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# Milnacipran versus other antidepressive agents for depression (Review)

Nakagawa A, Watanabe N, Omori IM, Barbui C, Cipriani A, McGuire H, Churchill R, Furukawa TA

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INDEX TERMS 100



#### [Intervention Review]

# Milnacipran versus other antidepressive agents for depression

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# ABSTRACT

#### Background

Although pharmacological and psychological interventions are both effective for major depression, antidepressant drugs are frequently used as first-line treatment in primary and secondary care settings. Milnacipran, a dual serotonin-norepinephrine reuptake inhibitor (SNRI), is one of the antidepressant drugs that clinicians use for routine depression care.

#### Objectives

To assess the evidence for the efficacy, acceptability and tolerability of milnacipran in comparison with tricyclic antidepressants (TCAs), heterocyclics, SSRIs and other newer antidepressive agents in the acute-phase treatment of major depression.

#### Search methods

The Cochrane Collaboration Depression, Anxiety & Neurosis review group Controlled Trials Register (CCDANCTR-Studies and CCDANCTR-References) were electronically searched in August 2008. References of relevant trials and other reviews were also checked. Trial databases of the drug-approving agencies and ongoing clinical trial registers for all published and unpublished trials were hand-searched in 2007. All relevant authors were contacted for supplemental data. No language restriction was applied.

#### **Selection criteria**

Randomised controlled trials comparing milnacipran with any other active antidepressive agents (including non-conventional agents such as herbal products like hypericum) as monotherapy in the acute phase of major depression were selected.

#### Data collection and analysis

Two reviewers independently checked eligibility, assessed methodological quality and extracted data from the eligible trials using a standardised data extraction form. The number of participants who responded to treatment or those who achieved remission were calculated on an intention-to-treat basis. Random-effects meta-analyses were conducted, combining data from the included trials.



#### **Main results**

A total of 16 randomised controlled trials (n=2277) were included in the meta-analysis.Despite the size of this sample, the pooled 95% confidence intervals were rather wide and there were no statistically significant differences in efficacy, acceptability and tolerability when comparing milnacipran with other antidepressive agents. However, compared with TCAs, patients taking milnacipran were associated with fewer dropouts due to adverse events (OR 0.55; 95%CI 0.35 to 0.85). There was also some weak evidence to suggest that patients taking milnacipran experienced fewer adverse events of sleepiness/ drowsiness, dry mouth or constipation compared with TCAs.

#### **Authors' conclusions**

Currently, there is inadequate evidence to conclude whether milnacipran is superior, inferior or the same as other antidepressive agents in terms of efficacy, acceptability and tolerability in the acute phase treatment of major depression. However, there is some evidence in favour of milnacipran over TCAs in terms of dropouts due to adverse events (acceptability) and the rates of experiencing adverse events (tolerability). Information about other clinically meaningful outcomes such as cost-effectiveness and social functioning, including the ability to return to work, is lacking. Further study is needed to answer whether milnacipran would be the better choice of antidepressant for acute major depression.

# PLAIN LANGUAGE SUMMARY

#### Milnacipran versus other antidepressive agents for depression

Major depression, also known as major depressive disorder or unipolar depression, is a common mental disorder characterised by a combination of symptoms that interfere with a person's ability to work, sleep, study, eat, and enjoy pleasurable activities. An episode of major depression may occur only once in a person's lifetime, but more often, it recurs throughout a person's life.

Antidepressant drugs are frequently used as first-line treatment for major depression in primary and secondary care settings. Milnacipran, a dual serotonin-norepinephrine reuptake inhibitor, is one of the antidepressant drugs that clinicians use for routine depression care in some countries. This systematic review investigated the efficacy, acceptability and tolerability of milnacipran compared to that of other antidepressive agents in the acute phase treatment of major depression. A total of 16 randomised controlled trials (2277 participants) were included in this review. When we brought together the results of approximately 2000 patients, we were unable to say whether milnacipran is better, worse or the same when compared to other antidepressive agents used in practice in terms of efficacy, acceptability. However, there is some evidence that fewer people taking milnacipran stop taking the drug ('drop out') due to side effects and fewer people taking milnacipran experience side effects such as sleepiness, dry mouth or constipation than do people who take tricyclic antidepressants.



