terms of efficacy and tolerability. However, lack of statistically significant differences could be a matter of lack of power. Most Chinese trials were underpowered and except for

TCA, only a small number of trials within each class of interventions could be identified.

Deficiencies in the reporting quality of clinical trials conducted in China were also documented in many other reviews [22,59,142,150]. Even in the leading Chinese medical journals, 73% of RCTs failed to describe the method of sequence generation [142]. A recent study [22] showed that, without obvious evidence of difference, Chinese primary studies often concluded very positively with regard to experimental drugs, whilst primary outcomes, precision, adverse effects and the proportion of patient dropouts were rarely reported. Dropout rates reported were often very low. A review [150] showed that 44% of trials reported a zero dropout rate. Therefore, it is unclear whether response and remission rates could be successfully calculated according to the ITT principle to prevent bias associated with non-random loss of participants [62,64,65].

Whilst 45% of 616 Western clinical trials indexed in MEDLINE in 2006 described a sample size calculation [89], only one [86] of the studies in the current meta-analysis included reported such analysis. In 77% of studies less than 50 patients were allocated to each treatment group.

Striking similarities were found in three pairs of publications [32] and [67], [35] and [60], [47] and [34], and in one included study [80], which was found in a previous meta-analyse [59] to have similarities with another study [155]. This replication of duplicates of Chinese trials indicates that this might be a common problem in Chinese research literature.

Interpretation of findings and limitations

Several limitations of this review warrant comment. First, most Chinese trials are not large enough to provide accurate, generalizable results. Except for TCA, only a few trials within each class of interventions could be identified. These limit the power of this review to detect moderate but clinically meaningful differences between competing interventions

[2]. Second, Chinese RCTs were substantially more likely to report statistically significant results [149]. Third, although duration was not an inclusion criteria, all identified trials examined the short-term effects of SSRIs. Therefore, it is not possible to draw any conclusions about the clinical benefit of SSRIs in long-term treatment [104].

One of the most important limitations is incomplete and inaccurate reporting. Despite the fact that, in 2001, the Chinese Journal of Evidence-Based Medicine [79] published a Chinese version of the CONSORT statement, only a few Chinese medical journals recommend it in their "instructions for authors". As a consequence, important information was often not provided. For instance, only six of the studies included reported sponsorship. Empirical evidence points toward funding sources sometimes being associated with estimated treatment effects [10,25,27,66]. Trials sponsored by the pharmaceutical industry are more likely to be biased with results favouring the sponsor's drug than studies funded by other sources [5,9,56,58,66,115,136], although their methodological quality is at least equal to that of non-industry funded research [66].

Because of similarities in the efficacy of antidepressants the comparison of tolerability is very important. However, 47% of included studies did not mention dropout rates, 23% of the studies reported dropout rates of 5% or less. In addition, the number of people assessed for eligibility was rarely provided, and thus it is difficult to judge whether ITT analysis was appropriate and if participants were likely to be representative of all eligible participants. Preferences for or acceptability of an intervention are also unclear.

The identification of potentially relevant studies from China is difficult even for Chinese readers [22]. In only 55% of the studies included, the terms "randomised" and "double blind" were written in titles and abstracts. Seven studies lacked an abstract. Furthermore, without complete, clear and transparent reporting readers can hardly judge the

reliability and validity of trial findings nor extract information [89]. A recent study [161] found out that more than 90% of claimed RCTs published in China were not proper RCTs due to the original authors having misconceptions of randomization. Empirical evidence showed that some poorly conducted or poorly reported aspects of trials were associated with bias [110], which can cause overestimation of treatment effects in the review [88,133] and mislead decision making in health care. However, in this present work, no evidence of a relationship between quality and treatment estimates of efficacy and tolerability was found by Meta-regression analyses. This overestimation of treatment effects could also not be confirmed by another study [28,130].

Finally, only published articles were included in this work, although no publication bias was found and publication status was also not used as inclusion criterion. Some common criticisms of meta-analyses, such as the so called "file drawer problem" [105] i.e. the tendency to publish articles with significant findings only, should still be taken into consideration.

Conclusions

The present review shed light on the quality of Chinese medical articles and investigated the efficacy and tolerability of SSRIs in Chinese adult patients with depressive disorders. In spite of the limitations mentioned, the results of the present study made an important contribution and offered several important recommendations for future research. First, editors and researchers in China should pay more attention to the quality of their studies and reporting standards in Chinese scientific journals by using CONSORT guidelines [33,90]. Full contact addresses of authors should be provided to facilitate question and correspondence. Chinese journals should consider trials for publication only if they have been registered before recruiting the first participant. Second, only one study was listed in both Chinese and Western databases, thus, the

problem of the very low overlap of the Western and Chinese databases should be taken into account. Third, most included trials concentrated on comparisons between SSRIs and TCAs, therefore, more Chinese research is needed to examine differences between other competing treatments. The findings of a significant advantage of SSRI over TCA in terms of response rate and remission rate should be replicated by large high-quality Chinese studies. Finally, further effort is urgently warranted from both Western and Chinese researchers to utilize the research resource in China.

5 SUMMARY

This is the first systematic review and meta-analysis of Chinese studies comparing Selective Serotonin Reuptake Inhibitors (SSRIs) with other antidepressants, traditional Chinese medicine (TCM), and/or placebo. The objective is to evaluate the quality of Chinese double-blind randomised controlled trials (RCTs) and to determine the efficacy and tolerability of SSRI in the treatment of Chinese patients with depression.

Major Western and Chinese electronic databases were searched without limits on language, publication type, or date. Risk of bias was assessed using risk of bias instruments (Cochrane Collaboration). The proportions of fulfilled Consolidated Standards of Reporting Trials (CONSORT) 2010 Items were used to assess the quality of reporting. Effect size Hedges' g was used for mean total Hamilton Rating Scale of Depression (HAMD) scores at endpoint and sum scores of Treatment Emergent Symptom Scale (TESS). Mantel-Haenszel Risk ratio (MH RR) and 95% confidence interval (95% CI) were used for response rates, remission rates, and dropout rates. Data were combined with random effects models.

62 double-blind RCTs were included, involving 6078 study participants. All studies were conducted in China, only two were published in English. A total of 16 studies (17 comparisons) compared SSRI with any other SSRI. No significant differences between SSRIs were found. 47 studies (50 comparisons) were included in this meta-analysis comparing SSRIs with TCM, placebo, and/or other antidepressants. The findings provided evidence that SSRIs, in terms of efficacy, are superior to tricyclic antidepressants (TCA) (response rate: MH RR 1.09, 95% CI 1.03 to 1.16; remission rate: MH RR 1.25, 95% CI 1.12 to 1.40). However, these significant differences were not found in the four studies including elderly patients only. No significant differences were observed regarding dropout rates due to side effects, and there were no significant differences between SSRIs and other classes of antidepressants on any outcome.

The overlap of Western and Chinese databases was very low. Only one study was listed in both Chinese and Western databases. There was unclear reporting in most studies included. In 16% of articles the term "random" was used inappropriately, and only 21% of studies described adequate methods of sequence generation and adequate allocation concealment. On average, 41% items (range: 16-73%) of CONSORT 2010 were reported. None of the authors reported trial registration. Important information such as: sources of funding, limitations, informed consent, protocol, and email address were rarely reported. 47% of studies did not mention dropout. Furthermore, three pairs of publications showed striking similarities in both text and figures. They were excluded in sensitivity analyses, however, exclusion did not substantially affect the main findings.

Most Chinese trials recruited small patient samples, and except for studies with TCA comparator, only small numbers of trials were identified within each class of drug/TCM/placebo comparisons. Therefore, the lack of significant differences could be due to a lack of power.

In spite of these limitations, this work confirmed the poor reporting quality of Chinese studies and highlights problems of: (a) low overlap of studies included in Western and Chinese databases, (b) limited accessibility of Chinese placebo-controlled RCTs to the public, and (c) an urgent need to improve the quality of Chinese trial publications by using the CONSORT guideline. Further studies with larger sample sizes are required to confirm the findings of this review.

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APPENDIX 1: DRUG LIST

Drugs listed as ADs in ATC DDD 2011

Non-selective monoamine reuptake inhibitors

Desipramine, Imipramine, Imipramine oxide, clomipramine, Opipramol, trimipramine, lofepramine, dibenzepin, amitriptyline, nortriptyline, protriptyline, doxepin, iprindole, melitracen, butriptyline, dosulepin, amoxapine, dimetacrine, amineptine, maprotiline, quinupramine

SSRIs

zimeldine, fluoxetine, citalopram, paroxetine, sertraline, alaproclate, fluvoxamine, etoperidone, escitalopram

Monoamine oxidase inhibitors, non-selective

isocarboxazid, nialamide, phenelzine, tranylcypromine, iproniazide, iproclozide

Monoamine oxidase A inhibitors

moclobemide, toloxatone

other antidepressants

oxitriptan, tryptophan, mianserin, nomifensine, trazodone, nefazodone, minaprine, bifemelane, viloxazine, oxafluozane, mirtazapine, bupropion, medifoxamine, tianeptine, pivagabine, venlafaxine, milnacipran, reboxetine, gepirone, duloxetine, agomelatine, desvenlafaxine

Drugs listed as ADs in the current 17th version of New Pharmacy (新编药物学)

Amfetamine	苯丙胺	Methylphenidate	哌甲酯
Amitriptyline	阿米替林	Mianserin	米安色林
Amoxapine	阿莫沙平	Mirtazapine	米塔扎平
Atomoxetine	托莫西汀	Moclobemide	吗氯贝胺
Citalopram	西酞普兰	Nefazodone	萘法唑酮
Clomipramine	氯米帕明	Tianeptine	噻奈普汀
Duloxetine	度洛西汀	Toloxatone	托洛沙酮
Doxepin	多塞平	Trimipramine	曲米帕明
Escitalopram	艾司西酞普兰	Paroxetine	帕罗西汀
Fluoxetine	氟西汀	Pemoline	匹莫林
Fluvoxamine	氟伏沙明	Sertraline	舍曲林
Imipramine	丙咪嗪	Trazodone	曲唑酮
Isocarboxazid	异卡波肼	Venlafaxine	文拉法辛
Maprotiline	马普替林		

APPENDIX 2: SUBSTANCE AND TRADENAME FOR SSRIS

Substances	Tradenames for SSRIs
Fluoxetine 氟西汀	Prozac 百忧解 奥麦伦 奥贝汀 优克
Citalopram 西酞普兰	Cipramil 喜普妙 多弗
Escitalopram 艾司西酞普兰	Lexapro 来士普
Fluvoxamine 氟伏沙明 氟伏草胺	Luvox 兰释
Paroxetine 帕罗西汀	Seroxat Paxil 赛乐特
Sertraline 舍曲林	Zoloft 左洛复 郁乐复

APPENDIX 3: REFERENCES TO STUDIES EXCLUDED FROM THIS REVIEW

Exclusion Reason 1. not double-blind

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Exclusion Reason 5. no relevant control group

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Exclusion Reason 9. Crossover

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APPENDIX 4: ELECTRONIC SEARCH STRATEGY

CNKI:

(主题%抑郁 or 主题%depression) and (主题%fluoxetine or 主题%氟西汀 or 主题%prozac or 主题%百忧解 or 主题%奥麦伦 or 主题%奥贝汀 or 主题%优克 or 主题%citalopram or 主题%西酞普兰 or 主题%Cipramil or 主题%喜普妙 or 主题%多弗 or 主题%escitalopram or 主题%艾司西酞普兰 or 主题%Lexapro or 主题%来士普 or 主题% fluvoxamine or 主题%氟伏沙明 or 主题%氟伏草胺 or 主题%Luvox or 主题%兰释 or 主题%paroxetine or 主题%帕罗西汀 or 主题% Paxil or 主题%Seroxat or 主题%赛乐特 or 主题%sertraline or 主题%舍曲林 or 主题%Zoloft or 主题%左洛复 or 主题%郁乐复)

VIP:

R=(抑郁+depression)*R=(fluoxetine+氟西汀+prozac+百忧解+奥麦伦+奥贝汀+优克+citalopram+西酞普兰+Cipramil+喜普妙+多弗+escitalopram+艾司西酞普兰+Lexapro+来士普+fluvoxamine+氟伏沙明+氟伏草胺+Luvox+兰释+paroxetine+帕罗西汀+Paxil+Seroxat+赛乐特+sertraline+舍曲林+Zoloft+左洛复+郁乐复)

APPENDIX 5: CHARACTERISTICS OF INCLUDED STUDIES

Cai JY 2007

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17 ≥18 Baseline Values: HAMD score 22.4 ±3.2 (reboxetine), 22.6±3.6 (citalopram) Mean age: 32 years (reboxetine), 31 years (citalopram) Women: 47% (reboxetine), 45% (citalopram)
Interventions	Reboxetine 4-8 mg/d: N=32 Citalopram 10-20 mg/d: N=31
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Cao HJ 2008

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3, Age 18-55 HAMD-17 >18 Baseline Values: HAMD score 22.86 ±3.55 (bupropion), 22.71±3.67 (fluoxetine) Age: 18-55 years Women: 60% (bupropion), 58% (fluoxetine)
Interventions	Bupropion 300 mg/d: N=40 Fluoxetine 20 mg/d: N=40
Outcomes	HAMD, MAMA, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Chang SH 2006

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3, 60-70 HAMD≥24 Baseline Values: HAMD score 27.9 ±6.48 (sertraline), 28.61±6.73 (maprotiline) Mean age: 67 years (sertraline), 68 years (maprotiline) Women: 42% (sertraline), 45% (maprotiline)
Interventions	Sertraline 50-150 mg/d: N=31 Maprotiline 75-200 mg/d: N=31
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Chen EM 2010

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3, 18-60 HAMD-17 ≥18 Baseline Values: HAMD score 33.6 ±4.2 (venlafaxine ER), 32.3±4.6 (paroxetine) Mean age: 33 years (venlafaxine ER), 34 years (paroxetine) Women: 88% (venlafaxine ER), 85% (paroxetine)
Interventions	Venlafaxine ER 75-225 mg/d: N=40 Paroxetine 20-60 mg/d: N=40
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	41% items fulfilled

Chen LQ 2005

Methods	6 week double blind, double dummy RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 or DSM-IV HAMD ≥16 Baseline Values: HAMD score 27.7 ±6.23 (TCM), 27.1±5.65 (paroxetine) Mean age: 37 years (TCM), 34 years (paroxetine) Women: 36% (TCM), 37% (paroxetine)
Interventions	TCM 12 units/d: N=110 Paroxetine 20-40 mg/d: N=110
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	49% items fulfilled

Chen YH 2010

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17 ≥18, Age 60-75 Baseline Values: HAMD score 26.6 ±5.8 (escitalopram), 25.9±5.3 (mianserin) Mean age: 63 years (escitalopram), 63 years (mianserin) Women: 36% (escitalopram), 37% (mianserin)
Interventions	Escitalopram 5-15 mg/d: N=46 Mianserin 15-60 mg/d: N=46
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Du B 2007

Methods	6 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17 ≥17 and ≤28, Age 18-65 Baseline Values: HAMD score 20.49 ±2.6 (TCM), 20.5±2.28 (fluoxetine) Age: / Women: /
Interventions	TCM 1440 mg/d: N=360 Fluoxetine 20 mg/d: N=120
Outcomes	HAMD, HAMA, CGI
Informed consent	reported
Financial support	Not reported
CONSORT 2010	51% items fulfilled

Du XS 2007

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17 >18, Age 18-60 Baseline Values: HAMD score 30.1 ±4 (citalopram), 29.4±4.1 (fluoxetine) Mean age: 35 years (citalopram), 34 years (fluoxetine) Women: 44% (citalopram), 39% (fluoxetine)
Interventions	Citalopram 20 mg/d: N=36 Fluoxetine 20 mg/d: N=36
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Du XS 2009

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3 HAMD>18, Age >65 Baseline Values: HAMD score 27.6 ±5.6 (citalopram), 26.1±5.4 (sertraline) Age: / Women: 29% (citalopram), 36% (sertraline)
Interventions	Citalopram 20-40 mg/d: N=28 Sertraline 50-100 mg/d: N=28
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	38% items fulfilled

Du YM 2006

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18 Baseline Values: HAMD score 26.9 ±4.7 (fluoxetine), 26.8±5.2 (amitriptyline) Mean age: 40 years (fluoxetine), 36 years (amitriptyline) Women: 50% (fluoxetine), 50% (amitriptyline)
Interventions	Fluoxetine 20-40 mg/d: N=34 Amitriptyline 50-250 mg/d: N=34
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Fan HT 2007

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, PSD Baseline Values: HAMD score 25.38 ±5.25 (fluvoxamine), 26 ±5.63 (sertraline) Mean age: 55 years (fluvoxamine), 55 years (sertraline) Women: 43% (fluvoxamine), 48% (sertraline)
Interventions	Fluvoxamine N=46 Sertraline N=46
Outcomes	HAMD, MESSS, ADL
Informed consent	reported
Financial support	Not reported
CONSORT 2010	16% items fulfilled

Fang LQ 2007

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to DSM-IV HAMD-17≥18, PSD Baseline Values: HAMD score: / Mean age: 64 years (citalopram), 62 years (fluoxetine) Women: 35% (citalopram), 40% (fluoxetine)
Interventions	Citalopram 10-40 mg/d: N=20 Fluoxetine 20-40 mg/d: N=20
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	38% items fulfilled

Gao YL 2006

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 PSD Baseline Values: HAMD score: 27.98 $\pm$4.8 (fluoxetine), 28.12 $\pm$4.5 (amitriptyline) Mean age: 59 years (fluoxetine), 58 years (amitriptyline) Women: 51% (fluoxetine), 47% (amitriptyline)
Interventions	Fluoxetine 20 mg/d: N=37 Amitriptyline 50-175 mg/d: N=38
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Han GL 2006

Methods	6-8 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD>18, Age>60 Baseline Values: HAMD score: / Mean age: 65 years (amitriptyline), 62 years (fluoxetine) Women: 58% (amitriptyline), 60% (fluoxetine)
Interventions	Amitriptyline 50-200 mg/d: N=30 Fluoxetine 20-50 mg/d: N=30
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	reported
CONSORT 2010	41% items fulfilled
Notes	the third arm Fluoxetine+TCM was not extracted

Han ZL 2002

Methods	2 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-2-R Baseline Values: HAMD score: 23.7±12.8 (sertraline), 25.5±14.2 (fluoxetine), 24±14.4 (paroxetine) Age: 18-68 years, mean age 37.5 years Women: 63%
Interventions	Sertraline 59 ± 13 mg/d: N=26 Fluoxetine 23.6 ± 6.4 mg/d: N=23 Paroxetine 22.2 ± 4.4 mg/d: N=22
Outcomes	HAMD, HAMA, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled
Notes	$N_{randomized}$ not reported

Hong CJ 2003

Methods	6 week double blind RCT
Participants	Outpatients Inclusion criteria: Major Depression according to DSM-IV, HAMD-17≥15, Age 18-75 Baseline Values: HAMD score: 23.1±5.1 (mirtazapine), 24.3±5.2 (fluoxetine) Mean age: 47 years (mirtazapine), 47 (fluoxetine) Women: 62% (mirtazapine), 64% (fluoxetine)
Interventions	Mirtazapine 15-45 mg/d: N=66 Fluoxetine 20-40 mg/d: N=66
Outcomes	HAMD, CGI
Informed consent	reported
Financial support	reported
CONSORT 2010	62% items fulfilled
Notes	$N_{randomized}$ not reported for each group, English

Huang P 2006

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, PSD Baseline Values: HAMD score: 25.38±5.25 (citalopram), 26.05±5.63 (fluoxetine) Mean age: 55 years (citalopram), 57 years (fluoxetine) Women: 43% (citalopram), 48% (fluoxetine)
Interventions	Citalopram 20-40 mg/d: N=46 Fluoxetine 20-40 mg/d: N=46
Outcomes	HAMD, MESSS, ADL, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	46% items fulfilled

Hu MR 2009

Methods	6 week double blind RCT
Participants	Outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, Age 18-60 Baseline Values: HAMD score: 21.36±2.69 (escitalopram), 20.78±2.43 (citalopram) Mean age: 31 years (escitalopram), 31 years (citalopram) Women: 52% (escitalopram), 57% (citalopram)
Interventions	Escitalopram 10-20 mg/d: N=25 Citalopram 20-40 mg/d: N=23
Outcomes	HAMD, CGI
Informed consent	reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Jiang T 2010

Methods	6 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, Age 18-60 Baseline Values: HAMD score: 24±4 (nefazotone), 24±5 (fluoxetine) Age: 18-60 years (nefazotone), 18-60 years (fluoxetine) Women: 38% (nefazotone), 40% (fluoxetine)
Interventions	Nefazotone 300-500 mg/d: N=120 Fluoxetine 20-40 mg/d: N=120
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	51% items fulfilled

Jiang XY 2009

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, Age 18-60 Baseline Values: HAMD score: 23.82±2.53 (escitalopram), 23.46±2.06 (citalopram) Mean age: 39 years (escitalopram), 39 years (citalopram) Women: 56% (escitalopram), 53% (citalopram)
Interventions	Escitalopram 5-20 mg/d: N=32 Citalopram 20-60 mg/d: N=32
Outcomes	HAMD, HAMA, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	46% items fulfilled

Kong YB 2004

Methods	8 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, PSD Baseline Values: HAMD score: / Mean age: 63 years (citalopram), 62 years (amitriptyline) Women: 38% (citalopram), 43% (amitriptyline)
Interventions	Citalopram 10-40 mg/d: N=21 Amitriptyline 25-150 mg/d: N=21
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Li B 1996

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to ICD-10 HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 26.9$\pm$4.7 (sertraline), 26.8$\pm$5.2 (amitriptyline) Mean age: 40 years (sertraline), 36 years (amitriptyline) Women: 50% (sertraline), 49% (amitriptyline)
Interventions	Sertraline 50-200 mg/d: N=68 Amitriptyline 50-250 mg/d: N=68
Outcomes	HAMD, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Li GJ 2005

Methods	6 week double blind, double-dummy RCT
Participants	Outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 21.6±2.6 (bupropion), 22.5±4 (fluoxetine) Mean age: 41 years (bupropion), 40 years (fluoxetine) Women: 67% (bupropion), 63% (fluoxetine)
Interventions	Bupropion 150 mg/d: N=30 Fluoxetine 20 mg/d: N=30
Outcomes	HAMD, CGI, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	51% items fulfilled

Li HF 2006

Methods	6 week double blind, double-dummy RCT
Participants	Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 27.46±5.56 (bupropion), 26.8±5.46 (fluoxetine) Mean age: 38 years (bupropion), 41 years (fluoxetine) Women: 51% (bupropion), 53% (fluoxetine)
Interventions	Bupropion 300 mg/d: N=104 Fluoxetine 20 mg/d: N=104
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Li HF 2007

Methods	6 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, HAMA≥14, Age 18-65 Baseline Values: HAMD score: 26.28±4.64 (reboxetine), 26.16±4.86 (fluoxetine) Mean age: 39 years (reboxetine), 38 years (fluoxetine) Women: 55% (reboxetine), 63% (fluoxetine)
Interventions	Reboxetine 8 mg/d: N=67 Fluoxetine 20 mg/d: N=70
Outcomes	HAMD, HAMA, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Li J 2006

Methods	6 week double blind RCT
Participants	Outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 22.5±2.9 (escitalopram), 21.1±2.4 (citalopram) Mean age: 37 years (escitalopram), 34 years (citalopram) Women: 54% (escitalopram), 54% (citalopram)
Interventions	Escitalopram 10-20 mg/d: N=28 Citalopram 20-40 mg/d: N=28
Outcomes	HAMD, CGI, HAMA
Informed consent	reported
Financial support	Not reported
CONSORT 2010	62% items fulfilled

Li J 2007

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to ICD-10 HAMD-17≥20, Age 18-60, refractory depression Baseline Values: HAMD score: 32.8±4.8 (mirtazapine), 32.8±4.8 (paroxetine) Mean age: 34 years (mirtazapine), 33 years (paroxetine) Women: 85% (mirtazapine), 83% (paroxetine)
Interventions	Mirtazapine 30 mg/d: N=40 Paroxetine 20 mg/d: N=40
Outcomes	HAMD, TESS, QOL
Informed consent	reported
Financial support	Not reported
CONSORT 2010	41% items fulfilled

Li LJ 2010

Methods	8 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-24>18 Baseline Values: HAMD score: 22.36±5.82 (TCM), 23.38±5.64 (fluoxetine) Age: 54-78 years (TCM), 58-72 years (fluoxetine) Women: 53% (TCM), 57% (fluoxetine)
Interventions	TCM 4.05 g/d: N=30 Fluoxetine 20 mg/d: N=30
Outcomes	HAMD, MMSE, CGI, NDS
Informed consent	Not reported
Financial support	reported
CONSORT 2010	49% items fulfilled

Li N 2006

Methods	4 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD>14, Age 55-70 Baseline Values: HAMD score: 19.82±7.83 (reboxetine), 18.96±9.71 (fluoxetine) Mean age: 64 years (reboxetine), 65 years (fluoxetine) Women: 40% (reboxetine), 47% (fluoxetine)
Interventions	Reboxetine 4-8 mg/d: N=30 Fluoxetine 20-40 mg/d: N=30
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Li N 2007

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18 Baseline Values: HAMD score: 22.4±3.9 (duloxetine), 23±4.3 (fluoxetine) Mean age: 38 years (duloxetine), 37 years (fluoxetine) Women: 56% (duloxetine), 59% (fluoxetine)
Interventions	Duloxetine 30-60 mg/d: N=34 Fluoxetine 10-20 mg/d: N=34
Outcomes	HAMD, HAMA, CGI, AE
Informed consent	reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Li XX 2010

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depression according to CCMD-3 Age 18-65 Baseline Values: HAMD score: / Age: 18-65 Women: /
Interventions	Escitalopram 10-20 mg/d: N=24 Citalopram 20-40 mg/d: N=24
Outcomes	HAMD, CGI
Informed consent	reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Lu XJ 2008

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18 Baseline Values: HAMD score: 27.4±4.1 (venlafaxine), 28.6±3.8 (paroxetine) Mean age: 41 years (venlafaxine), 40 years (paroxetine) Women: 55% (venlafaxine), 56% (paroxetine)
Interventions	Venlafaxine 50-250 mg/d: N=88 Paroxetine 20-40 mg/d: N=82
Outcomes	HAMD, HAMA, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	41% items fulfilled

Luo HC 2003

Methods	6 week double blind, double dummy RCT
Participants	Outpatients Inclusion criteria: Depression according to DSM-IV, ICD-10 HAMD≥20, Age 18-65 Baseline Values: HAMD score: 22.42±2.93 (TCM), 22.16±2.16 (fluoxetine), 22.84±3.47 (placebo) Mean age:30 years (TCM), 34 (fluoxetine), 32 (placebo) Women: 58%
Interventions	TCM: N=31 Fluoxetine 20 mg/d: N=32 Placebo: N=32
Outcomes	HAMD, SERS, SDS, CGI
Informed consent	reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Ma X 2007

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥17, PSD Baseline Values: HAMD score: 31.12±2.23 (TCM), 31.05±2.07 (fluoxetine) Mean age: 57 years (TCM), / years (fluoxetine) Women: 52% (TCM), / (fluoxetine)
Interventions	TCM: N=42 Fluoxetine 20 mg/d: N=35
Outcomes	HAMD
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Mao PX 2008

Methods	8 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to DSM-IV HAMD-17≥18, CGI-S≥4, Age 18-65 Baseline Values: HAMD: 24.7±5.4 (escitalopram), 24.1±4.5 (fluoxetine) Mean age: 37 years (escitalopram), 41 (fluoxetine) Women: 50% (escitalopram), 63% (fluoxetine)
Interventions	Escitalopram 10 mg/d: N=123 Fluoxetine 20 mg/d: N=117
Outcomes	HAMD, MADRS
Informed consent	Not reported
Financial support	Reported (by Pharmaceutical Company)
CONSORT 2010	73% items fulfilled
Notes	English and design in accordance with the regulations of the Chinese State Food and Drug Administration on clinical trial guidelines for imported drugs

Mao PX 2010

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to DSM-IV HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 23±3 (reboxetine), 22±3 (fluoxetine) Mean age: 38 years (reboxetine), 39 years (fluoxetine) Women: 54% (reboxetine), 64% (fluoxetine)
Interventions	Reboxetine 4-8 mg/d: N=120 Fluoxetine 10-20 mg/d: N=120
Outcomes	HAMD, HAMA, CGI-I, CGI-S
Informed consent	reported
Financial support	Not reported
CONSORT 2010	54% items fulfilled

Meng Y 2002

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-2-R HAMD≥24, Age ≥60 Baseline Values: HAMD score: 26.8±4.8 (sertraline), 26.8±5 (amitriptyline) Mean age: 68 years (sertraline), 70 years (amitriptyline) Women: 42% (sertraline), 47% (amitriptyline)
Interventions	Sertraline 50-150 mg/d: N=19 Amitriptyline 50-200 mg/d: N=21
Outcomes	HAMD, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Ou HX 2001

Methods	6 week double blind, double dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-2-R HAMD-17≥18, Age 18-64 Baseline Values: HAMD score: 28.9±5.5 (venlafaxine), 28.4±4.6 (fluoxetine) Age: 18-64 years Women: /
Interventions	Venlafaxine: N=15 Fluoxetine: N=15
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Peng YX 2007

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, PSD Baseline Values: HAMD score: / Mean age: 64 years (fluoxetine), 64 (amitriptyline) Women: 38% (fluoxetine), 43% (amitriptyline)
Interventions	Fluoxetine 10-40 mg/d: N=21 Amitriptyline 25-150 mg/d: N=21
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Qu M 2007

Methods	6 week double blind RCT
Participants	Outpatients Inclusion criteria: Depression according to CCMD-3 HAMD≤35, Age ≤65 Baseline Values: HAMD score: 24.52±3.95 (TCM), 21.35±6.76 (fluoxetine) Age: 21-65 years, mean age 42 years Women: 60%
Interventions	TCM: N=38 Fluoxetine 20 mg/d: N=35
Outcomes	HAMD
Informed consent	Not reported
Financial support	reported
CONSORT 2010	49% items fulfilled

Shi SX 1997

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depression according to CCMD-2, DSM-III-R HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 27.43±5.32 (paroxetine), 28.23±5.49 (amitriptyline) Mean age: 39 years (paroxetine), 42 years (amitriptyline) Women: 41% (paroxetine), 30% (amitriptyline)
Interventions	Paroxetine 20-30 mg/d: N=32 Amitriptyline 175 mg/d: N=33
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	41% items fulfilled

Shu DH 2004

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to ICD-10 HAMD-21≥22, Age >65 Baseline Values: HAMD score: 31.3±4.3 (paroxetine), 30.7±3.9 (amitriptyline) Mean age: 39 years (paroxetine), 42 years (amitriptyline) Women: 41% (paroxetine), 30% (amitriptyline)
Interventions	Paroxetine 20 mg/d: N=19 Amitriptyline 50 mg/d: N=19
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	27% items fulfilled

Sun SH 2001

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-2-R HAMD-17≥18 Baseline Values: HAMD score: 28.82±7.01 (fluoxetine), 27.96±6.64 (doxepin) Mean age: 37 years
Interventions	Fluoxetine 20-40 mg/d: N=30 Doxepin 50-150 mg/d: N=30
Outcomes	HAMD, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Sun XL 1997

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-2-R, HAMD≥17 Baseline Values: HAMD score: 25.53±4.58 (paroxetine), 24±4.9 (sertraline), 25.13±5.27 (amitriptyline) Mean age: 39 years (paroxetine), 32 (sertraline), 35 (amitriptyline) Women: 29% (paroxetine), 29% (sertraline), 53% (amitriptyline)
Interventions	Paroxetine 20-30 mg/d: N=17 Sertraline 20-40 mg/d: N=17 Amitriptyline 140-210 mg/d: N=19
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	43% items fulfilled

Tan XG 2004

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3, HAMD-17>18, Age>65 Baseline Values: HAMD score: 30.5±2.1 (citalopram), 31.2±2.3 (amitriptyline) Mean age: 68 years (citalopram), 69 (amitriptyline) Women: 28% (citalopram), 23% (amitriptyline)
Interventions	Citalopram 20-40 mg/d: N=25 Amitriptyline 100-200 mg/d: N=26
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Wang XQ 2009

Methods	6 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to ICD-10 HAMD-17>17 and ≤24, Age 18-65 Baseline Values: HAMD score: 20.9±1.9 (TCM high), 20.8±2 (TCM), 20.9±2 (fluoxetine) Mean age: 40 y (TCM high), 40 (TCM), 40 (fluoxetine) Women: 56% (TCM high), 61% (TCM), 53% (fluoxetine)
Interventions	TCM high 400 or 800 mg/d: N=119 TCM 300 or 600 mg/d: N=121 Fluoxetine 20-30 mg/d: N=121
Outcomes	HAMD, CGI
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	49% items fulfilled

Wei J 2008

Methods	8 week double blind RCT
Participants	In- and outpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17≥18, PSD Baseline Values: HAMD score: 28.4±3.1 (citalopram), 27.8±4.6 (amitriptyline) Mean age: 63 years (citalopram), 62 years (amitriptyline) Women: 38% (citalopram), 43% (amitriptyline)
Interventions	Citalopram 10-40 mg/d: N=21 Amitriptyline 50-250 mg/d: N=21
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Wu Y 2009

Methods	6 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18 and HAMA≥14, Age 18-65 Baseline Values: HAMD score: / Mean age: / Women: /
Interventions	Bupropion 300 mg/d: N=89 Fluoxetine 20 mg/d: N=80
Outcomes	HAMD, HAMA, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	46% items fulfilled

Xiang H 1998

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depressive episode according to CCMD-2-R HAMD>18, Age 18-65 Baseline Values: HAMD score: 27.6±1.93 (paroxetine), 26.9±1.72 (amitriptyline) Mean age: 37 years (paroxetine), 35 years (amitriptyline) Women: 53% (paroxetine), 57% (amitriptyline)
Interventions	Paroxetine 20-40 mg/d: N=30 Amitriptyline 25-250 mg/d: N=30
Outcomes	HAMD, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Xiao JS 2005

Methods	8 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to CCMD-3, ICD-10 PSD Baseline Values: HAMD score: 20.8±3.7 (TCM), 21.4±2.2 (fluoxetine) Age: 22-80 years Women: 33%
Interventions	TCM 1000-2000 mg/d: N=52 Fluoxetine 20-40 mg/d: N=50
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Xie GR 1998

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-2-R, DSM-III-R HAMD-21≥18, Age 18-65 Baseline Values: HAMD score: 27±5.24 (paroxetine), 26.96±5.16 (amitriptyline) Mean age: 37 years (paroxetine), 38 years (amitriptyline) Women: 39% (paroxetine), 50% (amitriptyline)
Interventions	Paroxetine 20-30 mg/d: N=44 Amitriptyline 25-175 mg/d: N=46
Outcomes	HAMD, HAMA, CGI, TESS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	41% items fulfilled

Xie SY 2008

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3 HAMD-17>18, first episode depression, Age 18-60 Baseline Values: HAMD score: 28.7±6.4 (sertraline), 27.3±5.8 (fluoxetine) Mean age: 35 years (sertraline), 33 years (fluoxetine) Women: 44% (sertraline), 39% (fluoxetine)
Interventions	Sertraline 50 mg/d: N=36 Fluoxetine 20 mg/d: N=36
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	49% items fulfilled

Xu YC 1998

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depression according to CCMD-2, DSM-III-R HAMD-17≥18, Age 18-65 Baseline Values: HAMD score: 27.43±5.32 (sertraline), 28.23±5.49 (amitriptyline) Mean age: / Women: /
Interventions	Sertraline 50-200 mg/d: N=32 Amitriptyline 50-250 mg/d: N=33
Outcomes	HAMD, CGI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Xun GL 2009

Methods	6 week double blind, double-dummy RCT
Participants	In- and outpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥17, Age 18-65 Baseline Values: HAMD score: 23±4 (escitalopram), 23±4 (citalopram) Mean age: 37 years (escitalopram), 36 years (citalopram) Women: 56% (escitalopram), 53% (citalopram)
Interventions	Escitalopram 10-20 mg/d: N=120 Citalopram 20-40 mg/d: N=120
Outcomes	HAMD, CGI
Informed consent	reported
Financial support	Not reported
CONSORT 2010	51% items fulfilled

You NX 2000

Methods	4 week double blind RCT
Participants	Inclusion criteria: Depression according to CCMD-II-R HAMD≥17, SDS≥53 Baseline Values: HAMD score: 25.5±7.4 (citalopram), 24.2±2.3 (fluoxetine) Age: 20-60 years Women: 69%
Interventions	Citalopram 20 mg/d: N=36 Fluoxetine 20 mg/d: N=36
Outcomes	HAMD, SDS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	22% items fulfilled

Yu MH 1996

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-2-R, DSM-III-R HAMD-17>20, Age≥55 Baseline Values: HAMD score: 39.22±2.86 (fluoxetine), 38.81±4.29 (amitriptyline) Mean age: 64 years (fluoxetine), 60 years (amitriptyline) Women: 44% (fluoxetine), 50% (amitriptyline)
Interventions	Fluoxetine 20-80 mg/d: N=9 Amitriptyline 100-300 mg/d: N=16
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	30% items fulfilled

Yu XL 2004

Methods	4 week double blind RCT
Participants	Inclusion criteria: Depressive episode according to CCMD-3 HAMD-24≥18, PSD Baseline Values: HAMD score: 29.67±8.24 (citalopram), 31.02±8.82 (amitriptyline) Age: 36-69 years, mean age 50 years Women: 42%
Interventions	Citalopram 40 mg/d: N=30 Amitriptyline 150 mg/d: N=30
Outcomes	HAMD, ADL, SSS, ASBS
Informed consent	reported
Financial support	Not reported
CONSORT 2010	24% items fulfilled

Zhang XL 2000

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depression according to CCMD-2-R HAMD-17≥18 Baseline Values: HAMD score: 26.9±4.7 (paroxetine), 26.7±5.1 (amitriptyline) Mean age: 40 years (paroxetine), 41 years (amitriptyline) Women: 45% (paroxetine), 48% (amitriptyline)
Interventions	Paroxetine 20 mg/d: N=31 Amitriptyline 75 mg/d: N=31
Outcomes	HAMD, CGI-SI, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Zhang YL 2007

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depressive episode according to CCMD-3 HAMD-17≥18, Age 20-60 Baseline Values: HAMD score: 21.92±3.4 (citalopram), 28.96±6.9 (fluoxetine) Mean age: 37 years (citalopram), 37 years (fluoxetine) Women: 50% (citalopram), 53% (fluoxetine)
Interventions	Citalopram 10-40 mg/d: N=30 Fluoxetine 40-80 mg/d: N=30
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

Zhang Z 2001

Methods	6 week double blind RCT
Participants	Inclusion criteria: Depressive episode according to CCMD-2-R HAMD-17≥18, PSD Baseline Values: HAMD score: 30.5±4.2 (sertraline), 31.4±4 (amitriptyline) Mean age: 62 years Women: 45%
Interventions	Sertraline 50-100 mg/d: N=31 Amitriptyline 75-225 mg/d: N=31
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	35% items fulfilled

Zhou J 2005

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD-3 HAMD-24>26 Baseline Values: HAMD score: 54.26±5.34 (paroxetine), 53.58±5.32 (imipramine) Mean age: 35 years (paroxetine), 37 years (imipramine) Women: 43% (paroxetine), 33% (imipramine)
Interventions	Paroxetine 20 mg/d: N=30 Imipramine 50-275 mg/d: N=30
Outcomes	HAMD, HAMA, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	32% items fulfilled

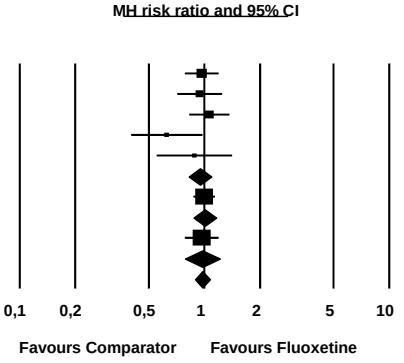
Zhu GK 2005

Methods	6 week double blind RCT
Participants	Inpatients Inclusion criteria: Depression according to CCMD HAMD>18, Age>65 Baseline Values: HAMD score: 27.6±1.9 (citalopram), 26.7±1.7 (maprotiline) Mean age: 69 years (citalopram), 70 (maprotiline) Women: 40% (citalopram), 53% (maprotiline)
Interventions	Citalopram 20-40 mg/d: N=30 Maprotiline 25 mg/d: N=30
Outcomes	HAMD, TESS
Informed consent	Not reported
Financial support	Not reported
CONSORT 2010	27% items fulfilled

APPENDIX 6: DATA AND ANALYSES

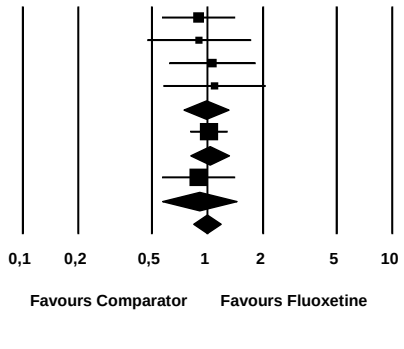
Analysis 1.1. Comparison 1 Fluoxetine versus any other SSRIs Response rate (with Overall effects and effects in subgroups)

Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Citalopram	Du XS 2007	29 / 36	30 / 36	0,97	0,78	1,20
	Fang LQ 2007	16 / 20	17 / 20	0,94	0,71	1,25
	Huang P 2006	34 / 46	32 / 46	1,06	0,82	1,37
	You NX 2000	15 / 36	24 / 36	0,63	0,40	0,98
	Zhang YL 2007	15 / 30	17 / 30	0,88	0,55	1,42
Citalopram		109 / 168	120 / 168	0,94	0,81	1,08
Escitalopram	Mao PX 2008	89 / 117	94 / 123	1,00	0,86	1,15
Escitalopram		89 / 117	94 / 123	1,00	0,86	1,15
Sertraline	Xie SY 2008	29 / 36	30 / 36	0,97	0,78	1,20
Sertraline		29 / 36	30 / 36	0,97	0,78	1,20
Overall		227 / 321	244 / 327	0,97	0,88	1,06



Analysis 1.2. Comparison 1 Fluoxetine versus any other SSRIs Remission rate (with Overall effects and effects in subgroups)

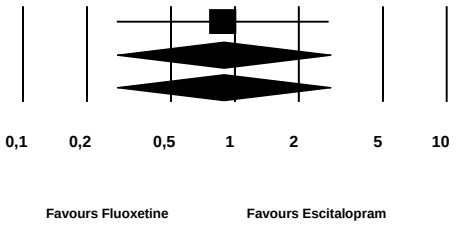
Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Citalopram	Du XS 2007	17 / 36	19 / 36	0,89	0,56	1,42
	Fang LQ 2007	9 / 20	10 / 20	0,90	0,47	1,73
	Huang P 2006	17 / 46	16 / 46	1,06	0,61	1,84
	Zhang YL 2007	12 / 30	11 / 30	1,09	0,57	2,07
Citalopram		55 / 132	56 / 132	0,97	0,74	1,29
Escitalopram	Mao PX 2008	62 / 117	64 / 123	1,02	0,80	1,30
Escitalopram		62 / 117	64 / 123	1,02	0,80	1,30
Sertraline	Xie SY 2008	17 / 36	19 / 36	0,89	0,56	1,42
Sertraline		17 / 36	19 / 36	0,89	0,56	1,42
Overall		134 / 285	139 / 291	0,98	0,83	1,17



Analysis 1.3. Comparison 1 Fluoxetine versus any other SSRIs

Dropout rate due to side effects (with Overall effects and effects in subgroups)

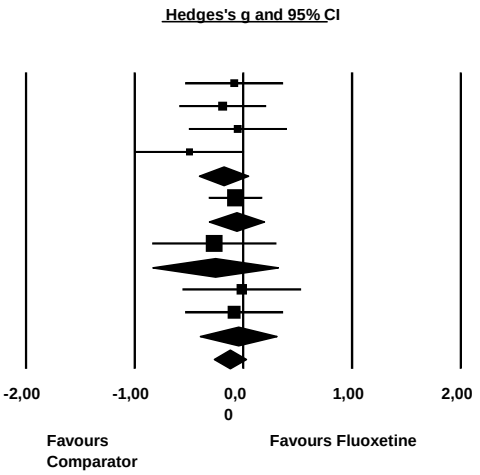
Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Escitalopram	Mao PX 2008	5 / 117	6/ 123	0,88	0,27	2,79
Escitalopram		5 / 117	6/ 123	0,88	0,27	2,79
Overall		5 / 117	6/ 123	0,88	0,27	2,79



Analysis 1.4. Comparison 1 Fluoxetine versus any other SSRIs

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

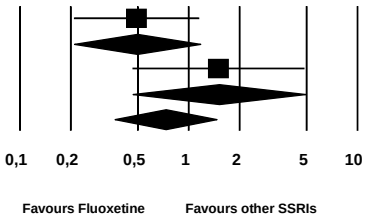
Group by Comparator	Study name	Outcome	Sample size		Statistics for each study		
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
Citalopram	Du XS 2007		36	36	-0,08	-0,54	0,37
	Huang P 2006		46	46	-0,19	-0,60	0,22
	You NX 2000		36	36	-0,05	-0,51	0,41
	Zhang YL 2007		30	30	-0,50	-1,00	0,01
Citalopram			148	148	-0,19	-0,42	0,04
Escitalopram	MaoPX 2008		123	117	-0,07	-0,32	0,18
Escitalopram			123	117	-0,07	-0,32	0,18
Paroxetine	Han ZL 2002	HAMD_flx_parox	22	23	-0,27	-0,84	0,31
Paroxetine			22	23	-0,27	-0,84	0,31
Sertraline	Han ZL 2002	HAMD_flx_sertr	26	23	-0,01	-0,57	0,54
	Xie SY 2008		36	36	-0,08	-0,54	0,37
Sertraline			62	59	-0,06	-0,41	0,30
Overall			355	347	-0,13	-0,28	0,02