### BACKGROUND

#### **Description of the condition**

Major depression, also known as major depressive disorder or unipolar depression, is a common metal disorder characterised by a combination of persistent symptoms (including depressed mood, loss of interest, loss of appetite, insomnia, fatigue, poor concentration, extreme guilt and suicide ideation) that interfere with a person's ability to work, study and enjoy pleasurable activities (APA 1994). Compared with other medical diagnoses, depression is very common. Lifetime prevalence estimates for major depression in the community range from 15 to 17% (APA 1994), 12-month prevalence from 6 to 7% (Kessler 2003). The prevalence of major depression in the medical outpatient is 5 to 13% (Coyne 1994). Major depression is the third leading cause of burden among all diseases after lower respiratory infections and diarrhoeal diseases, accounting for 4.3% of human suffering in terms of illhealth; moreover, it is expected to show a rising trend during the coming 20 years (WHO 2004). This condition is associated with a marked personal, social and economic morbidity, loss of functioning and productivity, and creates significant demands on service providers in terms of workload (NICE 2007). In the USA, the economic burden of depression has been estimated at just over \$83 billion in 2000, of which \$26 billion were direct treatment costs, \$5 billion were suicide-related costs, and \$52 billion were workplace costs (Greenberg 2003). It is also suspected that these figures are still underestimates of the true economic burden of the disease, which may in addition involve burden on family members and caregivers, the cost of lost productivity while at work, and cost associated with those who remain untreated (Greenberg 2005).

#### **Description of the intervention**

Although pharmacological and psychological interventions are both effective for major depression, in primary and secondary care settings antidepressant (AD) drugs remain the mainstay of treatment (APA 2000; Ellis 2004; NICE 2007) (see below for other references to the relevant evidence). Amongst ADs many different agents are available, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs: venlafaxine, duloxetine, milnacipran), and other newer agents (mirtazapine, reboxetine, bupropion). In many western countries, during the last 20 years, ADs consumption has dramatically risen, mainly because of the increasing consumption of SSRIs and newer ADs, which have progressively become the most commonly prescribed ADs (Ciuna 2004; Guaiana 2005). SSRIs are generally better tolerated than TCAs (Barbui 2007), and there is evidence of similar efficacy (Anderson 2000a; Geddes 2000; Williams 2000). However, head-to-head comparisons provide contrasting findings. Amitriptyline, for example, may have the edge over SSRIs in terms of efficacy (Guaiana 2007), and individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Cipriani 2005; Smith 2002).

#### How the intervention might work

Milnacipran has been available as an antidepressant since 1997 in many countries including France and Japan (34 countries and regions as of 2006). Milnacipran appears to act exclusively at presynaptic sites to inhibit noradrenaline (norepinephrine) and Cochrane Database of Systematic Reviews

serotonin uptake (Moret 1985), but unlike TCAs, has no significant effect on any neurotransmitter receptor (Briley 1996). Thus, compared with TCAs, milnacipran has shown a lower incidence of anticholinergic-like side effects, less sedation due to histamine H1-receptor binding and lower incidence of postural hypotension due to alpha-1 adrenoceptor antagonism (Spencer 1998). The pharmacokinetic profile of the drug indicates that milnacipran has a high bioavailability, low plasma protein binding (13%) and is mostly eliminated in urine: 50% as the unchanged drug, 30% as a glucuronide (main metabolite) and the remaining 20% by oxidative transformation (Puozzo 1996). Milnacipran does not affect the activities of CYP-2D6, 2C19, 1A2 and 3A4 isoforms, and its pharmacokinetics are not modified in poor metabolizers of CYP-2D6 and CYP-2C9 (Puozzo 1996; Sawada 2001; Puozzo 2005). Furthermore, studies in patients with liver dysfunction suggest that dose adjustment is not necessary or to be minor when milnacipran is administered to these patients (Puozzo 1996).

#### Why it is important to do this review

Given that the most recent available evidence refers to the SSRIs as an homogeneous group (Arroll 2005; Geddes 2000; Hansen 2005), it is still unclear how each newer antidepressive agent compares with other antidepressants in terms of effects and adverse events. A group of researchers therefore agreed to join forces under the rubric of the Multiple meta-Analyses of New Generation Antidepressants (MANGA) Study to systematically review all available evidence for each specific newer antidepressant.

In terms of milnacipran, only limited evidence has been established regarding the efficacy, acceptability and tolerability in comparison with other antidepressive agents, to date. Some RCTs have reported that milnacipran has an antidepressant efficacy similar to other antidepressants, such as imipramine (Tignol 1998; Van Amerongen 2002; Lopez-Ibor 2004), clomipramine (Leinonen 1997; Steen 1997), fluoxetine (Guelfi 1998), fluvoxamine (Clerc 2001) and paroxetine (Sechter 2004). In a systematic review (Puech 1997), milnacipran has shown superior antidepressant efficacy in comparison with SSRIs and the tolerability has been comparable to that of the SSRIs. However, this review was sponsored by a pharmaceutical company marketing milnacipran and was published more than a decade ago. Therefore, there is a good reason to conduct an up-to-date comprehensive systematic quantitative review using currently best-available evidence on comparative efficacy and adverse effects of milnacipran against other antidepressive agents.

The primary objective of this systematic review is to assess the evidence for the efficacy, acceptability and tolerability of milnacipran in comparison with TCAs, heterocyclics, SSRIs and other newer antidepressive agents, including non-conventional agents, in the acute-phase treatment of major depression.

#### OBJECTIVES

- 1. To determine the efficacy of milnacipran in comparison with other antidepressive agents in alleviating the acute symptoms of depression.
- 2. To review acceptability of treatment with milnacipran in comparison with other antidepressive agents.
- 3. To investigate the adverse effects of milnacipran in comparison with other antidepressive agents.



# METHODS

# Criteria for considering studies for this review

#### **Types of studies**

Only randomised controlled trials were included. Quasirandomised trials, such as those allocating by using alternate days of the week, were excluded. For trials which have a crossover design only results from the first randomisation period were considered.

# **Types of participants**

Patients aged 18 or older, of both sexes with a primary diagnosis of major depression. Studies adopting any standardised criteria to define patients suffering from unipolar major depression were included. Studies from the 1990s onwards were likely to have used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Ealier studies may have used ICD-9 (WHO 1978), DSM-III (APA 1980) / DSM- III-R (APA 1987) or other diagnostic systems. ICD-9 is not operationalised criteria, because it has only disease names and no diagnostic criteria, so studies using ICD-9 were excluded. On the other hand, studies using Feighner Criteria or Research Diagnostic Criteria were included. We included the following depression subtypes: chronic, with catatonic features, with melancholic features, with atypical features, with postpartum onset, and with seasonal pattern. Studies in which less than 20% of the participants may be suffering from bipolar depression were included. A concurrent secondary diagnosis of another psychiatric disorder was not considered as exclusion criteria.

Major depression with psychotic features were excluded. A concurrent primary diagnosis of Axis I or II disorders was an exclusion criteria. Antidepressant trials in depressive patients with a serious concomitant medical illness were also excluded.

#### **Types of interventions**

#### **Experimental intervention**

Milnacipran (as monotherapy). No restrictions on dose, frequency, intensity and duration were applied.

#### **Comparator intervention**

Other active agents in the treatment of acute major depression, including:

- 1. TCAs (imipramine, clomipramine, amitriptyline)
- 2. Heterocyclic antidepressants (mianserin)
- 3. SSRIs ( fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram, escitalopram)
- 4. Newer antidepressants (SNRIs such as venlafaxine and duloxetine, MAOIs or newer agents such as mirtazapine, bupropion, reboxetine
- 5. Non-conventional antidepressive agents such as herbal products like hypericum (Linde 2008) and fish oil (Appleton 2006).

No restrictions on dose, frequency, intensity and duration were applied.

Other type of psychopharmacological agent such as anxiolytics, antic-convulsants, anti-psychotics or mood-stabilizers were excluded. Trials in which milnacipran was used as an augmentation

strategy were excluded. Placebo-controlled trials were also excluded.

#### Types of outcome measures

Efficacy, acceptability and tolerability during and at the end of acute-phase treatment trials, defined as 6 to 12 weeks, was our outcome of interest. However, when data from trials longer than 12 weeks were available, we also included them.