Analysis 1.5. Comparison 1 Fluoxetine versus any other SSRIs

Dropout rate overall (with Overall effects and effects in subgroups)

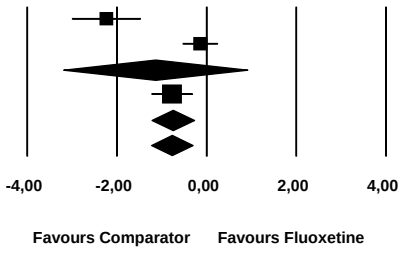
Group by Comparator		Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Escitalopram	Mao PX 2008	7 / 117	15 / 123	0,49	0,21	1,16
Escitalopram		7 / 117	15 / 123	0,49	0,21	1,16
Sertraline	Xie SY 2008	6 / 36	4 / 36	1,50	0,46	4,87
Sertraline		6 / 36	4 / 36	1,50	0,46	4,87
Overall		13 / 153	19 / 159	0,72	0,36	1,45



Analysis 1.6. Comparison 1 Fluoxetine versus any other SSRIs

Total TESS scores (with Overall effects and effects in subgroups)

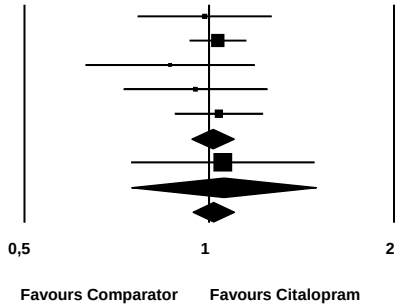
Group by Comparator	Study name	Sample size		Statistics for each study		
		Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
Citalopram	Fang LQ 2007	20	20	-2,23	-3,01	-1,45
	Huang P 2006	46	46	-0,14	-0,55	0,26
Citalopram		66	66	-1,16	-3,21	0,89
Sertraline	Xie SY 2008	36	36	-0,77	-1,24	-0,30
Sertraline		36	36	-0,77	-1,24	-0,30
Overall		102	102	-0,79	-1,25	-0,33



Analysis 2.1. Comparison 2 Citalopram versus any other SSRIs

Response rate (with Overall effects and effects in subgroups)

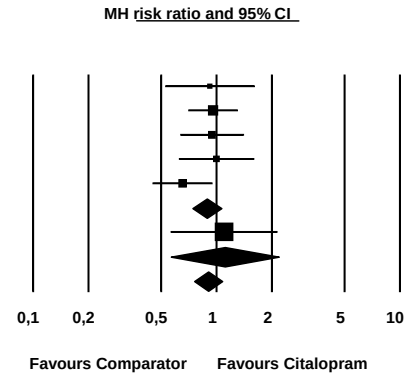
Group by Comparator	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Escitalopram	Hu MR 2009	19 / 23	21 / 25	0,98	0,76	1,27
	Jiang XY 2009	31 / 32	30 / 32	1,03	0,93	1,15
	Li J 2006	19 / 28	22 / 28	0,86	0,63	1,19
	Li XX 2010	19 / 24	20 / 24	0,95	0,72	1,25
	Xun GL 2009	85 / 120	82 / 120	1,04	0,88	1,23
Escitalopram		173 / 227	175 / 229	1,01	0,93	1,09
Sertraline	Du XS 2009	20 / 28	19 / 28	1,05	0,74	1,49
Sertraline		20 / 28	19 / 28	1,05	0,74	1,49
Overall		193 / 255	194 / 257	1,01	0,94	1,09



Analysis 2.2. Comparison 2 Citalopram versus any other SSRIs

Remission rate (with Overall effects and effects in subgroups)

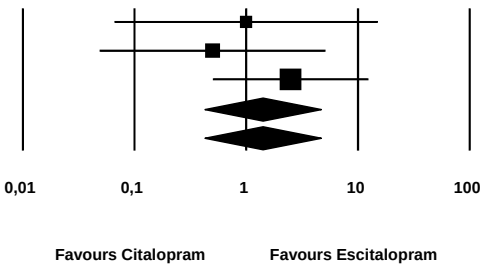
Group by Comparator	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Escitalopram	Hu MR 2009	11 / 23	13 / 25	0,92	0,52	1,63
	Jiang XY 2009	22 / 32	23 / 32	0,96	0,70	1,32
	Li J 2006	17 / 28	18 / 28	0,94	0,63	1,42
	Li XX 2010	14 / 24	14 / 24	1,00	0,62	1,61
	Xun GL 2009	30 / 120	46 / 120	0,65	0,44	0,96
Escitalopram		94 / 227	114 / 229	0,88	0,73	1,05
Sertraline	Du XS 2009	11 / 28	10 / 28	1,10	0,56	2,17
Sertraline		11 / 28	10 / 28	1,10	0,56	2,17
Overall		105 / 255	124 / 257	0,89	0,75	1,06



Analysis 2.3. Comparison 2 Citalopram versus any other SSRIs

Dropout rate due to side effects (with Overall effects and effects in subgroups)

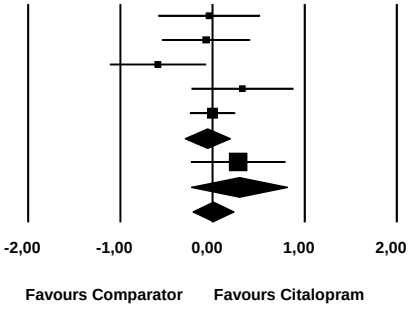
Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Escitalopram	Jiang XY 2009	1 / 32	1 / 32	1,00	0,07	15,30
	Li J 2006	1 / 28	2 / 28	0,50	0,05	5,20
	XunGL 2009	5/ 120	2 / 120	2,50	0,49	12,64
Escitalopram		7/ 180	5 / 180	1,38	0,42	4,56
Overall		7/ 180	5 / 180	1,38	0,42	4,56



Analysis 2.4. Comparison 2 Citalopram versus any other SSRIs

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

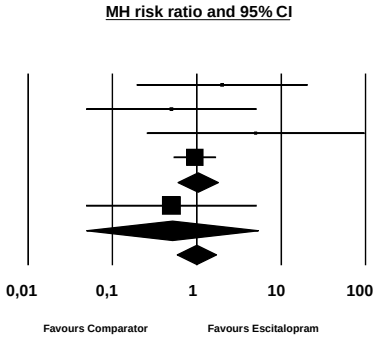
Group by Comparator	Study name	Sample size		Statistics for each study		
		Comparato	Experimentor	Hedges's g	Lower limit	Upper limit
Escitalopram	Hu MR 2009	25	23	-0,04	-0,59	0,52
	Jiang XY 2009	32	32	-0,07	-0,55	0,41
	Li J 2006	28	28	-0,59	-1,12	-0,06
	Li XX 2010	24	24	0,33	-0,24	0,89
	Xun GL 2009	120	120	0,00	-0,25	0,25
Escitalopram		229	227	-0,06	-0,31	0,18
Sertraline	Du XS 2009	28	28	0,28	-0,24	0,80
Sertraline		28	28	0,28	-0,24	0,80
Overall		257	255	-0,00	-0,22	0,22



Analysis 2.5. Comparison 2 Citalopram versus any other SSRIs

Dropout rate overall (with Overall effects and effects in subgroups)

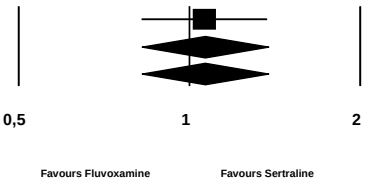
Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Escitalopram	Jiang XY 2009	2 / 32	1 / 32	2,00	0,19	20,97
	Li J 2006	1 / 28	2 / 28	0,50	0,05	5,20
	Li XX 2010	2 / 24	0 / 24	5,00	0,25	98,96
	Xun GL 2009	18 / 120	19 / 120	0,95	0,52	1,71
Escitalopram		23 / 204	22 / 204	1,01	0,58	1,74
Sertraline	Du XS 2009	1 / 28	2 / 28	0,50	0,05	5,20
Sertraline		1 / 28	2 / 28	0,50	0,05	5,20
Overall		24 / 232	24 / 232	0,97	0,57	1,66



Analysis 3.1. Comparison 3 Sertraline versus any other SSRIs

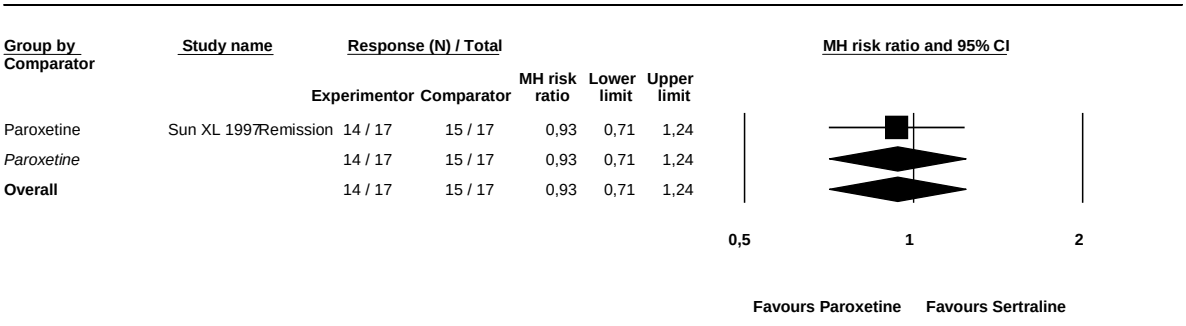
Response rate (with Overall effects and effects in subgroups)

Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Fluvoxamine	Fan HT 2007	34 / 46	32 / 46	1,06	0,82	1,37
Fluvoxamine		34 / 46	32 / 46	1,06	0,82	1,37
Overall		34 / 46	32 / 46	1,06	0,82	1,37



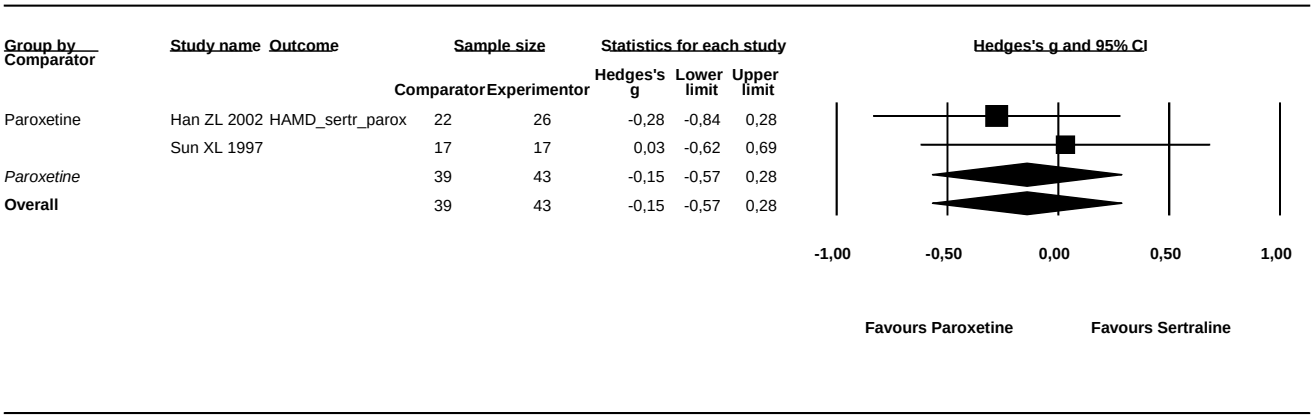
Analysis 3.2. Comparison 3 Sertraline versus any other SSRIs

Remission rate (with Overall effects and effects in subgroups)



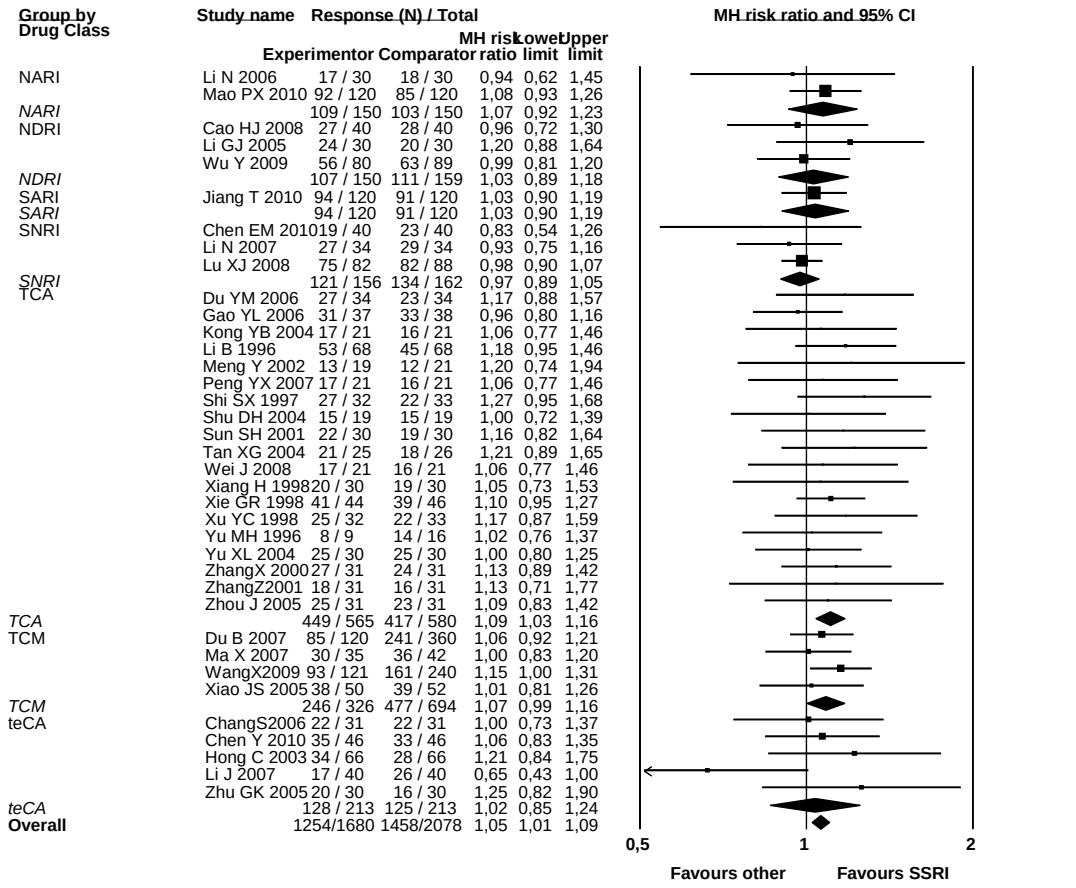
Analysis 3.3. Comparison 3 Sertraline versus any other SSRIs

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



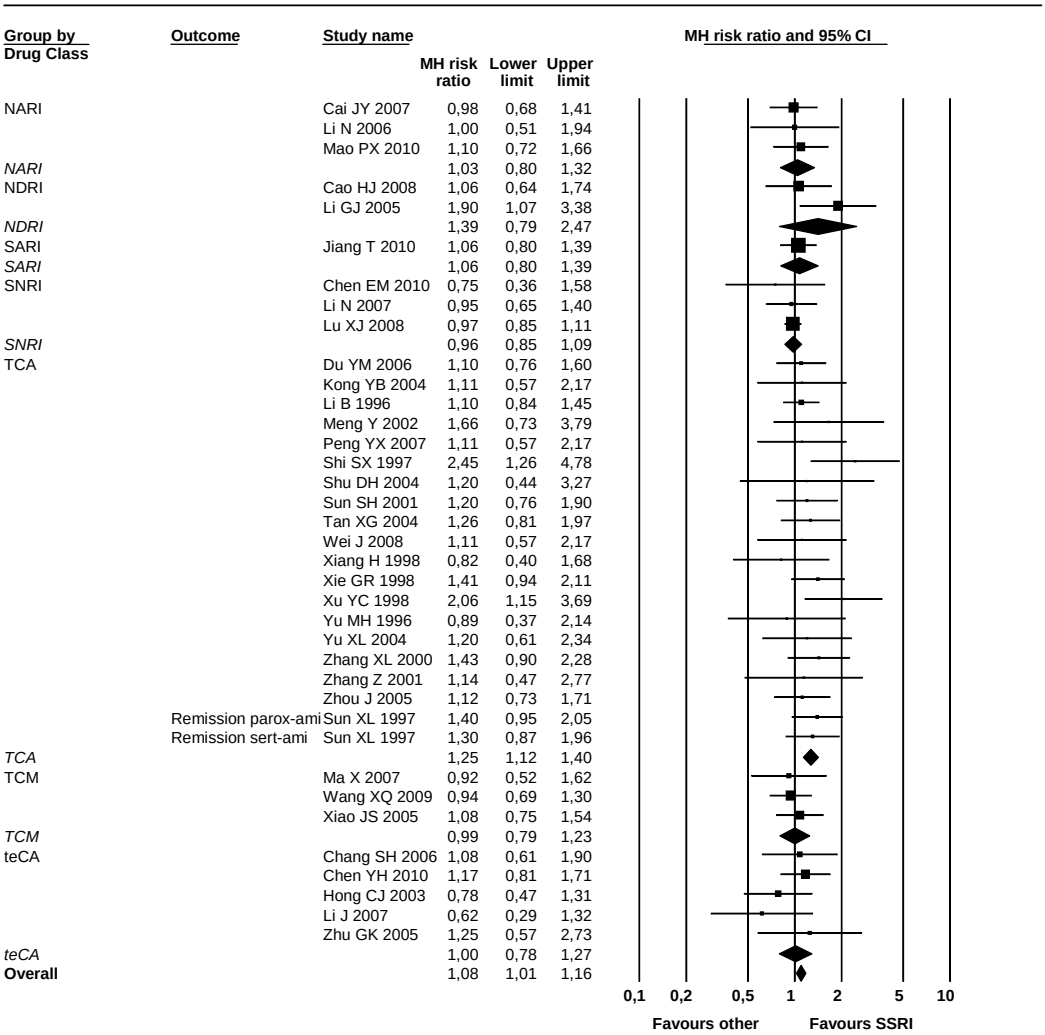
Analysis 4.1. Comparison 4 SSRI versus any other drug classes

Response rate (with Overall effects and effects in subgroups)



Analysis 4.2. Comparison 4 SSRI versus any other drug classes

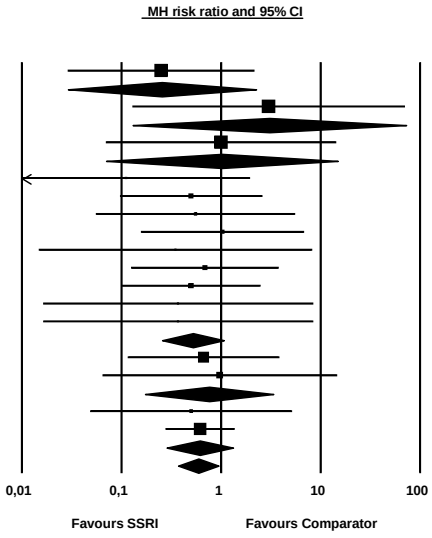
Remission rate (with Overall effects and effects in subgroups)



Analysis 4.3. Comparison 4 SSRI versus any other drug classes

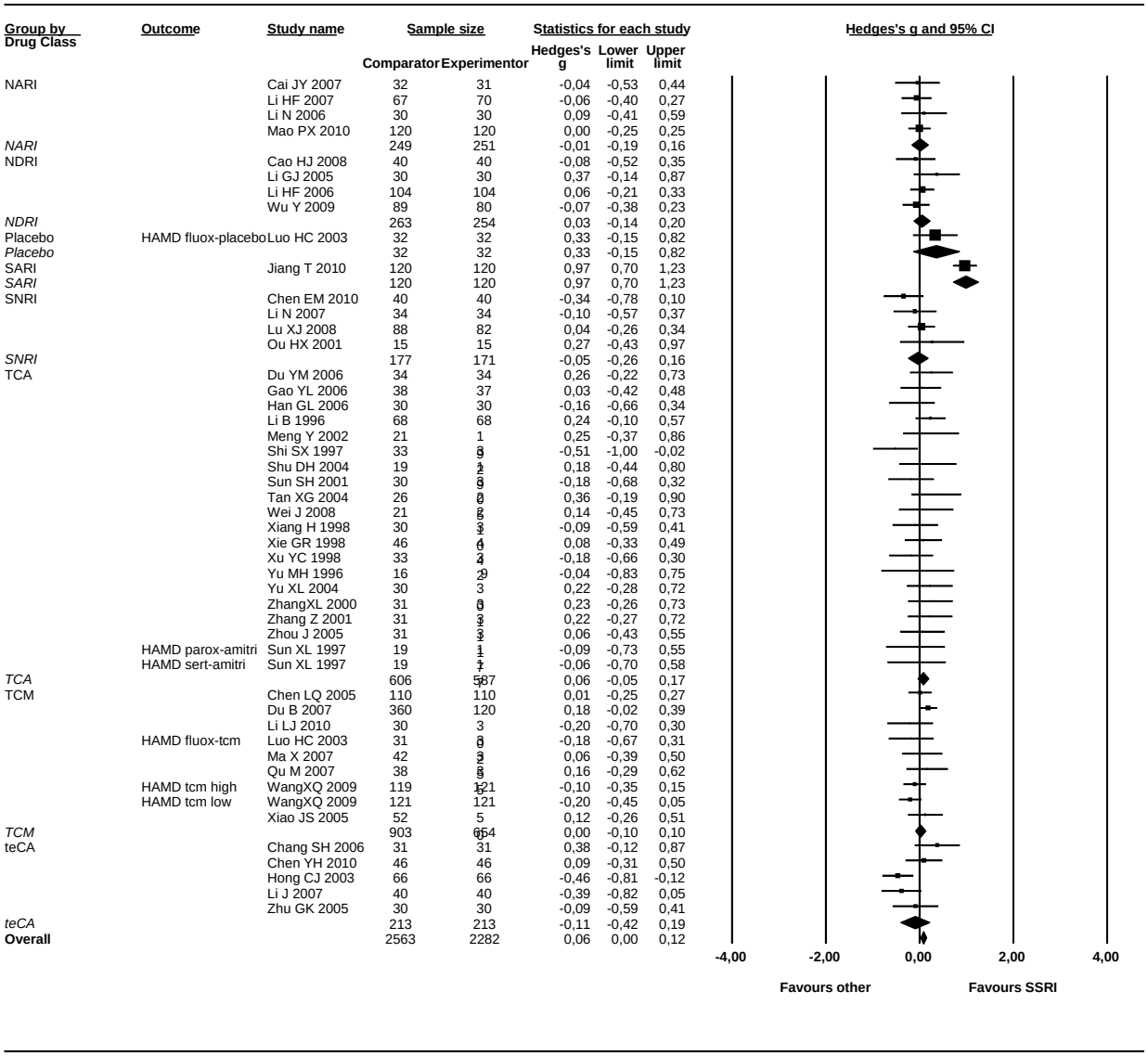
Dropout rate due to side effects (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimentor	Comparator			
NARI		Mao PX 2010	1 / 120	4 / 120	0,25	0,03	2,20
NARI			1 / 120	4 / 120	0,25	0,03	2,20
Placebo	Dropout side effects fluo-placebo	Luo HC 2003	1 / 32	0 / 32	3,00	0,13	71,00
Placebo			1 / 32	0 / 32	3,00	0,13	71,00
SNRI		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
SNRI			1 / 15	1 / 15	1,00	0,07	14,55
TCA		Han GL 2006	0 / 30	4 / 30	0,11	0,01	1,98
		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
		Shi SX 1997	2 / 32	2 / 33	1,03	0,15	6,89
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout side effects parox-amitri	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
	Dropout side effects sert-amitri	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
TCA			9 / 290	22 / 300	0,51	0,25	1,05
TCM		Chen LQ 2005	2 / 110	3 / 110	0,67	0,11	3,91
	Dropout side effects fluox-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
TCM			3 / 142	4 / 141	0,74	0,17	3,29
teCA		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
		Hong CJ 2003	8 / 66	13 / 66	0,62	0,27	1,39
teCA			9 / 97	15 / 97	0,60	0,28	1,30
Overall			24 / 696	46 / 705	0,58	0,36	0,93