#### **Primary outcomes**

Number of patients who responded to treatment, showing a reduction of at least 50% on the Hamilton Rating Scale of Depression (HAM-D) (Hamilton 1960) or Montgomery-Asberg Depression Scale (MADRS) (Montgomery 1979), or "much or very much improved" (score 1 or 2) on CGI-Improvement (Guy 1970) out of the total number of randomised patients. HAM-D has been the golden standard measure of depression severity for the clinical trials of antidepressants (Williams 2001).Therefore, we used the HAM-D for judging response whenever possible, even when we needed to impute SDs or response rates according to the procedures described in the Methods below.

When studies reported response rates at various time points of the trial, we subdivided the treatment indices as follows, according to criteria decided a priori:

- 1. Early phase treatment: between 1 and 4 weeks (preference was given to the time point closest to 2 weeks);.
- 2. Acute phase treatment : between 6 and 12 weeks (preference was given to the study endpoint);
- 3. Follow-up phase treatment: between 4 and 6 months (preference was given to the time point closest to 24 weeks)..

#### Secondary outcomes

- Number of patients who achieved remission. The cutoff point for remission was set a priori (1) at 7 or less for the 17-item HAM-D and at 8 or less for all the other longer versions of HAM-D, or (2) at 12 or less on the MADRS (Zimmerman 2004), or (3) "not ill or borderline mentally ill" (score 1 or 2) on CGI-Severity (Guy 1970). We used the HAM-D for judging remission whenever possible.
- 2. Severity of depression at the end of the trial as measured on continuous scale such as HAM-D, MADRS, etc. We applied 'loose' ITT analyses, whereby all the patients with at least one post-baseline measurement were represented by their last observations carried forward.
- 3. Social adjustment, social functioning including the Global Assessment of Function (GAF) (Luborsky 1962) scores.
- 4. Health-related quality of life : We will limit ourselves to SF-12/ SF-36 (Ware 1993), HoNOS (Wing 1994) and WHO-QOL (WHOQOL Group 1998).
- 5. Costs to health care services
- 6. Acceptability measures
  - a. Number of patients who dropped out during the trial as a proportion of the total number of randomised patients due to any cause
  - b. Number of patients who dropped out during the trial as a proportion of the total number of randomised patients due to inefficacy



- c. Number of patients who dropped out during the trial as a proportion of the total number of randomised patients due to adverse events
- 7. Tolerability measures:
  - a. Total number of patients experiencing at least some adverse events
  - b. Total number of patients experiencing the following specific adverse events was sought for:
    - i. sleepiness/drowsiness
    - ii. insomnia
    - iii. dry mouth
    - iv. constipation
    - v. urination problems
    - vi. hypotension
    - vii.agitation/anxiety
    - viiisuicide wishes/gestures/attempts
    - ix. completed suicide
    - x. vomiting/nausea
    - xi. diarrhoea

In order not to miss any relatively rare or unexpected yet important adverse events, in the data extraction phase, we collected all adverse event data reported in the literature and discussed ways to summarize them post hoc.

# Search methods for identification of studies

#### **Electronic searches**

We searched using the Cochrane Collaboration Depression, Anxiety & Neurosis Controlled Trials Registers (CCDANCTR-Studies and CCDAN-References) (searched in December 2006; updated in August 2008). This register of randomised controlled trials is compiled by methodical searches of CENTRAL, AMED, CINAHL, EMBASE, LILACS, MEDLINE, PSYCINFO, PSYNDEX supplemented with hand searching of both journals and conference proceedings.

CCDANCTR-Studies were searched using the following search strategy:

Diagnosis = Depress\* or Dysthymi\* or "Adjustment Disorder\*" or "Mood Disorder\*" or "Affective Disorder" or "Affective Symptoms" and Intervention = Milnacipran

CCDANCTR-References were searched using the following search strategy:

Keyword = Depress\* or Dysthymi\* or "Adjustment Disorder\*" or "Mood Disorder\*" or "Affective Disorder" or "Affective Symptoms" and Free-Text = Milnacipran

Trial databases of the following drug-approving agencies - (the Food and Drug Administration (FDA) in the USA, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the European Medicines Agency (EMEA) in the EU, the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan, the Therapeutic Goods Administration (TGA) in Australia and ongoing trial registers (clinicaltrials.gov in the USA, ISRCTN and National Research Register in the UK, Nederlands Trial Register in the Netherlands, EUDRACT in the EU, UMIN-CTR in Japan and the Australian Clinical Trials Registry in Australia) were hand-searched for published, unpublished and ongoing controlled trials

#### Searching other resources

#### Hand-searching

Appropriate journals and conference proceedings relating to milnacipran treatment for depression have been hand-searched and incorporated into the CCDANCTR databases up until August 2008.

#### Personal communications

Pharmaceutical companies and experts in this field were asked if they knew of any study which meets the inclusion criteria of this review (contacted in May 2007).

#### **Reference lists**

Reference lists of the included studies, previous systematic reviews and major textbooks of affective disorder written in English were checked for published reports and citations of unpublished research. The reference of all included studies were checked via Science Citation Index for articles which had cited the included study.

#### Data collection and analysis

#### **Selection of studies**

Studies relating to milnacipran generated by the electronic search of the CCDANCTR-Studies were scanned by one review authors (HMG).Full texts were retrieved of all those studies which met the following rough inclusion criteria:

- 1. Randomized trial
- 2. Comparing milnacipran against any other antidepressive agents
- 3. Patients with depression, regardless of the diagnostic criteria used.

Studies relating to milnacipran generated by the search strategies of the CCDANCTR-References and the other complementary searches were checked by the CCDAN Trial Search Coordinator (HMG), who is an author of this review, and another independent review author (AN and NW) to see if they met the inclusion criteria, firstly based on the title and abstracts. All the studies rated as possible candidates by either of the two reviewers (AN and NW) were added to the preliminary list and their full texts were retrieved. All the full text articles in this preliminary list were then assessed by two review authors (AN and NW) independently to see if they met strict inclusion criteria. If the raters disagreed the final rating was made by consensus with the involvement (if necessary) of another member of the review group. Non-congruence in selection of trials were reported as percentage disagreement. Considerable care was taken to exclude duplicate publications.

#### **Data extraction and management**

One review author (AN) first extracted data concerning participant characteristics (age, sex, depression diagnosis, comorbidity, depression severity, antidepressant treatment history for the index episode, study setting), intervention details (intended dosage range, mean daily dosage actually prescribed, co-intervention if any, milnacipran as investigational drug or as comparator drug, sponsorship) and outcome measures of interest from the included studies. We planned at protocol stage to compare results with those in relevant completed reviews of individual antidepressants in the Cochrane Library and feed back any discrepancies to their authors:

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in the event, there were insufficient existing reviews to make this possible.

# Assessment of risk of bias in included studies

We used the Cochrane risk-of-bias tool as recommended in RevMan 5.0.0 (Higgins 2008a; Higgins 2008b). This instrument consists of six items. Two of the items assess the strength of the randomisation process in preventing selection bias in the assignment of participants to interventions: adequacy of sequence generation and allocation concealment. The third item (blinding) assesses the influence of performance bias on the study results. The fourth item assesses the likelihood of incomplete outcome data, which raise the possibility of bias in effect estimates. The fifth item assesses selective reporting, the tendency to preferentially report statistically significant outcomes. It requires a comparison of published data with trial protocols, when such are available. The final item refers to other sources of bias that are relevant in certain circumstances, for example, in relation to trial design (methodological issues such as those related to crossover designs and early trial termination) or setting.

Two independent review authors (AN and NW) assessed risk of bias in each trial independently, in accordance with the Cochrane Handbook (Higgins 2008a). Where inadequate details of allocation concealment and other characteristics of trials were provided, the authors were contacted in order to obtain further information. If the raters disagreed the final rating was made by consensus with the involvement (if necessary) of another member of the review group.

# Measures of treatment effect

Data were checked and entered into RevMan 5 software by two review authors (AN and NW) (double data entry). For dichotomous, or event-like data, odds ratios (OR) were calculated with 95% confidence intervals. For continuous data, weighted mean differences (WMD) or standardized mean differences (SMD) (where different measurement scales are used) were calculated with 95% confidence intervals.

# Unit of analysis issues

We planned at protocol stage to compare results from the initial randomisation phase of a crossover trial or a trial involving three (or more)-armed trial with a placebo arm. However, none of the included studies required implementation of these plans.