Analysis 4.4. Comparison 4 SSRI versus any other drug classes

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

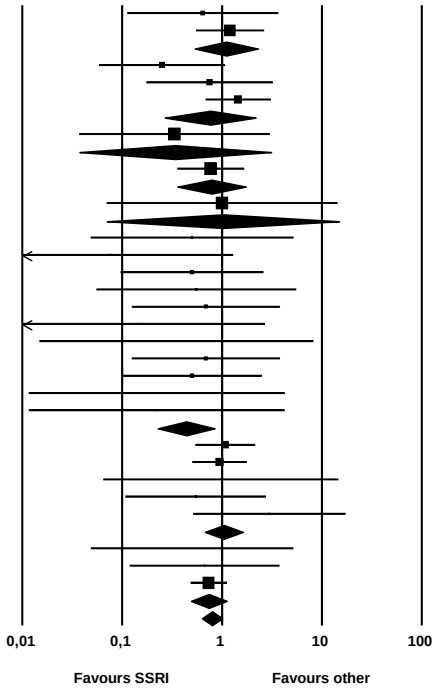


Group by Drug Class	Outcome	Study name	Sample size		Statistics for each study			Hedges's g and 95% CI
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit	
NARI		Cai JY 2007	32	31	-0,04	-0,53	0,44	
		Li HF 2007	67	70	-0,06	-0,40	0,27	
		Li N 2006	30	30	0,09	-0,41	0,59	
		Mao PX 2010	120	120	0,00	-0,25	0,25	
NARI			249	251	-0,01	-0,19	0,16	
NDRI		Cao HJ 2008	40	40	-0,08	-0,52	0,35	
		Li GJ 2005	30	30	0,37	-0,14	0,87	
		Li HF 2006	104	104	0,06	-0,21	0,33	
		Wu Y 2009	89	80	-0,07	-0,38	0,23	
NDRI			263	254	0,03	-0,14	0,20	
Placebo	HAMD fluox-placebo	Luo HC 2003	32	32	0,33	-0,15	0,82	
Placebo			32	32	0,33	-0,15	0,82	
SARI		Jiang T 2010	120	120	0,97	0,70	1,23	
SARI			120	120	0,97	0,70	1,23	
SNRI		Chen EM 2010	40	40	-0,34	-0,78	0,10	
		Li N 2007	34	34	-0,10	-0,57	0,37	
		Lu XJ 2008	88	82	0,04	-0,26	0,34	
		Ou HX 2001	15	15	0,27	-0,43	0,97	
SNRI			177	171	-0,05	-0,26	0,16	
TCA		Du YM 2006	34	34	0,26	-0,22	0,73	
		Gao YL 2006	38	37	0,03	-0,42	0,48	
		Han GL 2006	30	30	-0,16	-0,66	0,34	
		Li B 1996	68	68	0,24	-0,10	0,57	
		Meng Y 2002	21	1	0,25	-0,37	0,86	
		Shi SX 1997	33	3	-0,51	-1,00	-0,02	
		Shu DH 2004	19	1	0,18	-0,44	0,80	
		Sun SH 2001	30	3	-0,18	-0,68	0,32	
		Tan XG 2004	26	2	0,36	-0,19	0,90	
		Wei J 2008	21	2	0,14	-0,45	0,73	
		Xiang H 1998	30	3	-0,09	-0,59	0,41	
		Xie GR 1998	46	4	0,08	-0,33	0,49	
		Xu YC 1998	33	3	-0,18	-0,66	0,30	
		Yu MH 1996	16	2	-0,04	-0,83	0,75	
		Yu XL 2004	30	3	0,22	-0,28	0,72	
		ZhangXL 2000	31	3	0,23	-0,26	0,73	
		Zhang Z 2001	31	3	0,22	-0,27	0,72	
		Zhou J 2005	31	3	0,06	-0,43	0,55	
	HAMD parox-amitri	Sun XL 1997	19	1	-0,09	-0,73	0,55	
	HAMD sert-amitri	Sun XL 1997	19	1	-0,06	-0,70	0,58	
TCA			606	587	0,06	-0,05	0,17	
TCM		Chen LQ 2005	110	110	0,01	-0,25	0,27	
		Du B 2007	360	120	0,18	-0,02	0,39	
		Li LJ 2010	30	3	-0,20	-0,70	0,30	
	HAMD fluox-tcm	Luo HC 2003	31	3	-0,18	-0,67	0,31	
		Ma X 2007	42	3	0,06	-0,39	0,50	
		Qu M 2007	38	3	0,16	-0,29	0,62	
	HAMD tcm high	WangXQ 2009	119	121	-0,10	-0,35	0,15	
	HAMD tcm low	WangXQ 2009	121	121	-0,20	-0,45	0,05	
		Xiao JS 2005	52	5	0,12	-0,26	0,51	
TCM			903	654	0,00	-0,10	0,10	
teCA		Chang SH 2006	31	31	0,38	-0,12	0,87	
		Chen YH 2010	46	46	0,09	-0,31	0,50	
		Hong CJ 2003	66	66	-0,46	-0,81	-0,12	
		Li J 2007	40	40	-0,39	-0,82	0,05	
		Zhu GK 2005	30	30	-0,09	-0,59	0,41	
teCA			213	213	-0,11	-0,42	0,19	
Overall			2563	2282	0,06	0,00	0,12	

Analysis 4.5. Comparison 4 SSRI versus any other drug classes

Dropout rate overall (with Overall effects and effects in subgroups)

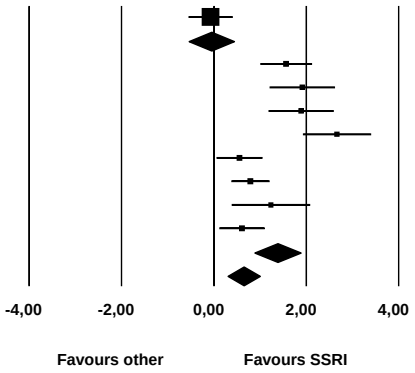
Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimental	Comparator			
NARI		Li HF 2007	2 / 70	3 / 67	0,64	0,11	3,70
		Mao PX 2010	12 / 120	10 / 120	1,20	0,54	2,67
NARI			14 / 190	13 / 187	1,08	0,52	2,23
NDRI		Li GJ 2005	2 / 30	8 / 30	0,25	0,06	1,08
		Li HF 2006	3 / 104	4 / 104	0,75	0,17	3,27
		Wu Y 2009	13 / 80	10 / 89	1,45	0,67	3,11
NDRI			18 / 214	22 / 223	0,75	0,26	2,12
Placebo	Dropout fluox-placebo	Luo HC 2003	1 / 32	3 / 32	0,33	0,04	3,04
Placebo			1 / 32	3 / 32	0,33	0,04	3,04
SAR		Jiang T 2010	10 / 120	13 / 120	0,77	0,35	1,69
SAR			10 / 120	13 / 120	0,77	0,35	1,69
SNRI		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
SNRI			1 / 15	1 / 15	1,00	0,07	14,55
TCA		Du YM 2006	1 / 34	2 / 34	0,50	0,05	5,26
		Han GL 2006	0 / 30	6 / 30	0,08	0,00	1,31
		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
		Shi SX 1997	2 / 32	3 / 33	0,69	0,12	3,85
		Tan XG 2004	0 / 25	3 / 26	0,15	0,01	2,73
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		XuYC 1998	2 / 32	3 / 33	0,69	0,12	3,85
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout parox-amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
	Dropout sert-Amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
TCA			10 / 349	32 / 360	0,43	0,22	0,82
TCM		Chen LQ 2005	14 / 110	13 / 110	1,08	0,53	2,18
		Du B 2007	11 / 120	35 / 360	0,94	0,49	1,80
	Dropout fluoxe-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
		Qu M 2007	2 / 35	4 / 38	0,54	0,11	2,78
		Wang XQ 2009	3 / 121	2 / 240	2,98	0,50	17,57
TCM			31 / 418	55 / 779	1,02	0,66	1,58
teCA		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
		Chen YH 2010	2 / 46	3 / 46	0,67	0,12	3,81
		Hong CJ 2003	22 / 66	30 / 66	0,73	0,48	1,13
teCA			25 / 143	35 / 143	0,72	0,48	1,09
Overall			110 / 1481	174 / 1859	0,78	0,62	0,98



Analysis 4.6. Comparison 4 SSRI versus any other drug classes

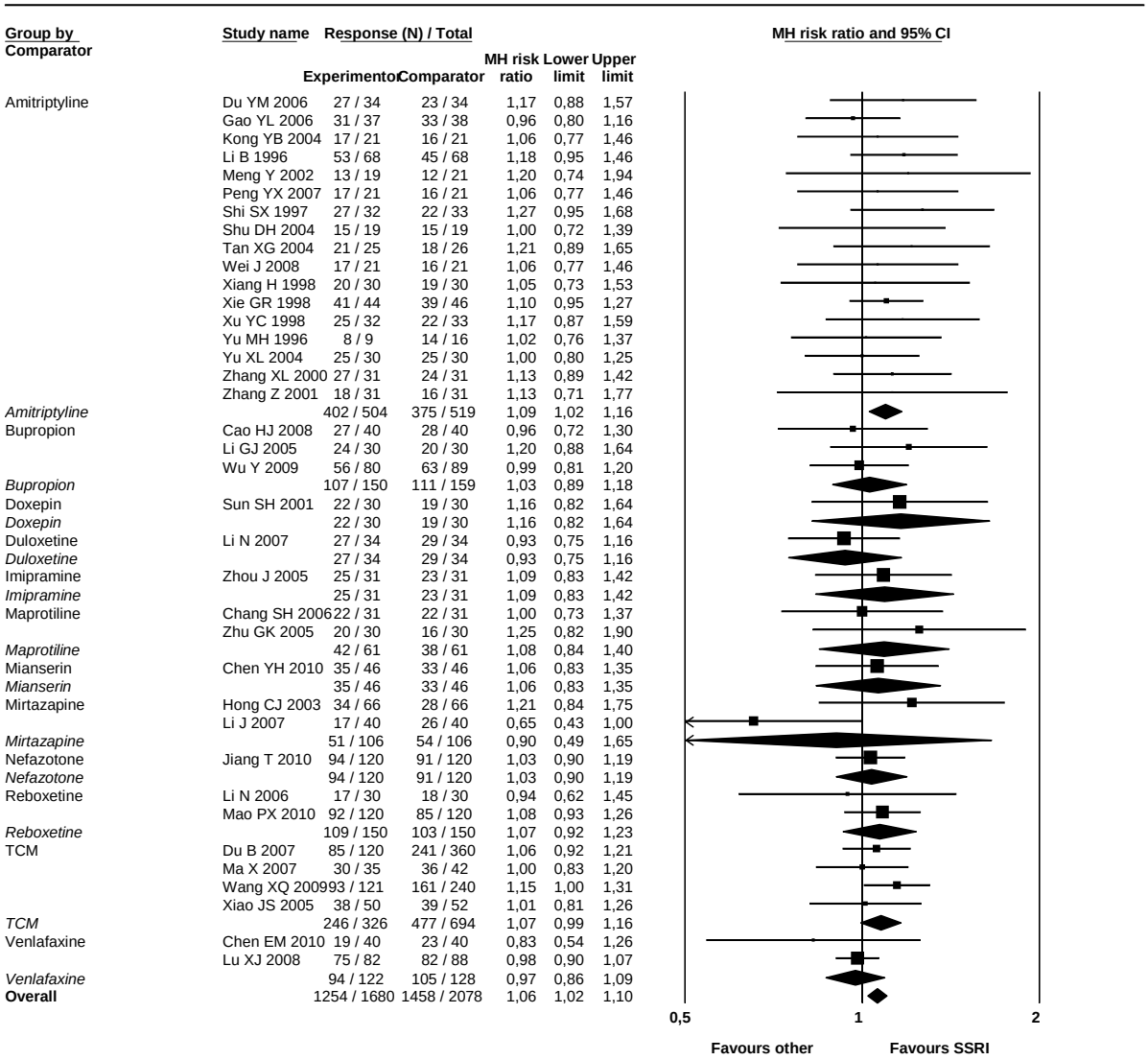
Total TESS scores (with Overall effects and effects in subgroups)

Group by Drug Class	Study name	Sample size		Statistics for each study			Hedges's g and 95% CI
		Comparator	Experimentor	Hedges's g	Lower limit	Upper limit	
NARI	Cai JY 2007	32	31	-0,07	-0,56	0,42	
NARI		32	31	-0,07	-0,56	0,42	
TCA	Han GL 2006	30	30	1,56	0,99	2,13	
	Kong YB 2004	21	21	1,91	1,19	2,63	
	Peng YX 2007	21	21	1,89	1,17	2,61	
	Tan XG 2004	26	25	2,66	1,92	3,41	
	Xiang H 1998	30	30	0,55	0,04	1,06	
	Xie GR 1998	46	44	0,79	0,36	1,22	
	Yu MH 1996	16	9	1,23	0,37	2,10	
	Zhou J 2005	31	31	0,61	0,11	1,11	
TCA		221	211	1,36	0,86	1,86	
Overall		253	242	0,63	0,28	0,98	



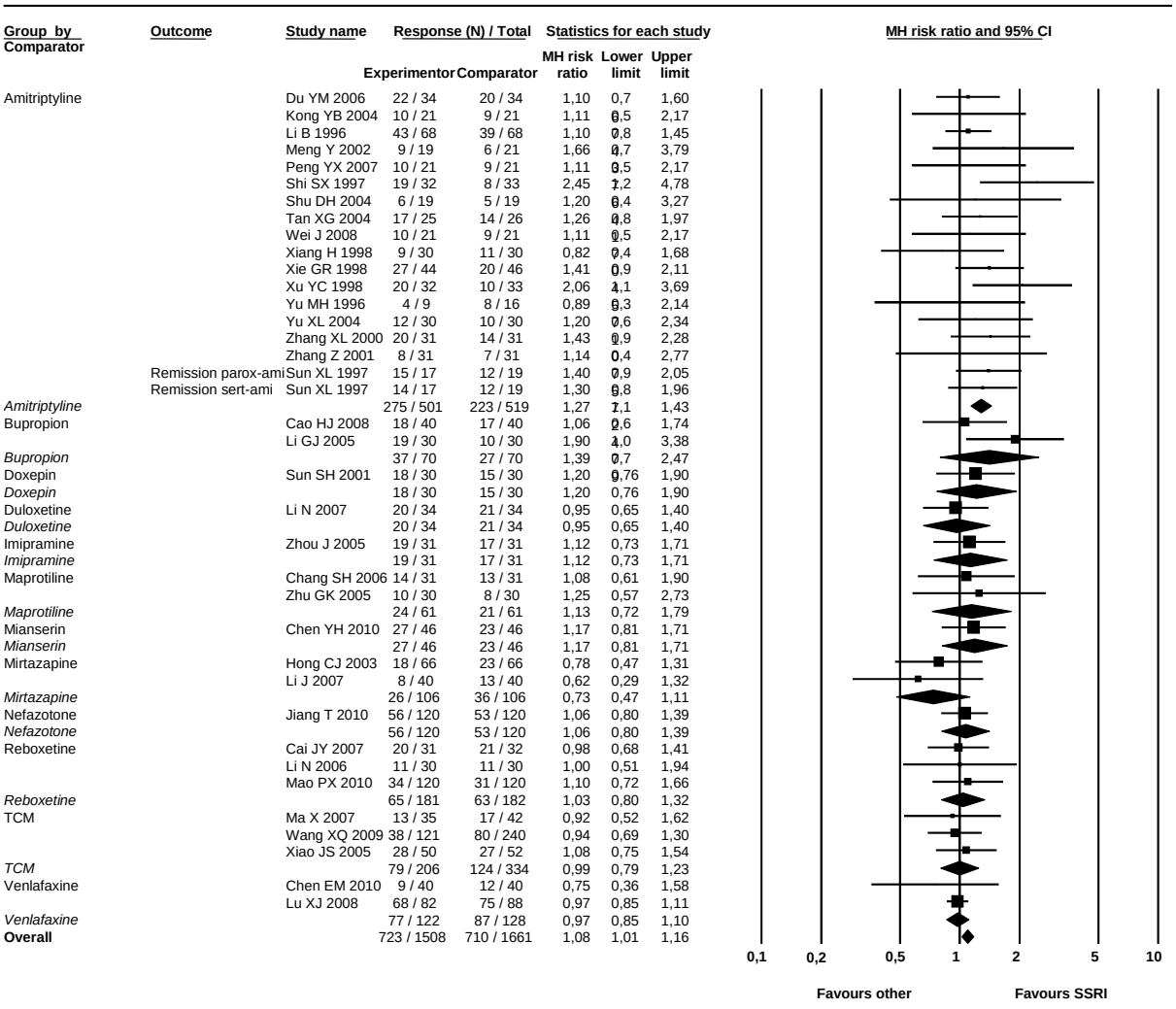
Analysis 5.1. Comparison 5 SSRI versus any other intervention

Response rate (with Overall effects and effects in subgroups)



Analysis 5.2. Comparison 5 SSRI versus any other intervention

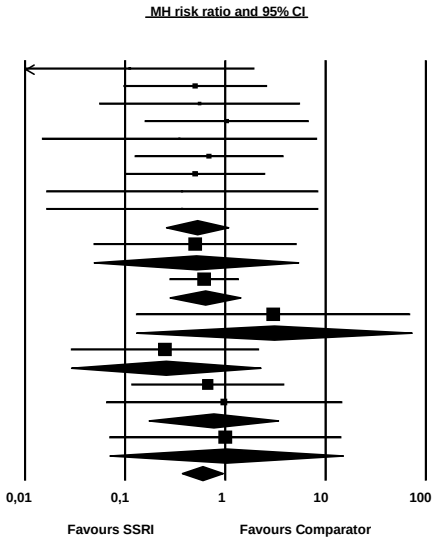
Remission rate (with Overall effects and effects in subgroups)



Analysis 5.3. Comparison 5 SSRI versus any other interventions

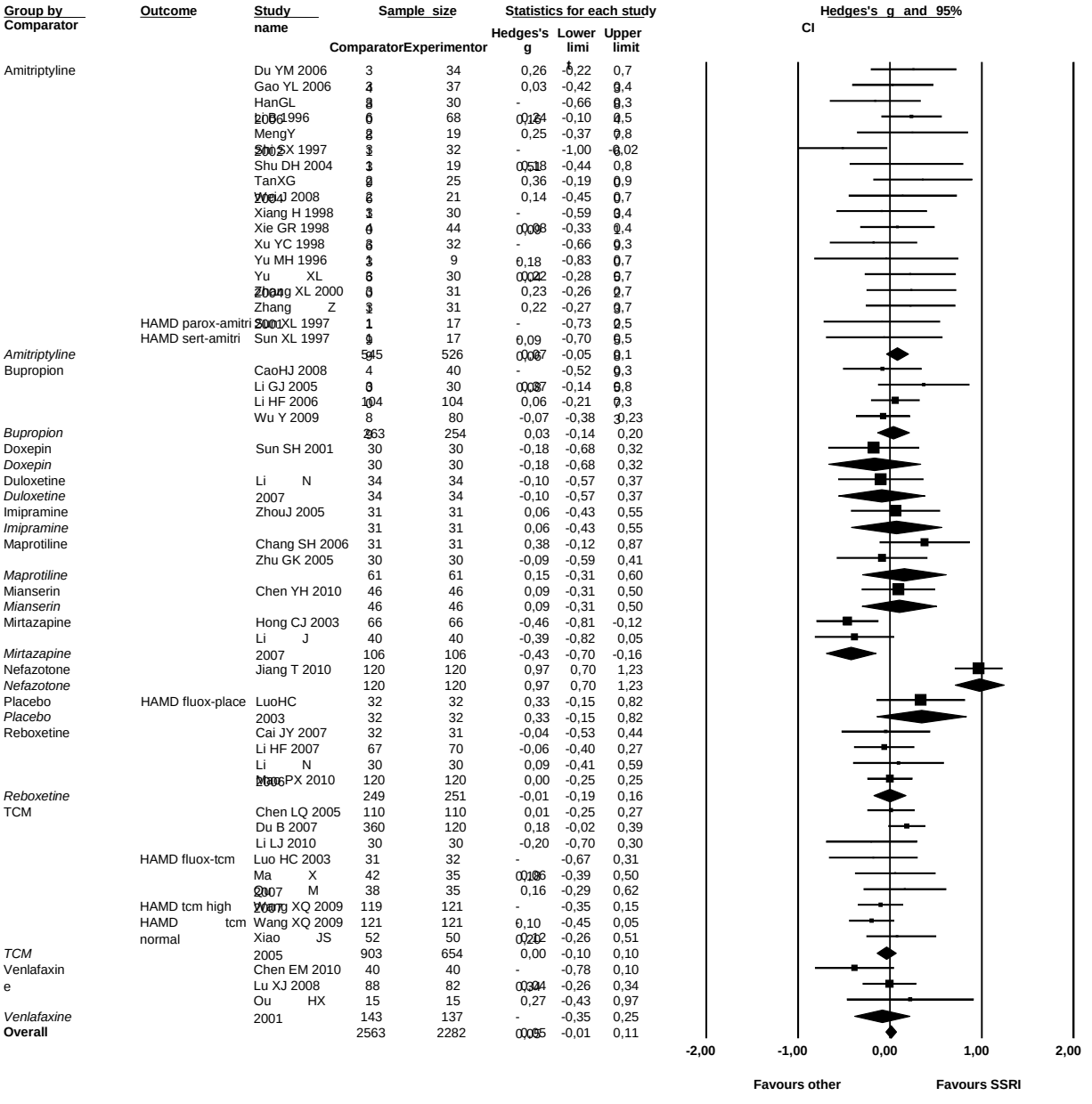
Dropout rate due to side effects (with Overall effects and effects in subgroups)

Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimentor	Comparator			
Amitriptyline		Han GL 2006	0 / 30	4 / 30	0,11	0,01	1,98
		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
		Shi SX 1997	2 / 32	2 / 33	1,03	0,15	6,89
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout side effects parox-amitri	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
	Dropout side effects sert-amitri	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
Amitriptyline			9 / 290	22 / 300	0,51	0,25	1,05
Maprotiline		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
Maprotiline			1 / 31	2 / 31	0,50	0,05	5,23
Mirtazapine		Hong CJ 2003	8 / 66	13 / 66	0,62	0,27	1,39
Mirtazapine			8 / 66	13 / 66	0,62	0,27	1,39
Placebo	Dropout side effects fluox-placebo	Luo HC 2003	1 / 32	0 / 32	3,00	0,13	71,00
Placebo			1 / 32	0 / 32	3,00	0,13	71,00
Reboxetine		Mao PX 2010	1 / 120	4 / 120	0,25	0,03	2,20
Reboxetine			1 / 120	4 / 120	0,25	0,03	2,20
TCM		Chen LQ 2005	2 / 110	3 / 110	0,67	0,11	3,91
	Dropout side effects fluox-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
TCM			3 / 142	4 / 141	0,74	0,17	3,29
Venlafaxine		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
Venlafaxine			1 / 15	1 / 15	1,00	0,07	14,55
Overall			24 / 696	46 / 705	0,58	0,36	0,93



Analysis 5.4. Comparison 5 SSRI versus any other interventions

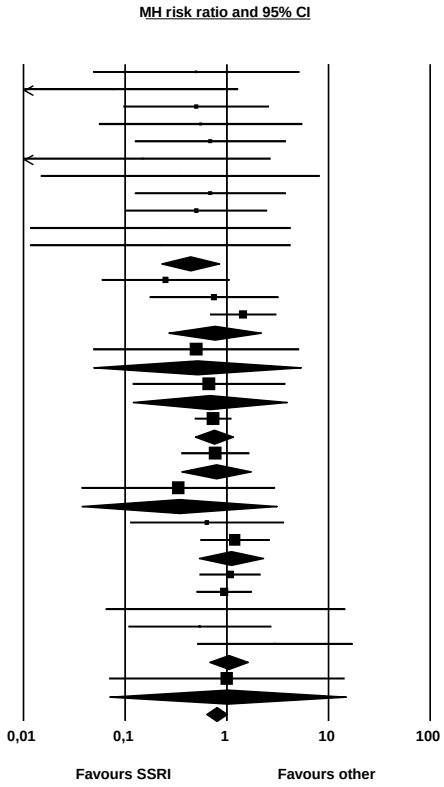
The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



Analysis 5.5. Comparison 5 SSRI versus any other interventions

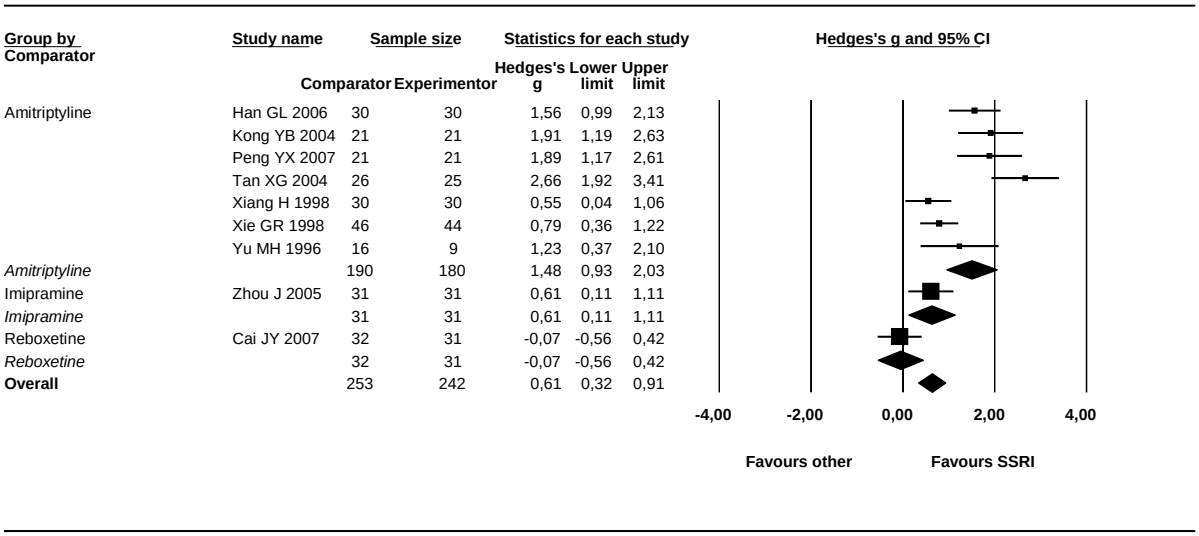
Dropout rate overall (with Overall effects and effects in subgroups)

Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimntor	Comparator			
Amitriptyline	Dropout	Du YM 2006	1 / 34	2 / 34	0,50	0,05	5,26
	Dropout	Han GL 2006	0 / 30	6 / 30	0,08	0,00	1,31
	Dropout	Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
	Dropout	Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
	Dropout	Shi SX 1997	2 / 32	3 / 33	0,69	0,12	3,85
	Dropout	Tan XG 2004	0 / 25	3 / 26	0,15	0,01	2,73
	Dropout	Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
	Dropout	Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85
	Dropout	ZhangXL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout parox-amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
	Dropout sert-Amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
Amitriptyline			10 / 349	32 / 360	0,43	0,22	0,82
Bupropion	Dropout	Li GJ 2005	2 / 30	8 / 30	0,25	0,06	1,08
	Dropout	Li HF 2006	3 / 104	4 / 104	0,75	0,17	3,27
	Dropout	Wu Y 2009	13 / 80	10 / 89	1,45	0,67	3,11
Bupropion			18 / 214	22 / 223	0,75	0,26	2,12
Maprotiline	Dropout	Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
Maprotiline			1 / 31	2 / 31	0,50	0,05	5,23
Mianserin	Dropout	Chen YH 2010	2 / 46	3 / 46	0,67	0,12	3,81
Mianserin			2 / 46	3 / 46	0,67	0,12	3,81
Mirtazapine	Dropout	Hong CJ 2003	22 / 66	30 / 66	0,73	0,48	1,13
Mirtazapine			22 / 66	30 / 66	0,73	0,48	1,13
Nefazotone	Dropout	Jiang T 2010	10 / 120	13 / 120	0,77	0,35	1,69
Nefazotone			10 / 120	13 / 120	0,77	0,35	1,69
Placebo	Dropout fluoxe-placebo	Luo HC 2003	1 / 32	3 / 32	0,33	0,04	3,04
Placebo			1 / 32	3 / 32	0,33	0,04	3,04
Reboxetine	Dropout	Li HF 2007	2 / 70	3 / 67	0,64	0,11	3,70
	Dropout	Mao PX 2010	12 / 120	10 / 120	1,20	0,54	2,67
Reboxetine			14 / 190	13 / 187	1,08	0,52	2,23
TCM	Dropout	Chen LQ 2005	14 / 110	13 / 110	1,08	0,53	2,18
	Dropout	Du B 2007	11 / 120	35 / 360	0,94	0,49	1,80
	Dropout fluoxe-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
	Dropout	QuM 2007	2 / 35	4 / 38	0,54	0,11	2,78
	Dropout	WangXQ 2009	3 / 121	2 / 240	2,98	0,50	17,57
TCM			31 / 418	55 / 779	1,02	0,66	1,58
Venlafaxine	Dropout	Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
Venlafaxine			1 / 15	1 / 15	1,00	0,07	14,55
Overall			110 / 1481	174 / 1859	0,78	0,62	0,98

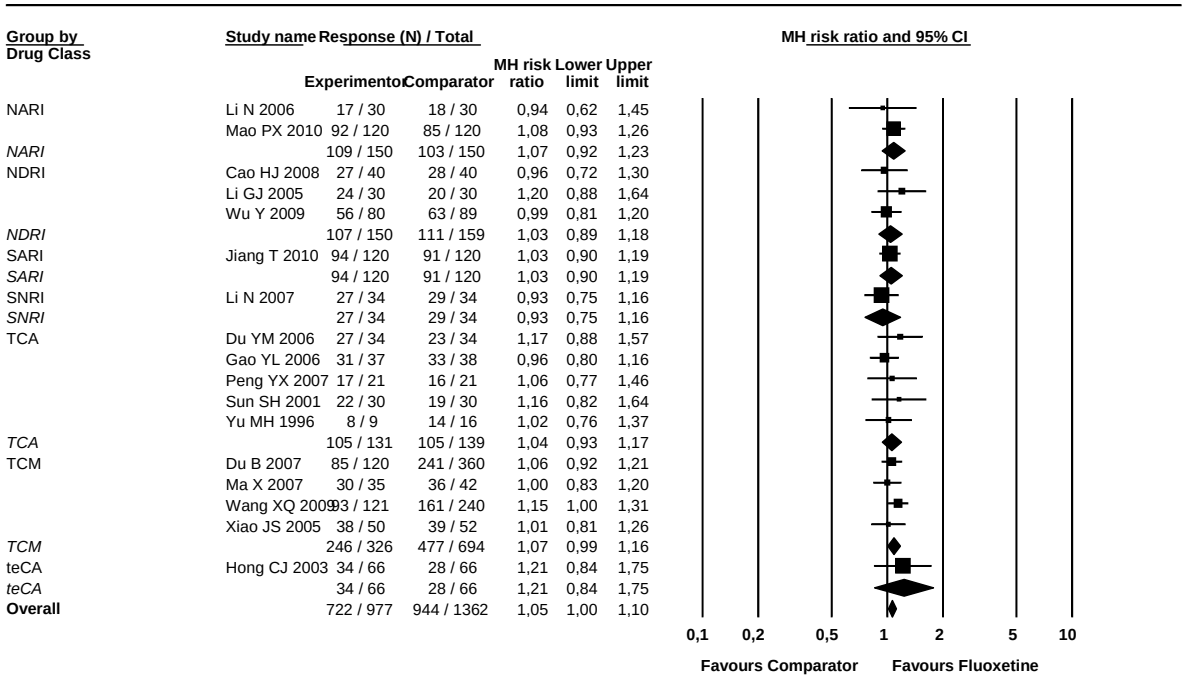


Analysis 5.6. Comparison 5 SSRI versus any other interventions

Total TESS scores (with Overall effects and effects in subgroups)

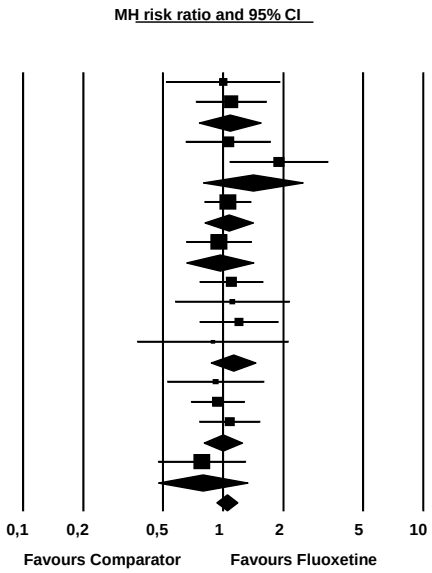


Analysis 6.1. Comparison 6 Fluoxetine versus other drug classes Response rate (with Overall effects and effects in subgroups)



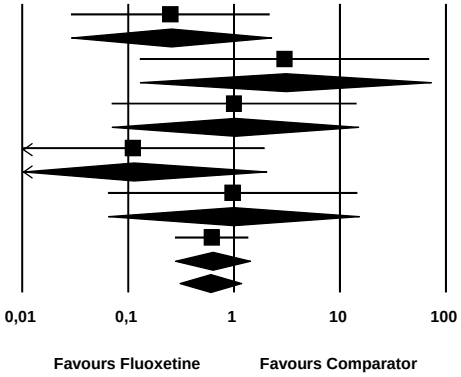
Analysis 6.2. Comparison 6 Fluoxetine versus other drug classes Remission rate (with Overall effects and effects in subgroups)

Group by Drug Class	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
NARI	LiN 2006	11 / 30	11 / 30	1,00	0,51	1,94
	Mao PX 2010	34/ 120	31 / 120	1,10	0,72	1,66
NARI		45/ 150	42 / 150	1,07	0,75	1,52
NDRI	Cao HJ 2008	18 / 40	17 / 40	1,06	0,64	1,74
	Li GJ 2005	19 / 30	10 / 30	1,90	1,07	3,38
NDRI		37 / 70	27 / 70	1,39	0,79	2,47
SARI	Jiang T 2010	56/ 120	53 / 120	1,06	0,80	1,39
SARI		56/ 120	53 / 120	1,06	0,80	1,39
SNRI	LiN 2007	20 / 34	21 / 34	0,95	0,65	1,40
SNRI		20 / 34	21 / 34	0,95	0,65	1,40
TCA	Du YM 2006	22 / 34	20 / 34	1,10	0,76	1,60
	Peng YX 2007	10 / 21	9 / 21	1,11	0,57	2,17
	Sun SH 2001	18 / 30	15 / 30	1,20	0,76	1,90
	Yu MH 1996	4 / 9	8 / 16	0,89	0,37	2,14
TCA		54 / 94	52 / 101	1,11	0,86	1,43
TCM	Ma X 2007	13 / 35	17 / 42	0,92	0,52	1,62
	Wang XQ 2009	38/ 121	80 / 240	0,94	0,69	1,30
	Xiao JS 2005	28 / 50	27 / 52	1,08	0,75	1,54
TCM		79/ 206	124 / 334	0,99	0,79	1,23
teCA	Hong CJ 2003	18 / 66	23 / 66	0,78	0,47	1,31
teCA		18 / 66	23 / 66	0,78	0,47	1,31
Overall		309/ 740	342 / 875	1,03	0,92	1,16



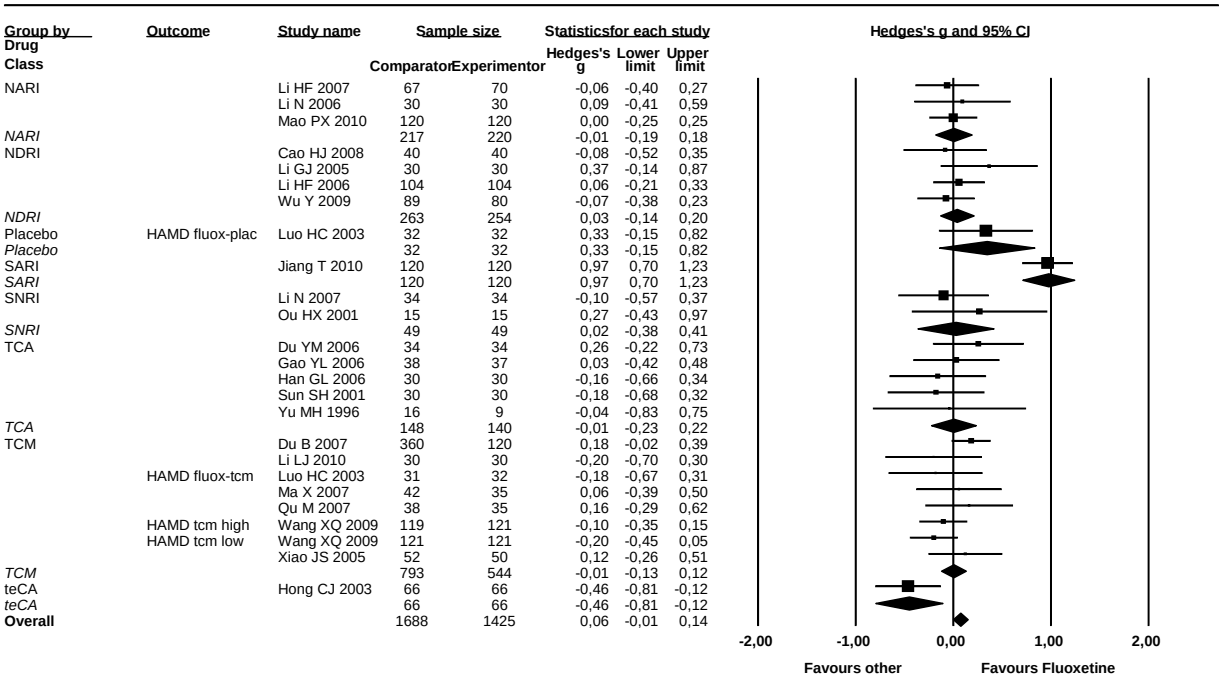
Analysis 6.3. Comparison 6 Fluoxetine versus other drug classes Dropout rate due to side effects (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimental	Comparator			
NARI		Mao PX 2010	1 / 120	4 / 120	0,25	0,03	2,20
NARI			1 / 120	4 / 120	0,25	0,03	2,20
Placeb	Dropout side effects fluo-plac	Luo HC 2003	1 / 32	0 / 32	3,00	0,13	71,00
Placeb			1 / 32	0 / 32	3,00	0,13	71,00
SNRI		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
SNRI			1 / 15	1 / 15	1,00	0,07	14,55
TCA		Han GL 2006	0 / 30	4 / 30	0,11	0,01	1,98
TCA			0 / 30	4 / 30	0,11	0,01	1,98
TCM	Dropout side effects fluox-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
TCM			1 / 32	1 / 31	0,97	0,06	14,82
teCA		Hong CJ 2003	8 / 66	13 / 66	0,62	0,27	1,39
teCA			8 / 66	13 / 66	0,62	0,27	1,39
Overall			12 / 295	23 / 294	0,59	0,30	1,15



Analysis 6.4. Comparison 6 Fluoxetine versus other drug classes

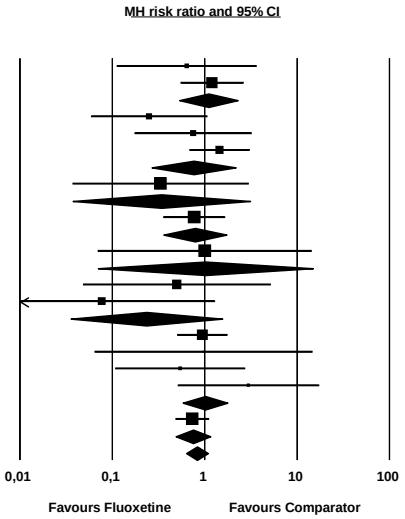
The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



Analysis 6.5. Comparison 6 Fluoxetine versus other drug classes

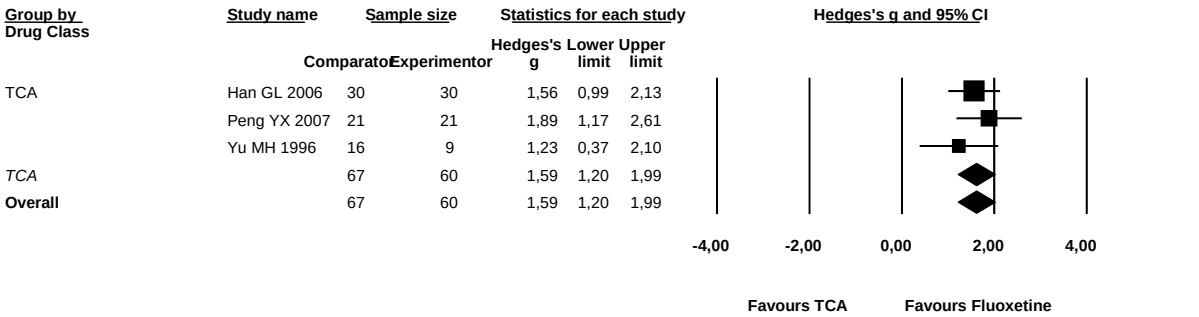
Dropout rate overall (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimentor	Comparator			
NARI		Li HF 2007	2 / 70	3 / 67	0,64	0,11	3,70
		Mao PX 2010	12 / 120	10 / 120	1,20	0,54	2,67
NARI			14 / 190	13 / 187	1,08	0,52	2,23
NDRI		Li GJ 2005	2 / 30	8 / 30	0,25	0,06	1,08
		Li HF 2006	3 / 104	4 / 104	0,75	0,17	3,27
		Wu Y 2009	13 / 80	10 / 89	1,45	0,67	3,11
NDRI			18 / 214	22 / 223	0,75	0,26	2,12
Placebo	Dropout fluoxe-place	Luo HC 2003	1 / 32	3 / 32	0,33	0,04	3,04
Placebo			1 / 32	3 / 32	0,33	0,04	3,04
SARI		Jiang T 2010	10 / 120	13 / 120	0,77	0,35	1,69
SARI			10 / 120	13 / 120	0,77	0,35	1,69
SNRI		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
SNRI			1 / 15	1 / 15	1,00	0,07	14,55
TCA		Du YM 2006	1 / 34	2 / 34	0,50	0,05	5,26
		Han GL 2006	0 / 30	6 / 30	0,08	0,00	1,31
TCA			1 / 64	8 / 64	0,23	0,03	1,52
TCM		Du B 2007	11 / 120	35 / 360	0,94	0,49	1,80
	Dropout fluoxe-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
		Qu M 2007	2 / 35	4 / 38	0,54	0,11	2,78
		Wang XQ 2009	3 / 121	2 / 240	2,98	0,50	17,57
TCM			17 / 308	42 / 669	0,99	0,57	1,73
teCA		Hong CJ 2003	22 / 66	30 / 66	0,73	0,48	1,13
teCA			22 / 66	30 / 66	0,73	0,48	1,13
Overall			84 / 1009	132 / 1376	0,81	0,62	1,06



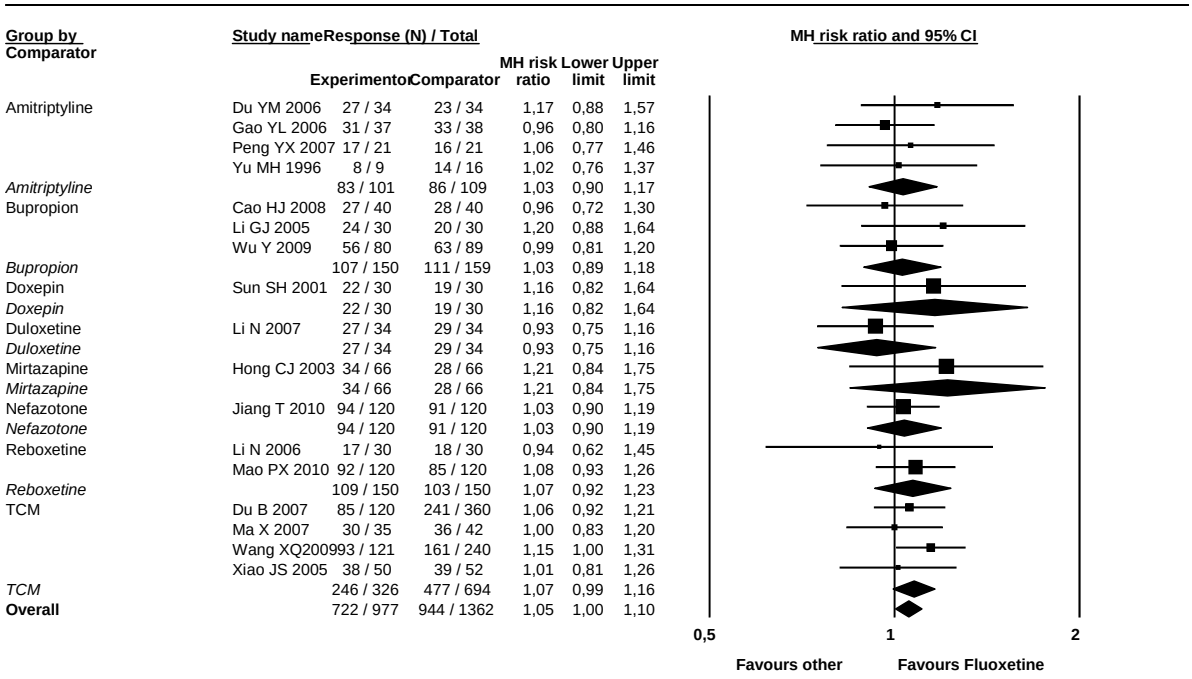
Analysis 6.6. Comparison 6 Fluoxetine versus other drug classes