# Dealing with missing data

Responders and remitters to treatment were calculated on an intention-to-treat (ITT) basis: drop-outs were always included in this analysis. Where participants had withdrawn from the trial before the endpoint, it was assumed they would have experienced the negative outcome by the end of the trial (e.g. failure to respond to treatment). When there were missing data and the method of "last observation carried forward" (LOCF) were been used to do an ITT analysis, then the LOCF data were used, with due consideration of the potential bias and uncertainty introduced. When dichotomous or continuous outcomes were not reported, trial authors were asked to supply these data.

When only the SE or t statistics or p values were reported, SDs were calculated according to Altman (Altman 1996). In the absence of supplemental data from the authors, the SDs of the HAM-D (or any other depression scale) and response and remission rates

were calculated according to validated methods (Furukawa 2005; Furukawa 2006). We examined the validity of these imputation in the sensitivity analyses.

# Assessment of heterogeneity

We planned at protocol stage to present the skewed data and nonquantitative data descriptively, however, no such relevant data were identified from the included studies. Should they be identified in future updates, any outcome whose minimum score is zero will be considered skewed when the mean is smaller than twice the SD.

Heterogeneity between studies was investigated by the I-squared statistic (I-squared equal to or more than 50% was considered indicative of heterogeneity) and the p value from the chi-squared test (Higgins 2003), and by visual inspection of the forest plots.

### Assessment of reporting biases

Where a sufficient number of trials were available, a funnel plot analysis was performed to check for existence of small study effects including publication bias.

#### Data synthesis

A random effects model was used to pool the results of single studies, because this model is more conservative than fixed effects model and incorporates both within-study and betweenstudy variance. Further, a random effects model OR was used for the primary analysis rather than a random effect risk ratio (RR) because it has been shown that the highest generalisability in our empirical examination of summary effect measures for meta-analyses (Furukawa 2002a). The robustness of this summary measure was routinely examined by checking the fixed effect model OR and the random effects model RR. Fixed effect analyses were done routinely for the continuous outcomes as well, to investigate the effect of the choice of method on the estimates. Material differences between the models were reported.

#### Subgroup analysis and investigation of heterogeneity

Subgroup analyses should be performed and interpreted with caution because multiple analyses will lead to false positive conclusions (Oxman 1992). However, we performed the following subgroup analyses, where possible, for the following reasons, which were stated a priori in our protocol.

- Milnacipran dosing (fixed low dosage, fixed standard dosage, fixed high dosage; flexible low dosage, flexible standard dosage, flexible high dosage), because there was evidence to suspect that low dosage antidepressant might be associated with better outcomes both in terms of effectiveness and side effects than standard or high dosage antidepressants (Bollini 1999; Furukawa 2002b) and also because fixed versus flexible dosing schedule might affect estimates of treatment effectiveness (Khan 2003). In the case of milnacipran, based on previous reports (Lecrubier 1996; Lopez-Ibor 1996; Okamura 2006), low dosage refers to <100, standard dosage to >=100 but <150, and high dosage to >=150 mg/day.
- 2. Comparator dosing (low effective range, medium to high effective range), as it is easy to imagine that there were greater chances of completing the study on the experimental drug than on the comparator drug that is increased to the maximum dosage.



- Depression severity (severe major depression, moderate/mild major depression).
- 4. Treatment settings due to difference in severity of illness (psychiatric inpatients, psychiatric outpatients, primary care).
- 5. Elderly patients (>=65 years of age), separately from other adult patients

#### Sensitivity analysis

The following sensitivity analyses were planned a priori. By limiting the studies to be included to those with higher quality, we examined if the results changed, and checked for the robustness of the observed findings.

- 1. Excluding trials with unclear concealment of random allocation and/or unclear double blinding.
- 2. Excluding trials whose drop out rate is greater than 20%. Performing the worst case scenario ITT (all the patients in the experimental group experience the negative outcome and all those allocated to the comparison group experience the positive outcome) and the best case scenario ITT (all the patients in the experimental group experience the positive outcome and all those allocated to the comparison group experience the positive outcome and all those allocated to the comparison group experience the negative outcome and all those allocated to the comparison group experience the negative outcome).
- 3. Excluding trials for which the response rates had to be calculated based on the imputation method (Furukawa 2005) and those for which the SD had to be borrowed from other trials (Furukawa 2006).
- 4. Examination of "wish bias" by comparing milnacipran as investigational drug vs milnacipran as comparator, as there was evidence to suspect that a new antidepressant might perform worse when used as a comparator than when used as an experimental agent (Barbui 2004).
- 5. Excluding studies funded by the pharmaceutical company marketing milnacipran. This sensitivity analysis was particularly important in view of the recent repeated findings that funding strongly affects outcomes of research studies (Als-Nielsen 2003; Bhandari 2004; Lexchin 2003; Montgomery 2004; Perlis 2005; Procyshyn 2004) and because industry sponsorship and authorship of clinical trials are increasing over the past 20 years (Buchkowsky 2004).

Our routine application of random effects models as well as our secondary outcomes of remission rates and continuous severity measures may be considered additional forms of sensitivity analyses. At protocol stage we planned (in the event of any of the subgroup or sensitivity analyses turning out to be significant) to run meta-regression for exploratory analyses of their additive or multiplicative influences. However, it was impossible to run any analyses due to non-significant results.

# RESULTS

#### **Description of studies**

See:Characteristics of included studies; Characteristics of excluded studies.

#### **Results of the search**

Twenty-nine studies (38 references) were initially identified through an electronic search of the CCDAN register in May 2007 (see above). Seven additional studies were identified through hand search including contact with the manufacturing company of milnacipran (Pierre Fabre). Searches of the CCDAN register were rerun in August 2008 and a further two studies (two references) were identified. After looking over titles and abstracts, 25 studies were considered potentially relevant for further inspection. No ongoing studies were identified; one study currently awaits assessment and its data may appear in an update of this review (Yoshimura 2007).

#### **Included studies**

It was possible to include16 randomised controlled trials of milnacipran comparing other antidepressants in the meta-analysis. In total, the studies included 2277 participants. The data reporting of most studies was incomplete even after supplementing the data provided by the two authors (Lee 2002b; Shinkai 2004). Therefore, with three exceptions (Tignol 1998; Sechter 2000; Shinkai 2004), the numbers of patients with response and remission were imputed. Except for Shinkai 2004, all the studies were sponsored by a pharmaceutical company.

#### Design

The median of number of participants per study was 120 (range: 41-302), and the total participants of the entire study revealed to be 2277. The mean length of the trial was 7 weeks (SD 5.5). Most of the trials were conducted throughout the acute treatment phase (6 to12 weeks). However, six trials were limited to the early treatment phase (4 weeks: Annseau 1989a; Annseau 1989c; Annseau 1991c; Endo 1995; Shinkai 2004; Yamashita 1995). One trial had a longer length that ran up to 26 weeks (Leinonen 1997).

#### Milnacipran versus TCAs

Three studies were 4-week trials (Annseau 1989a; Annseau 1989c; Yamashita 1995), two were 6-week trials (Van Amerongen 2002; Lopez-Ibor 2004), one was a 8-week trial (Tignol 1998), and the remaining was a 26-week trial (Leinonen 1997).

#### Milnacipran versus heterocyclics

A single study was a 4-week trial (Endo 1995).

#### **Milnacipran versus SSRIs**

Two studies were 4-week trials (Annseau 1991c;Shinkai 2004), four were 6-week trials (Annseau 1994; Clerc 2001; Lee 2002b;Sechter 2000), one was a 8-week trial (Yang 2003), and the remaining was a 12-week trial (Guelfi 1998a).

#### Setting

Four studies enrolled out-patients (Annseau 1994; Sechter 2000; Lee 2002b; Yang 2003), five both in- and out-patients (Endo 1995; Yamashita 1995; Leinonen 1997; Tignol 1998; Clerc 2001), while the remaining studies were conducted in in-patient facilities.

#### Milnacipran versus TCAs

Four studies were recruited in in-patient settings (Annseau 1989a; Annseau 1989c; Van Amerongen 2002; Lopez-Ibor 2004) and three were recruited in both in- and out-patient settings (Leinonen 1997; Tignol 1998; Yamashita 1995).

#### Milnacipran versus heterocyclics

A single study was recruited in a both in- and out-patient setting (Endo 1995).



#### Milnacipran versus SSRIs

Three studies were recruited in in-patient settings (Annseau 1991c; Guelfi 1998a; Shinkai 2004), four were recruited in out-patient settings (Annseau 1994; Lee 2002b; Sechter 2000; Yang 2003), and the remaining was recruited in a both in- and out-patient setting (Clerc 2001).