Total TESS scores (with Overall effects and effects in subgroups)



Analysis 7.1. Comparison 7 Fluoxetine versus other interventions

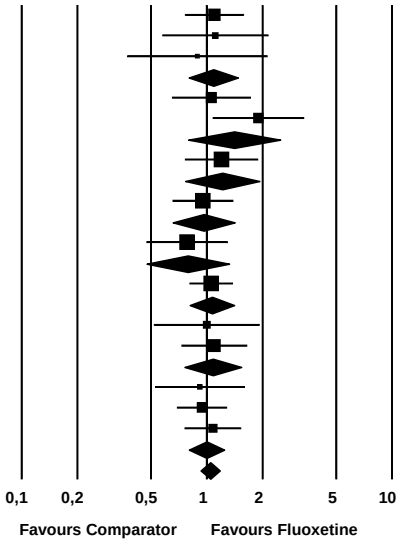
Response rate (with Overall effects and effects in subgroups)



Analysis 7.2. Comparison 7 Fluoxetine versus other interventions

Remission rate (with Overall effects and effects in subgroups)

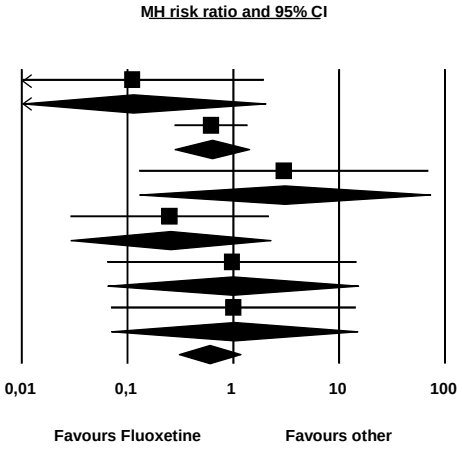
Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimental	Comparator			
Amitriptyline	Remission	Du YM 2006	22 / 34	20 / 34	1,10	0,76	1,60
	Remission	Peng YX 2007	10 / 21	9 / 21	1,11	0,57	2,17
	Remission	Yu MH 1996	4 / 9	8 / 16	0,89	0,37	2,14
Amitriptyline			36 / 64	37 / 71	1,07	0,79	1,46
Bupropion	Remission	Cao HJ 2008	18 / 40	17 / 40	1,06	0,64	1,74
	Remission	Li GJ 2005	19 / 30	10 / 30	1,90	1,07	3,38
Bupropion			37 / 70	27 / 70	1,39	0,79	2,47
Doxepin	Remission	Sun SH 2001	18 / 30	15 / 30	1,20	0,76	1,90
Doxepin			18 / 30	15 / 30	1,20	0,76	1,90
Duloxetine	Remission	Li N 2007	20 / 34	21 / 34	0,95	0,65	1,40
Duloxetine			20 / 34	21 / 34	0,95	0,65	1,40
Mirtazapine	Remission	Hong CJ 2003	18 / 66	23 / 66	0,78	0,47	1,31
Mirtazapine			18 / 66	23 / 66	0,78	0,47	1,31
Nefazotone	Remission	Jiang T 2010	56 / 120	53 / 120	1,06	0,80	1,39
Nefazotone			56 / 120	53 / 120	1,06	0,80	1,39
Reboxetine	Remission	Li N 2006	11 / 30	11 / 30	1,00	0,51	1,94
	Remission	Mao PX 2010	34 / 120	31 / 120	1,10	0,72	1,66
Reboxetine			45 / 150	42 / 150	1,07	0,75	1,52
TCM	Remission	Ma X 2007	13 / 35	17 / 42	0,92	0,52	1,62
	Remission	Wang XQ 2009	88 / 121	80 / 240	0,94	0,69	1,30
	Remission	Xiao JS 2005	28 / 50	27 / 52	1,08	0,75	1,54
TCM			79 / 206	124 / 334	0,99	0,79	1,23
Overall			309 / 740	342 / 875	1,03	0,92	1,16



Analysis 7.3. Comparison 7 Fluoxetine versus other interventions

Dropout rate due to side effects (with Overall effects and effects in subgroups)

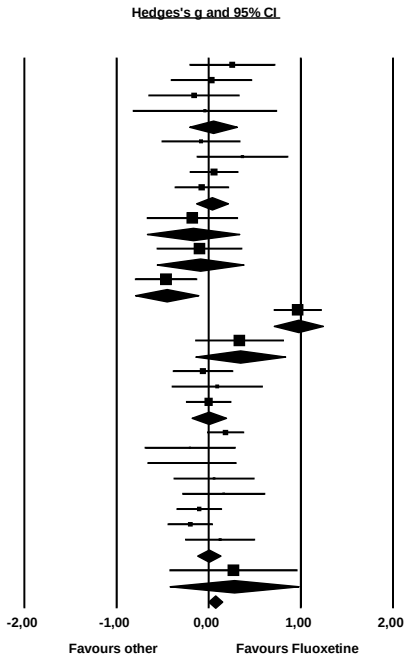
Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimento	Comparator			
Amitriptyline		Han GL 2006	0 / 30	4 / 30	0,11	0,01	1,98
Amitriptyline			0 / 30	4 / 30	0,11	0,01	1,98
Mirtazapine		Hong CJ 2003	8 / 66	13 / 66	0,62	0,27	1,39
Mirtazapine			8 / 66	13 / 66	0,62	0,27	1,39
Placebo	Dropout side effects fluox-plac	Luo HC 2003	1 / 32	0 / 32	3,00	0,13	71,00
Placebo			1 / 32	0 / 32	3,00	0,13	71,00
Reboxetine		MaoPX 2010	1 / 120	4 / 120	0,25	0,03	2,20
Reboxetine			1 / 120	4 / 120	0,25	0,03	2,20
TCM	Dropout side effects fluox-tcm	Luo HC 2003	1 / 32	1 / 31	0,97	0,06	14,82
TCM			1 / 32	1 / 31	0,97	0,06	14,82
Venlafaxine		Ou HX 2001	1 / 15	1 / 15	1,00	0,07	14,55
Venlafaxine			1 / 15	1 / 15	1,00	0,07	14,55
Overall			12 / 295	23 / 294	0,59	0,30	1,15



Analysis 7.4. Comparison 7 Fluoxetine versus other interventions

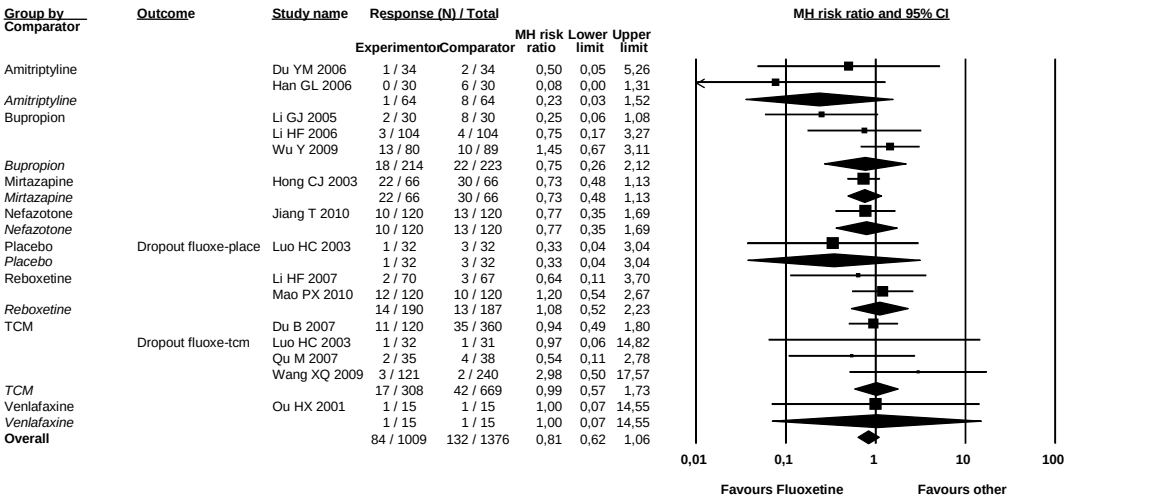
The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

Group by Comparator	Outcome	Study name	Sample size		Statistics for each study		
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
Amitriptyline		Du YM 2006	34	34	0,26	-0,22	0,73
		Gao YL 2006	38	37	0,03	-0,42	0,48
		Han GL 2006	30	30	-0,16	-0,66	0,34
		Yu MH 1996	16	9	-0,04	-0,83	0,75
Amitriptyline			118	110	0,04	-0,22	0,30
Bupropion		Cao HJ 2008	40	40	-0,08	-0,52	0,35
		Li GJ 2005	30	30	0,37	-0,14	0,87
		Li HF 2006	104	104	0,06	-0,21	0,33
		Wu Y 2009	89	80	-0,07	-0,38	0,23
Bupropion			263	254	0,03	-0,14	0,20
Doxepin		Sun SH 2001	30	30	-0,18	-0,68	0,32
Doxepin			30	30	-0,18	-0,68	0,32
Duloxetine		Li N 2007	34	34	-0,10	-0,57	0,37
Duloxetine			34	34	-0,10	-0,57	0,37
Mirtazapine		Hong CJ 2003	66	66	-0,46	-0,81	-0,12
Mirtazapine			66	66	-0,46	-0,81	-0,12
Nefazotone		Jiang T 2010	120	120	0,97	0,70	1,23
Nefazotone			120	120	0,97	0,70	1,23
Placebo	HAMD fluox-placebo	Luo HC 2003	32	32	0,33	-0,15	0,82
Placebo			32	32	0,33	-0,15	0,82
Reboxetine		Li HF 2007	67	70	-0,06	-0,40	0,27
		Li N 2006	30	30	0,09	-0,41	0,59
		Mao PX 2010	120	120	0,00	-0,25	0,25
Reboxetine			217	220	-0,01	-0,19	0,18
TCM		Du B 2007	360	120	0,18	-0,02	0,39
		Li LJ 2010	30	30	-0,20	-0,70	0,30
	HAMD fluox-tcm	Luo HC 2003	31	32	-0,18	-0,67	0,31
		Ma X 2007	42	35	0,06	-0,39	0,50
		Qu M 2007	38	35	0,16	-0,29	0,62
	HAMD tcm high	Wang XQ 2009	119	121	-0,10	-0,35	0,15
	HAMD tcm low	Wang XQ 2009	121	121	-0,20	-0,45	0,05
		Xiao JS 2005	52	50	0,12	-0,26	0,51
TCM			793	544	-0,01	-0,13	0,12
Venlafaxine		Ou HX 2001	15	15	0,27	-0,43	0,97
Venlafaxine			15	15	0,27	-0,43	0,97
Overall			1688	1425	0,06	-0,01	0,14



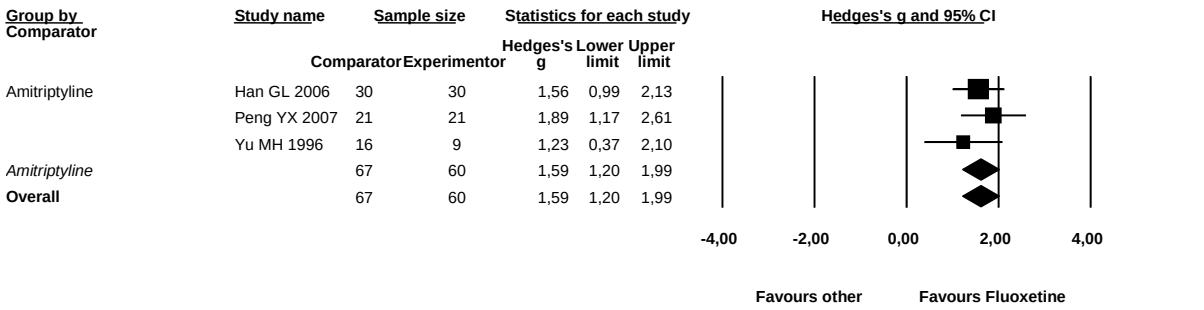
Analysis 7.5. Comparison 7 Fluoxetine versus other interventions

Dropout rate overall (with Overall effects and effects in subgroups)



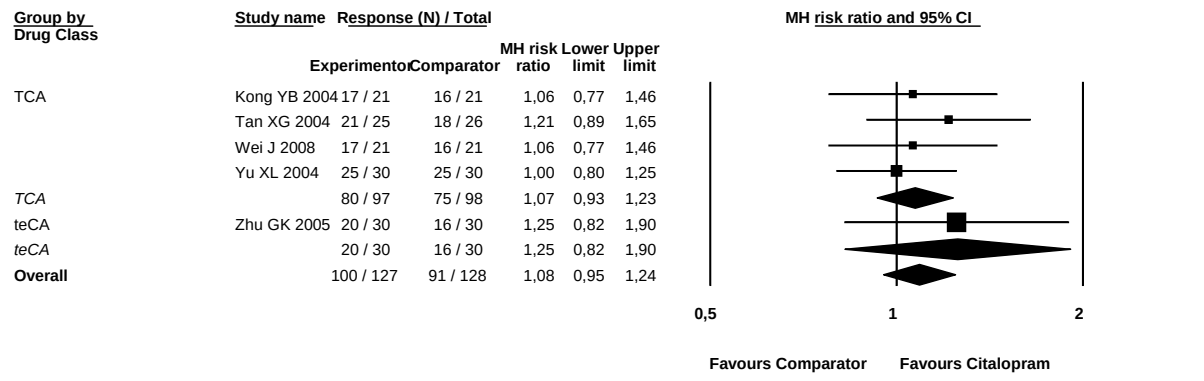
Analysis 7.6. Comparison 7 Fluoxetine versus other interventions

Total TESS scores (with Overall effects and effects in subgroups)



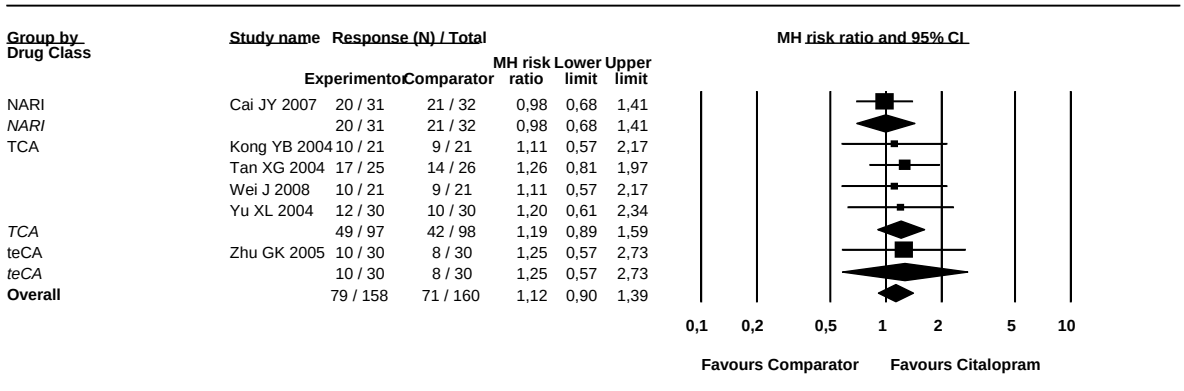
Analysis 8.1. Comparison 8 Citalopram versus other drug classes

Response rate (with Overall effects and effects in subgroups)



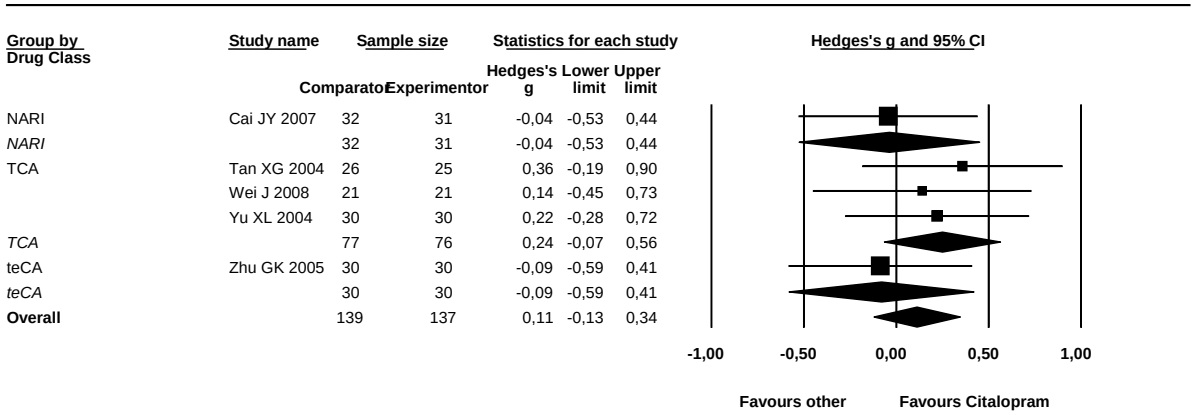
Analysis 8.2. Comparison 8 Citalopram versus other drug classes

Remission rate (with Overall effects and effects in subgroups)



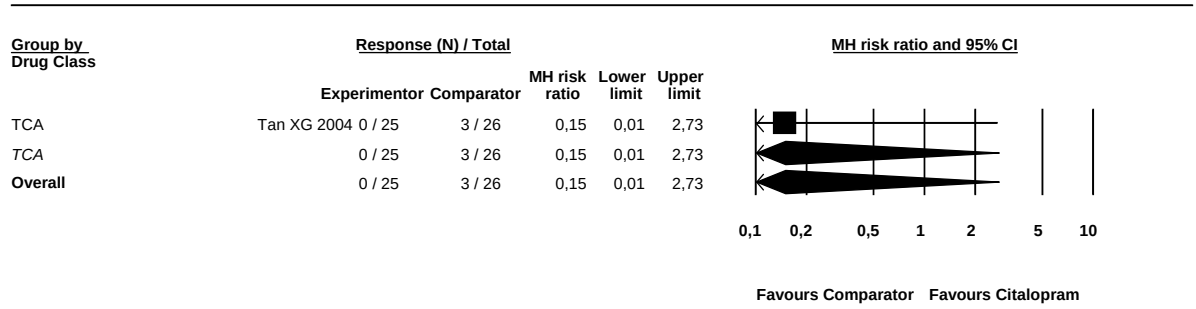
Analysis 8.3. Comparison 8 Citalopram versus other drug classes

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



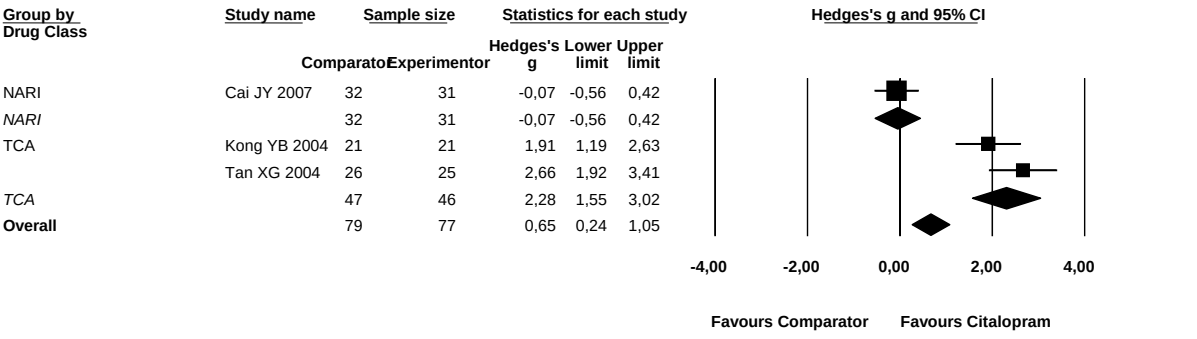
Analysis 8.4. Comparison 8 Citalopram versus other drug classes

Dropout rate overall (with Overall effects and effects in subgroups)

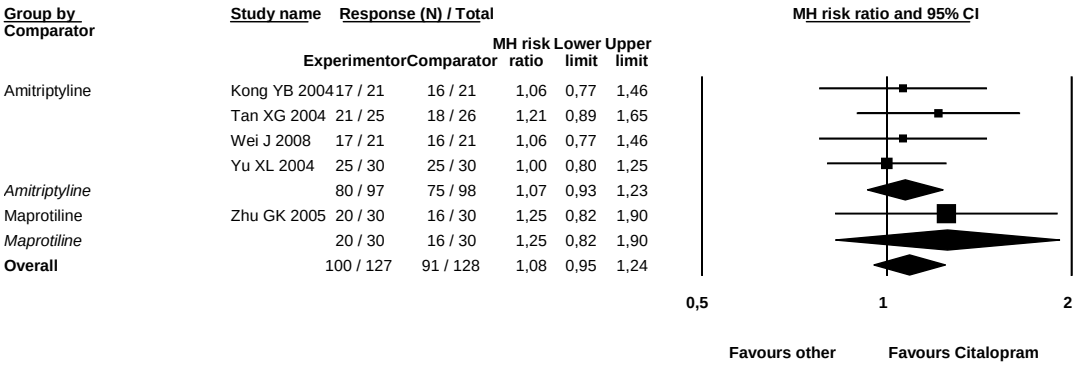


Analysis 8.5. Comparison 8 Citalopram versus other drug classes

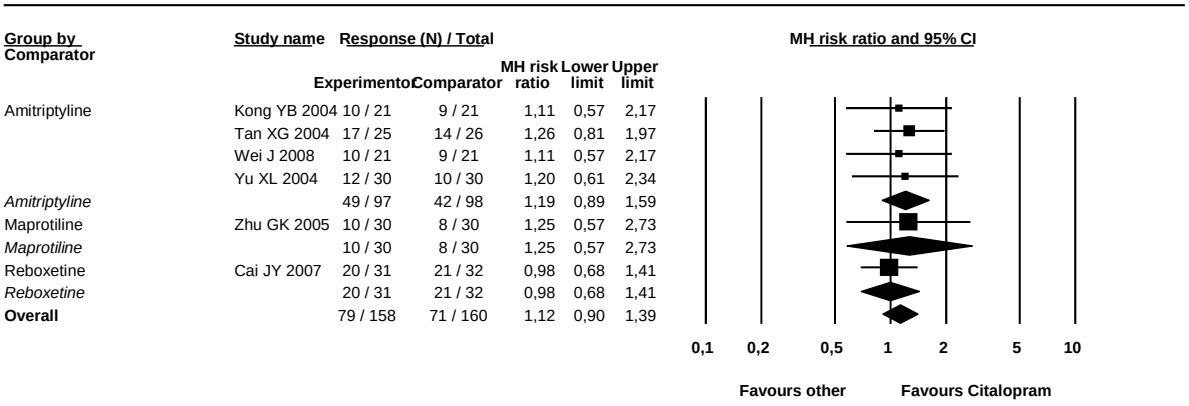
Sum score of TESS (with Overall effects and effects in subgroups)



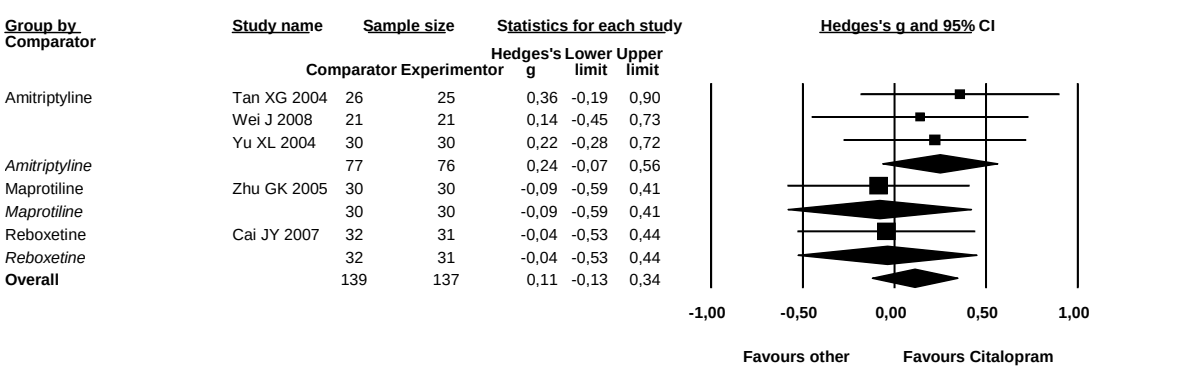
Analysis 9.1. Comparison 9 Citalopram versus other interventions Response rate (with Overall effects and effects in subgroups)



Analysis 9.2. Comparison 9 Citalopram versus other interventions Remission rate (with Overall effects and effects in subgroups)

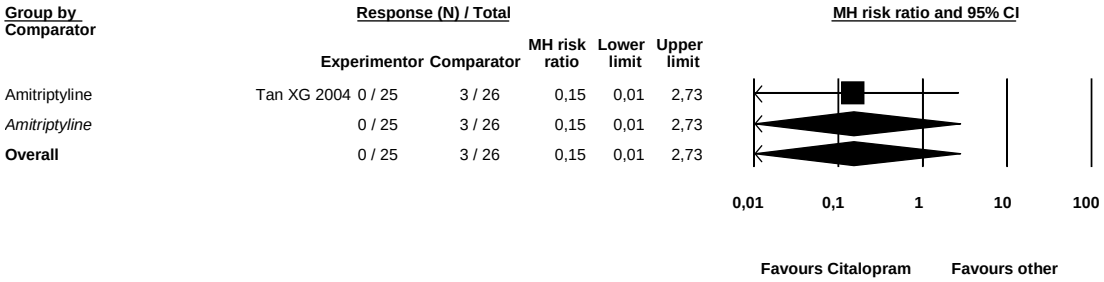


Analysis 9.3. Comparison 9 Citalopram versus other interventions The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



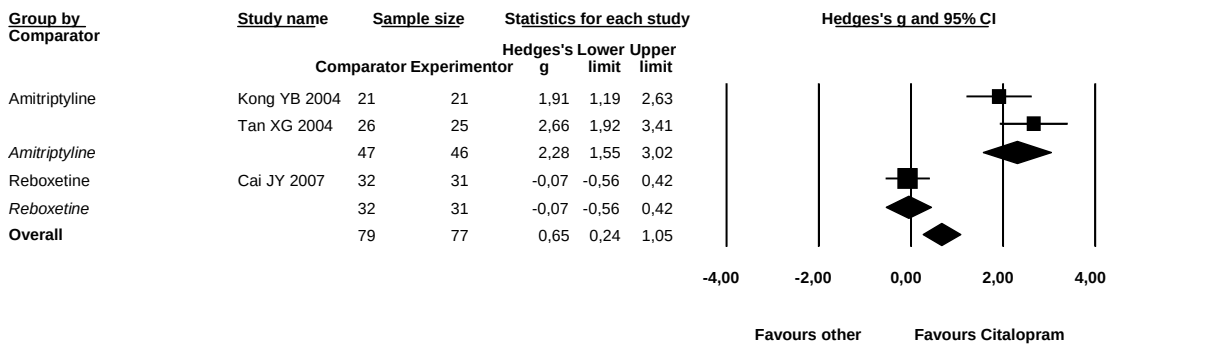
Analysis 9.4. Comparison 9 Citalopram versus other interventions

Dropout overall (with Overall effects and effects in subgroups)



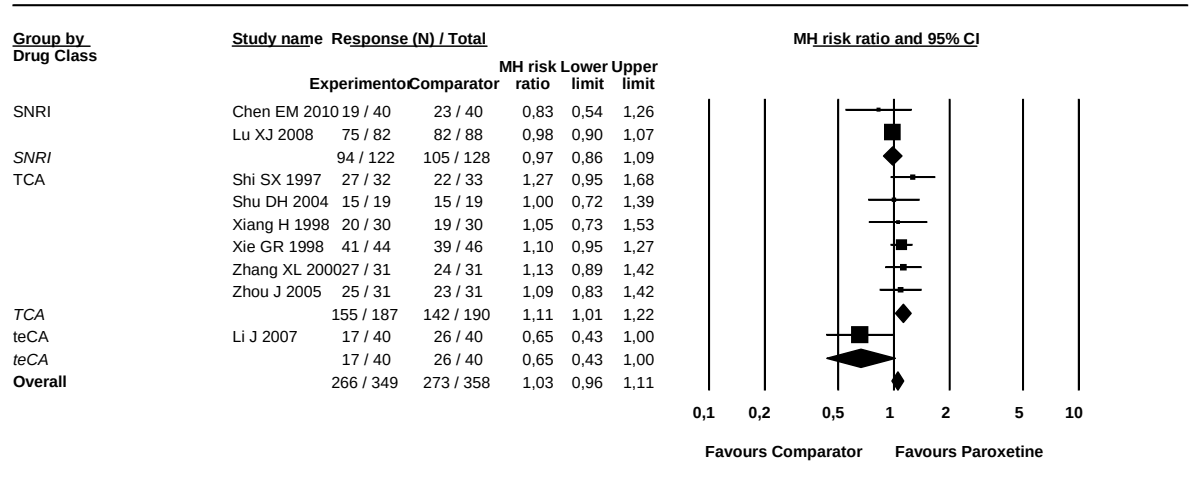
Analysis 9.5. Comparison 9 Citalopram versus other interventions

Total TESS scores (with Overall effects and effects in subgroups)



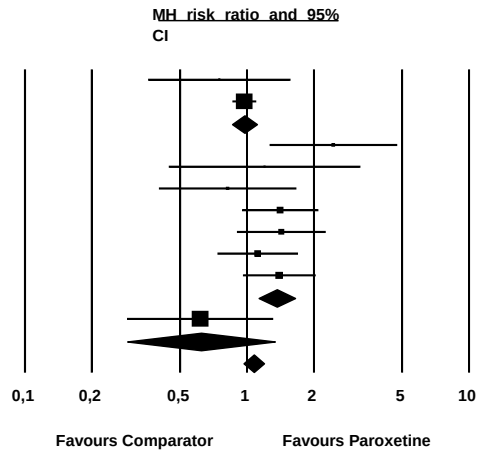
Analysis 10.1. Comparison 10 Paroxetine versus other drug classes

Response rate (with Overall effects and effects in subgroups)



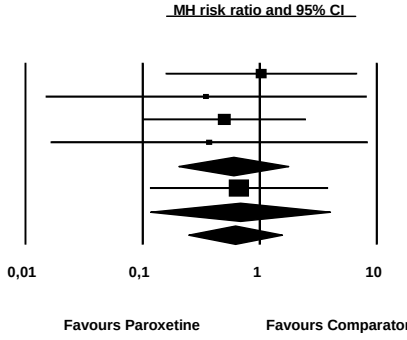
Analysis 10.2. Comparison 10 Paroxetine versus other drug classes Remission rate (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
SNRI		Chen EM 2010	9 / 40	12 / 40	0,75	0,36	1,58
		Lu XJ 2008	68 / 82	75 / 88	0,97	0,85	1,11
SNRI			77 / 122	87 / 128	0,97	0,85	1,10
TCA		Shi SX 1997	19 / 32	8 / 33	2,45	1,26	4,78
		Shu DH 2004	6 / 19	5 / 19	1,20	0,44	3,27
		Xiang H 1998	9 / 30	11 / 30	0,82	0,40	1,68
		Xie GR 1998	27 / 44	20 / 46	1,41	0,94	2,11
		Zhang XL 2000	20 / 31	14 / 31	1,43	0,90	2,28
		Zhou J 2005	19 / 31	17 / 31	1,12	0,73	1,71
	Remission parox-amitri	Sun XL 1997	15 / 17	12 / 19	1,40	0,95	2,05
TCA			115 / 204	87 / 209	1,35	1,12	1,63
teCA		Li J	8 / 40	13 / 40	0,62	0,29	1,32
teCA		2007	8 / 40	13 / 40	0,62	0,29	1,32
Overall			200 / 366	187 / 377	1,06	0,96	1,18



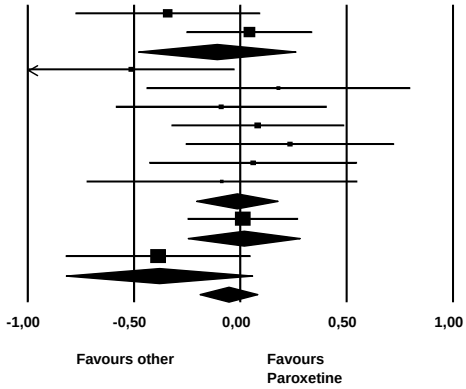
Analysis 10.3. Comparison 10 Paroxetine versus other drug classes Dropout rate due to side effects (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk rati o	Lower limit	Upper limit
TCA		Shi SX 1997	2 / 32	2 / 33	1,03	0,15	6,89
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		ZhangXL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout side effects parox-amitri	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
TCA			4 / 124	8 / 129	0,58	0,20	1,72
TCM		Chen LQ 2005	2 / 110	3 / 110	0,67	0,11	3,91
TCM			2 / 110	3 / 110	0,67	0,11	3,91
Overall			6 / 234	11 / 239	0,61	0,24	1,52



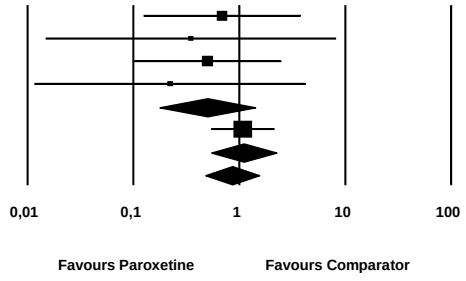
Analysis 10.4. Comparison 10 Paroxetine versus other drug classes The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Sample size		Statistics for each study		
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
SNRI	HAMD	Chen EM 2010	40	40	-0,34	-0,78	0,10
	HAMD	Lu XJ 2008	88	82	0,04	-0,26	0,34
SNRI			128	122	-0,12	-0,48	0,25
TCA	HAMD	Shi SX 1997	33	32	-0,51	-1,00	-0,02
	HAMD	Shu DH 2004	19	19	0,18	-0,44	0,80
	HAMD	Xiang H 1998	30	30	-0,09	-0,59	0,41
	HAMD	Xie GR 1998	46	44	0,08	-0,33	0,49
	HAMD	Zhang XL 2000	31	31	0,23	-0,26	0,73
	HAMD	Zhou J 2005	31	31	0,06	-0,43	0,55
	HAMD parox-amitri	Sun XL 1997	19	17	-0,09	-0,73	0,55
TCA			209	204	-0,02	-0,21	0,17
TCM	HAMD	Chen LQ 2005	110	110	0,01	-0,25	0,27
TCM			110	110	0,01	-0,25	0,27
teCA	HAMD	Li J 2007	40	40	-0,39	-0,82	0,05
teCA			40	40	-0,39	-0,82	0,05
Overall			487	476	-0,06	-0,20	0,08

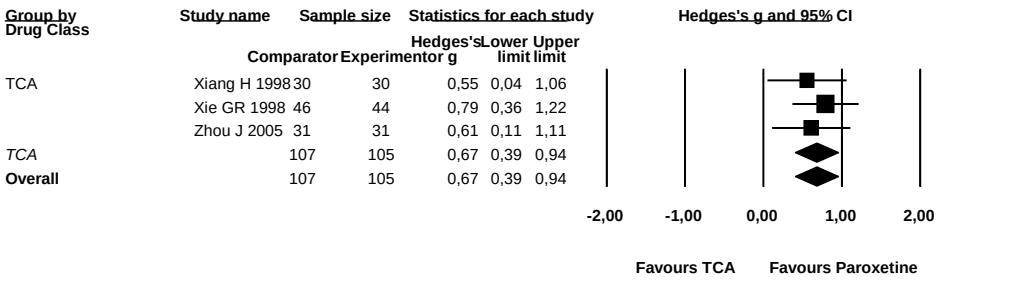


Analysis 10.5. Comparison 10 Paroxetine versus other drug classes Dropout rate overall (with Overall effects and effects in subgroups)

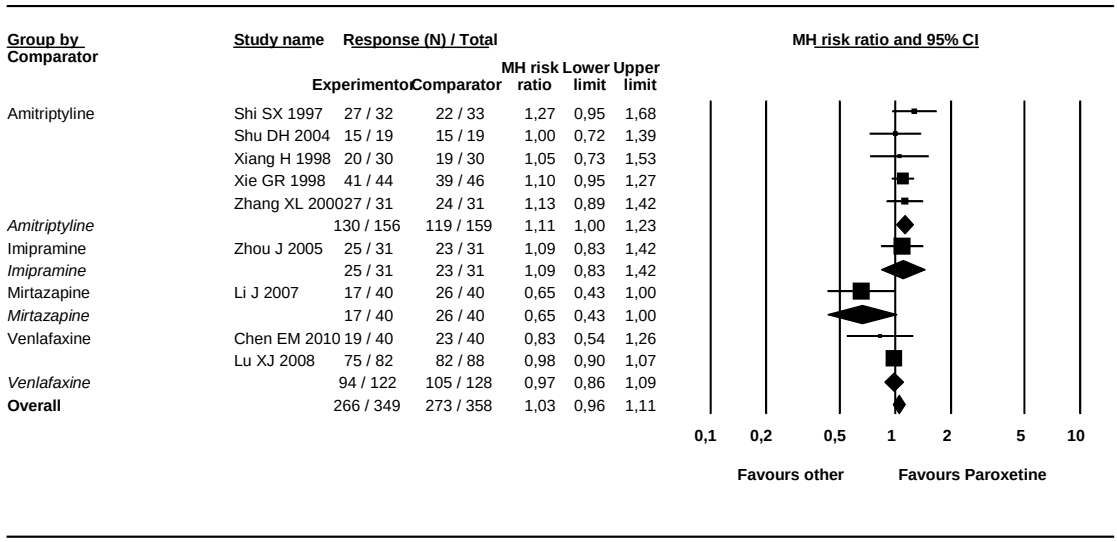
Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimentor	Comparator			
TCA		Shi SX 1997	2 / 32	3 / 33	0,69	0,12	3,85
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout parox-amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
TCA			4 / 124	10 / 129	0,49	0,17	1,38
TCM		Chen LQ 2005	14 / 110	13 / 110	1,08	0,53	2,18
TCM			14 / 110	13 / 110	1,08	0,53	2,18
Overall			18 / 234	23 / 239	0,84	0,47	1,50



Analysis 10.6. Comparison 10 Paroxetine versus other drug classes Total TESS scores (with Overall effects and effects in subgroups)



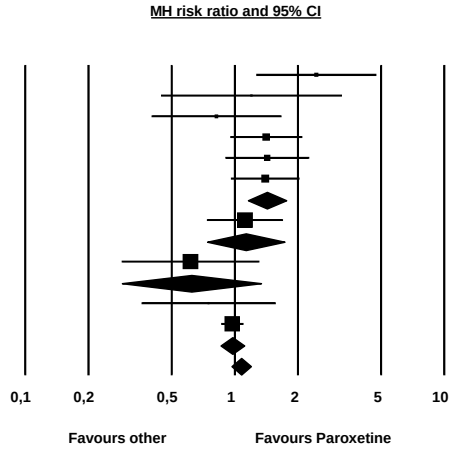
Analysis 11.1. Comparison 11 Paroxetine versus other interventions Response rate (with Overall effects and effects in subgroups)



Analysis 11.2. Comparison 11 Paroxetine versus other interventions

Remission rate (with Overall effects and effects in subgroups)

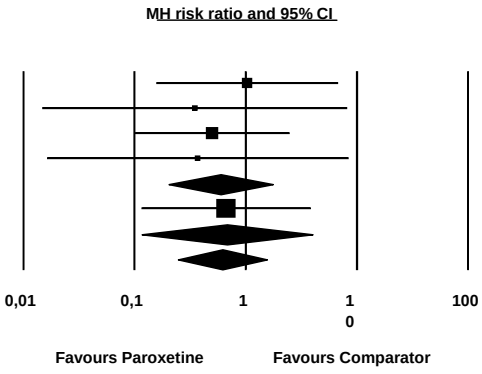
Group by Comparator	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Amitriptyline		Shi SX 1997	19 / 32	8 / 33	2,45	1,26	4,78
		Shu DH 2004	6 / 19	5 / 19	1,20	0,44	3,27
		Xiang H 1998	9 / 30	11 / 30	0,82	0,40	1,68
		Xie GR 1998	27 / 44	20 / 46	1,41	0,94	2,11
		Zhang XL 2000	20 / 31	14 / 31	1,43	0,90	2,28
	Remission parox-amitri	Sun XL 1997	15 / 17	12 / 19	1,40	0,95	2,05
Amitriptyline			96 / 173	70 / 178	1,41	1,14	1,74
Imipramine		Zhou J 2005	19 / 31	17 / 31	1,12	0,73	1,71
Imipramine			19 / 31	17 / 31	1,12	0,73	1,71
Mirtazapine		Li J 2007	8 / 40	13 / 40	0,62	0,29	1,32
Mirtazapine			8 / 40	13 / 40	0,62	0,29	1,32
Venlafaxine		Chen EM 2010	9 / 40	12 / 40	0,75	0,36	1,58
		Lu XJ 2008	68 / 82	75 / 88	0,97	0,85	1,11
Venlafaxine			77 / 122	87 / 128	0,97	0,85	1,10
Overall			200 / 366	187 / 377	1,06	0,96	1,18



Analysis 11.3. Comparison 11 Paroxetine versus other interventions

Dropout rate due to side effects (with Overall effects and effects in subgroups)

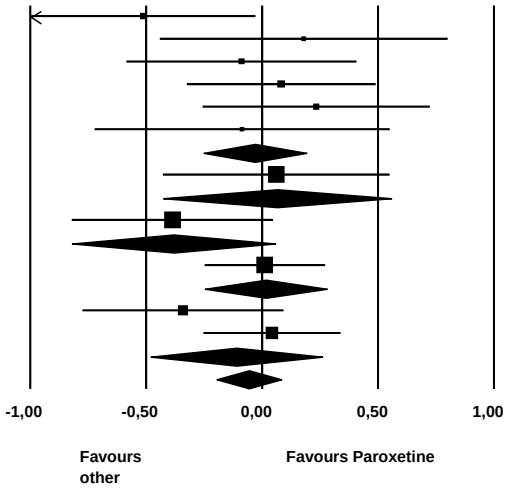
Group by Comparator	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Amitriptyline		Shi SX 1997	2 / 32	2 / 33	1,03	0,15	6,89
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout side effects paro-amit	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
Amitriptyline			4 / 124	8 / 129	0,58	0,20	1,72
TCM		Chen LQ 2005	2 / 110	3 / 110	0,67	0,11	3,91
TCM			2 / 110	3 / 110	0,67	0,11	3,91
Overall			6 / 234	11 / 239	0,61	0,24	1,52



Analysis 11.4. Comparison 11 Paroxetine versus other interventions

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

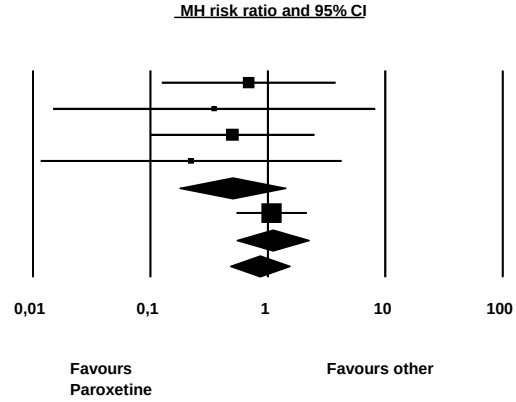
Group by Comparator	Outcome	Study name	Sample size		Statistics for each study		
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
Amitriptyline		Shi SX 1997	33	32	-0,51	-1,00	-0,02
		Shu DH 2004	19	19	0,18	-0,44	0,80
		Xiang H 1998	30	30	-0,09	-0,59	0,41
		Xie GR 1998	46	44	0,08	-0,33	0,49
		Zhang XL 2000	31	31	0,23	-0,26	0,73
	HAMD parox-amitri	Sun XL 1997	19	17	-0,09	-0,73	0,55
Amitriptyline			178	173	-0,04	-0,26	0,19
Imipramine		Zhou J 2005	31	31	0,06	-0,43	0,55
Imipramine			31	31	0,06	-0,43	0,55
Mirtazapine		Li J 2007	40	40	-0,39	-0,82	0,05
Mirtazapine			40	40	-0,39	-0,82	0,05
TCM		Chen LQ 2005	110	110	0,01	-0,25	0,27
TCM			110	110	0,01	-0,25	0,27
Venlafaxine		ChenEM 2010	40	40	-0,34	-0,78	0,10
		Lu XJ 2008	88	82	0,04	-0,26	0,34
Venlafaxine			128	122	-0,12	-0,48	0,25
Overall			487	476	-0,06	-0,20	0,08



Analysis 11.5. Comparison 11 Paroxetine versus other interventions

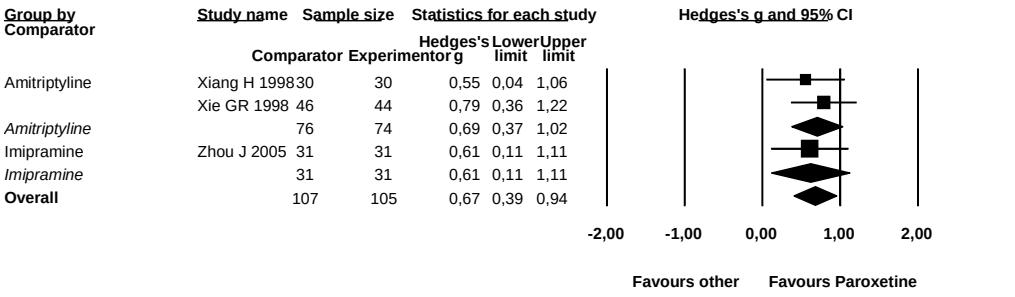
Dropout rate overall (with Overall effects and effects in subgroups)

Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limi
			Experimentor	Comparator			
Amitriptyline		Shi SX 1997	2 / 32	3 / 33	0,69	0,12	t3,85
		Xie GR 1998	0 / 44	1 / 46	0,35	0,01	8,33
		Zhang XL 2000	2 / 31	4 / 31	0,50	0,10	2,53
	Dropout parox-amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33
Amitriptyline			4 / 124	10 / 129	0,49	0,17	1,38
TCM		Chen LQ 2005	14 / 110	13 / 110	1,08	0,53	2,18
TCM			14 / 110	13 / 110	1,08	0,53	2,18
Overall			18 / 234	23 / 239	0,84	0,47	1,50



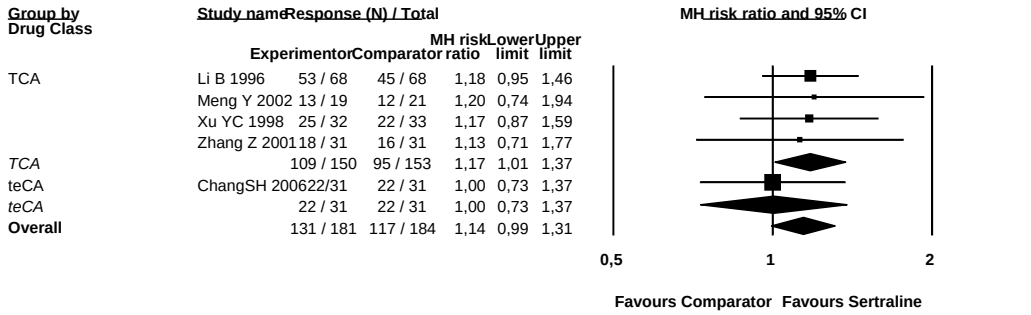
Analysis 11.6. Comparison 11 Paroxetine versus other interventions

Total TESS scores (with Overall effects and effects in subgroups)



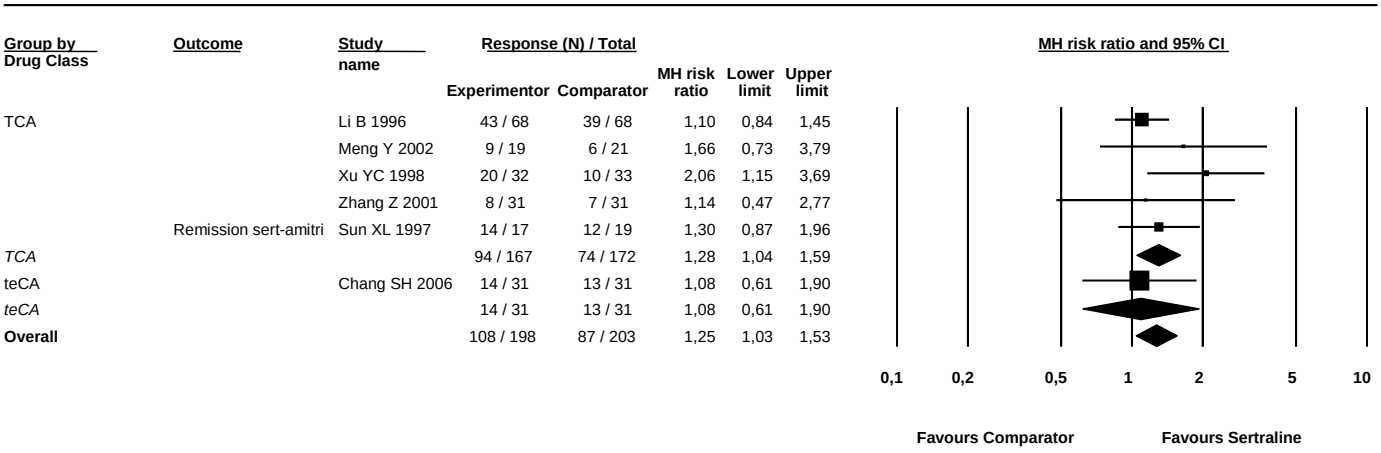
Analysis 12.1. Comparison 12 Sertraline versus other drug classes

Response rate (with Overall effects and effects in subgroups)



Analysis 12.2. Comparison 12 Sertraline versus other drug classes

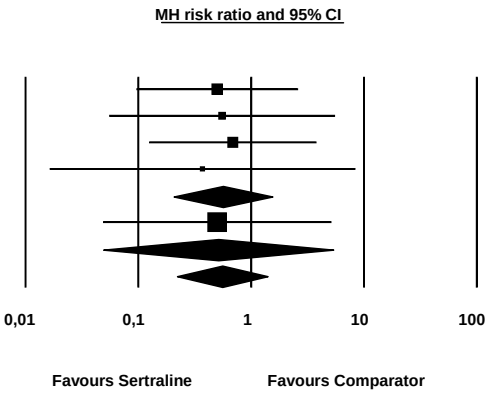
Remission rate (with Overall effects and effects in subgroups)



Analysis 12.3. Comparison 12 Sertraline versus other drug classes

Dropout rate due to side effects (with Overall effects and effects in subgroups)

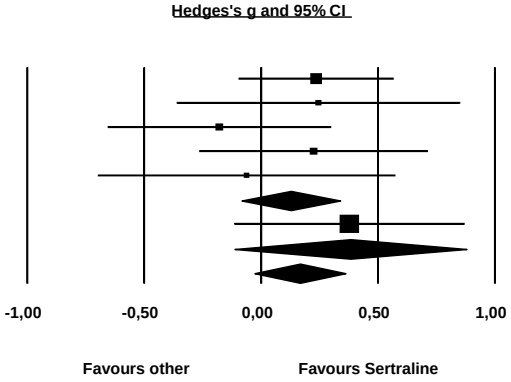
Group by Drug Class	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
			Experimentor	Comparator			
TCA		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
		Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85
	Dropout side effects sert-amitr	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
TCA			5 / 136	10 / 141	0,55	0,20	1,51
teCA		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
teCA			1 / 31	2 / 31	0,50	0,05	5,23
Overall			6 / 167	12 / 172	0,54	0,22	1,37



Analysis 12.4. Comparison 12 Sertraline versus other drug classes

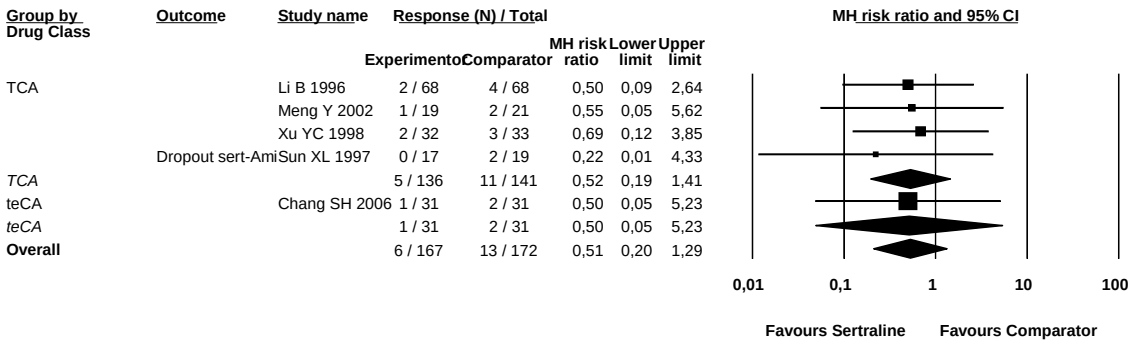
The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

Group by Drug Class	Outcome	Study name	Sample size		Statistics for each study		
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit
TCA		Li B 1996	68	68	0,24	-0,10	0,57
		Meng Y 2002	21	19	0,25	-0,37	0,86
		Xu YC 1998	33	32	-0,18	-0,66	0,30
		ZhangZ 2001	31	31	0,22	-0,27	0,72
	HAMD sert-amitri	SunXL 1997	19	17	-0,06	-0,70	0,58
TCA			172	167	0,12	-0,09	0,33
teCA		Chang SH 2006	31	31	0,38	-0,12	0,87
teCA			31	31	0,38	-0,12	0,87
Overall			203	198	0,16	-0,03	0,36



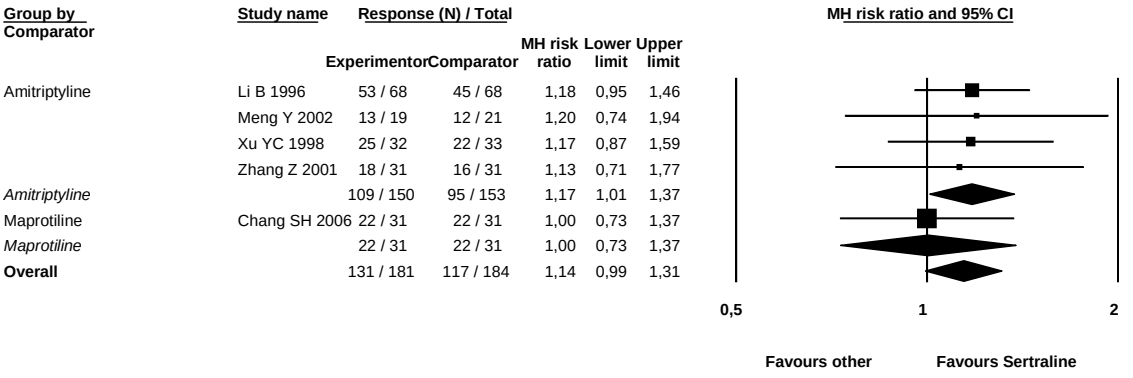
Analysis 12.5. Comparison 12 Sertraline versus other drug classes

Dropout rate overall (with Overall effects and effects in subgroups)

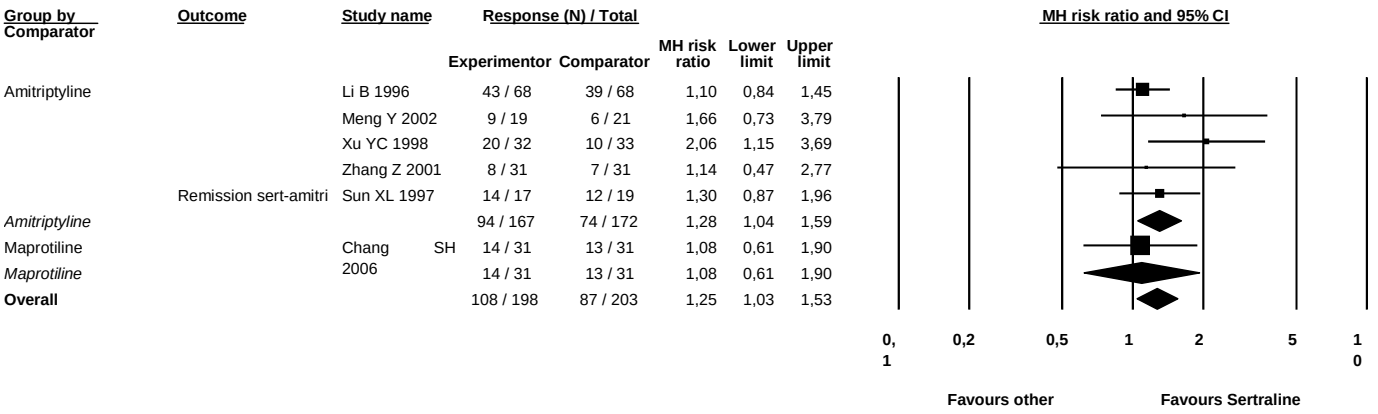


Analysis 13.1. Comparison 13 Sertraline versus other interventions

Response rate (with Overall effects and effects in subgroups)

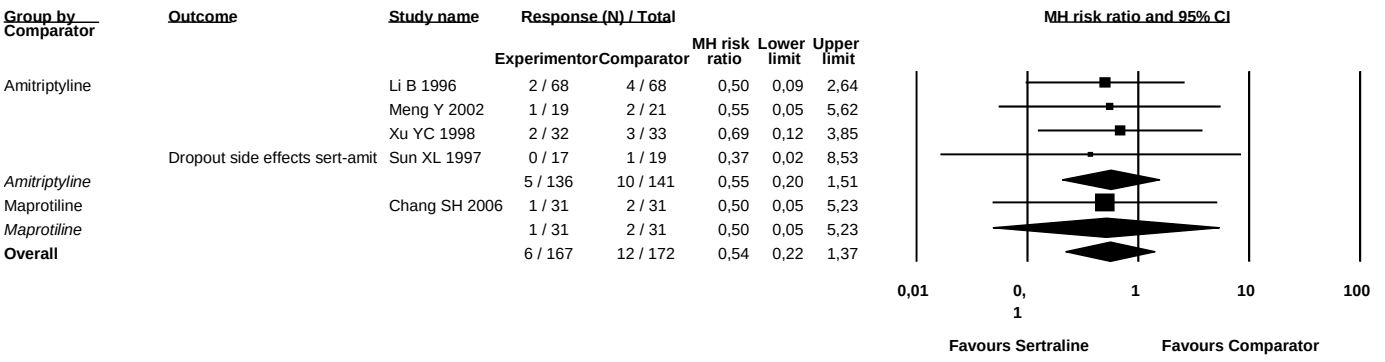


Analysis 13.2. Comparison 13 Sertraline versus other interventions Remission rate (with Overall effects and effects in subgroups)



Group by Comparator	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Amitriptyline		Li B 1996	43 / 68	39 / 68	1,10	0,84	1,45
		Meng Y 2002	9 / 19	6 / 21	1,66	0,73	3,79
		Xu YC 1998	20 / 32	10 / 33	2,06	1,15	3,69
		Zhang Z 2001	8 / 31	7 / 31	1,14	0,47	2,77
	Remission sert-amitri	Sun XL 1997	14 / 17	12 / 19	1,30	0,87	1,96
Amitriptyline			94 / 167	74 / 172	1,28	1,04	1,59
Maprotiline		Chang SH 2006	14 / 31	13 / 31	1,08	0,61	1,90
Maprotiline			14 / 31	13 / 31	1,08	0,61	1,90
Overall			108 / 198	87 / 203	1,25	1,03	1,53

Analysis 13.3. Comparison 13 Sertraline versus other interventions Dropout rate due to side effects (with Overall effects and effects in subgroups)

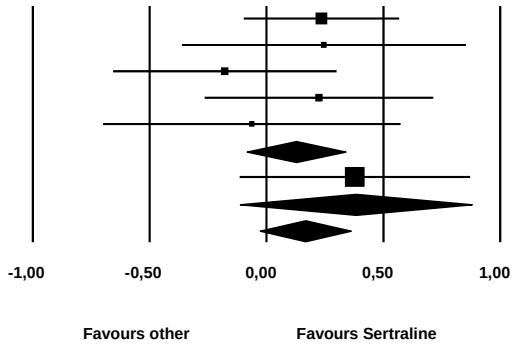


Group by Comparator	Outcome	Study name	Response (N) / Total Experimentor	Comparator	MH risk ratio	Lower limit	Upper limit
Amitriptyline		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62
		Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85
	Dropout side effects sert-amit	Sun XL 1997	0 / 17	1 / 19	0,37	0,02	8,53
Amitriptyline			5 / 136	10 / 141	0,55	0,20	1,51
Maprotiline		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23
Maprotiline			1 / 31	2 / 31	0,50	0,05	5,23
Overall			6 / 167	12 / 172	0,54	0,22	1,37

Analysis 13.4. Comparison 13 Sertraline versus other interventions

The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)

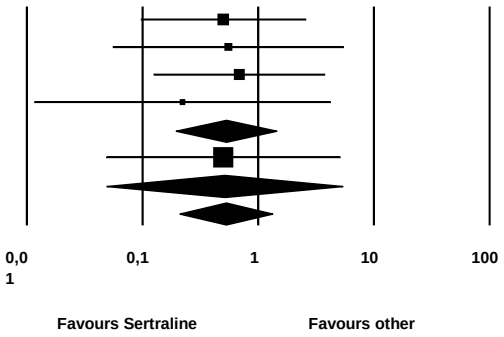
Group by Comparator	Outcome	Study name	Sample size		Statistics for each study			Hedges's g and 95% CI
			Comparator	Experimentor	Hedges's g	Lower limit	Upper limit	
Amitriptyline		Li B 1996	68	68	0,24	-0,10	0,57	
		MengY 2002	21	19	0,25	-0,37	0,86	
		Xu YC 1998	33	32	-0,18	-0,66	0,30	
		Zhang Z 2001	31	31	0,22	-0,27	0,72	
	HAMD sert-amitri	Sun XL 1997	19	17	-0,06	-0,70	0,58	
Amitriptyline			172	167	0,12	-0,09	0,33	
Maprotiline		Chang SH 2006	31	31	0,38	-0,12	0,87	
Maprotiline			31	31	0,38	-0,12	0,87	
Overall			203	198	0,16	-0,03	0,36	



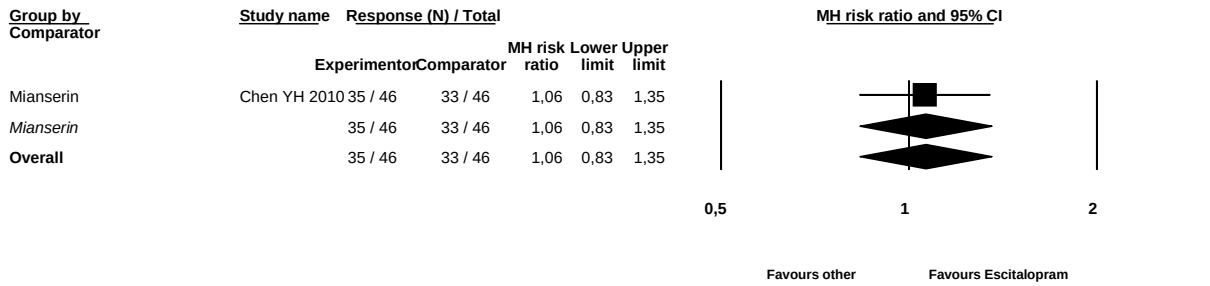
Analysis 13.5. Comparison 13 Sertraline versus other interventions

Dropout rate overall (with Overall effects and effects in subgroups)

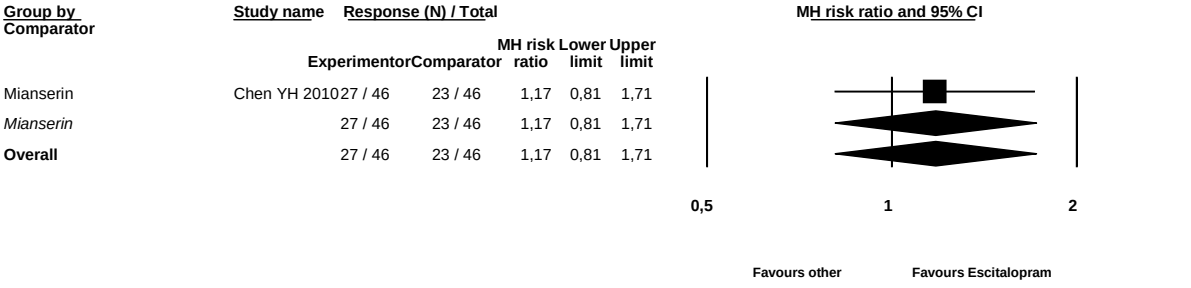
Group by Comparator	Outcome	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit	MH risk ratio and 95% CI
			Experimentor	Comparator				
Amitriptyline		Li B 1996	2 / 68	4 / 68	0,50	0,09	2,64	
		Meng Y 2002	1 / 19	2 / 21	0,55	0,05	5,62	
		Xu YC 1998	2 / 32	3 / 33	0,69	0,12	3,85	
	Dropout sert-Amitri	Sun XL 1997	0 / 17	2 / 19	0,22	0,01	4,33	
Amitriptyline			5 / 136	11 / 141	0,52	0,19	1,41	
Maprotiline		Chang SH 2006	1 / 31	2 / 31	0,50	0,05	5,23	
Maprotiline			1 / 31	2 / 31	0,50	0,05	5,23	
Overall			6 / 167	13 / 172	0,51	0,20	1,29	



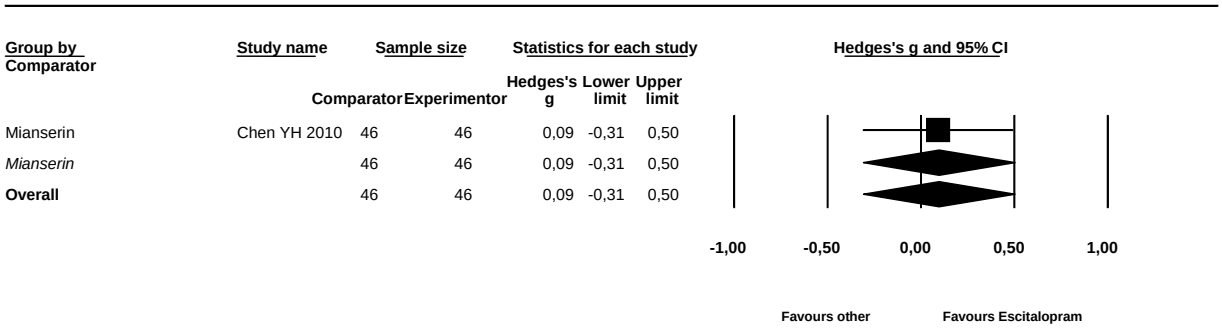
Analysis 14.1. Comparison 14 Escitalopram versus other interventions Response rate (with Overall effects and effects in subgroups)



Analysis 14.2. Comparison 14 Escitalopram versus other interventions Remission rate (with Overall effects and effects in subgroups)



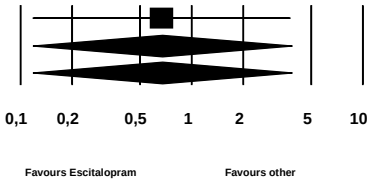
Analysis 14.3. Comparison 14 Escitalopram versus other interventions The mean total HAMD scores at endpoint (with Overall effects and effects in subgroups)



Analysis 14.4. Comparison 14 Escitalopram versus other interventions

Dropout rate overall (with Overall effects and effects in subgroups)

Group by Comparator	Study name	Response (N) / Total		MH risk ratio	Lower limit	Upper limit
		Experimentor	Comparator			
Mianserin	Chen YH 2010	2 / 46	3 / 46	0,67	0,12	3,81
Mianserin		2 / 46	3 / 46	0,67	0,12	3,81
Overall		2 / 46	3 / 46	0,67	0,12	3,81



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