#### Participants

#### Diagnosis

The majority of studies enrolled participants with pure unipolar major depression, whilst five studies enrolled participants with major depression that included bipolar depression (less than 20% of the participants) (Annseau 1994; Yamashita 1995; Leinonen 1997; Tignol 1998; Lopez-Ibor 2004).

#### Milnacipran versus TCAs

Four studies enrolled patients with unipolar depression (Annseau 1989a; Annseau 1989c; Yamashita 1995; Van Amerongen 2002) while three studies enrolled patients with unipolar or bipolar depression (Leinonen 1997; Tignol 1998; Lopez-Ibor 2004).

#### Milnacipran versus heterocyclics

Only one study enrolled patients with unipolar depression (Endo 1995).

#### Milnacipran versus SSRIs

Seven studies enrolled patients with unipolar depression (Annseau 1991c; Guelfi 1998a; Sechter 2000; Clerc 2001; Lee 2002b; Yang 2003; Shinkai 2004) while the remaining study enrolled patients with unipolar or bipolar depression (Annseau 1994).

#### Age

All participants were aged 18 or above and included some elderly participants (65 years or older). One study by Tignol 1998 was limited only to elderly participants and another study by Yang 2003 did not report age of the participants.

#### Interventions

#### **Comparator intervention**

There were seven studies comparing milnacipran with TCAs, one study with heterocyclics, and eight studies with SSRIs. We were not able to identify any study that compared milnacipran with newer antidepressants such as SNRIs, MAOIs or non-conventional antidepressive agents. No study included a placebo arm.

#### Milnacipran versus TCAs

Four studies compared milnacipran with imipramine (Yamashita 1995; Tignol 1998; Van Amerongen 2002; Lopez-Ibor 2004), two with amitriptyline (Annseau 1989a; Annseau 1989c), and the remaining one with clomipramine (Leinonen 1997). One study (Annseau 1989a) presented a comparison between three arms: milnacipran 50mg/day, milnacipran 100mg and amitriptyline 150mg/day.

#### Milnacipran versus heterocyclics

Only one study compared milnacipran with mianserin (Endo 1995).

#### Milnacipran versus SSRIs

Three studies compared milnacipran with fluoxetine (Annseau 1994; Guelfi 1998a; Lee 2002b), two with fluvoxamine (Annseau 1991c; Clerc 2001), two with paroxetine (Sechter 2000; Shinkai 2004), and the remaining one with sertraline (Yang 2003). One study (Guelfi 1998a) presented a comparison between three arms: milnacipran 100mg/day, milnacipran 200mg and fluoxetine 20mg/ day, and other study (Annseau 1991c) presented a comparison between three arms: milnacipran 150-300mg/day, milnacipran 200mg and fluoxamine 200mg/day.

#### Dosage of the study drugs

In 8 out of the 16 studies, the dosage of milnacipran were within the standard therapeutic range (100-150 mg/day), three within the higher dosage range (>150mg/day) (Annseau 1989c Annseau 1991c; Leinonen 1997), three within the lower dosage range (<100mg/ day) (Endo 1995; Yamashita 1995; Shinkai 2004), and the two had combined dosage range due to three arms. Of the combined dosage studies, one study (Annseau 1989a) had one arm within the standard therapeutic range and other in the lower dosage range, and another study (Guelfi 1998a) had one arm within the standard therapeutic range and other in the higher dosage range. On the other hand, the dosage of the comparator drug were within the standard therapeutic range for all the studies, except Clerc 2001 that had higher dosage range and Yamashita 1995 that had lower dosage range.

The use of a fixed- or a flexible-dose regimen was consistent among comparisons within the same study in all of included trials. Six studies (Endo 1995; Yamashita 1995; Leinonen 1997; Tignol 1998; Yang 2003; Shinkai 2004) involved a flexible-dose scheduling design, whereas the remainder of included trials involved a fixeddose scheduling design.

#### Outcomes

Outcome concerning efficacy during acute phase treatment (6-12 weeks) were obtained from ten studies (n=1565). Of the ten studies, six studies were assessed at 6 weeks, 3 at 8 weeks and one at 12 weeks. Efficacy data during early phase were obtained from 13 studies (n=1934), and in 11 studies were assessed at two weeks. All studies used intention to treat analyses based on the last observation carried forward method for the efficacy outcome. Either 17, 21 or 24-item HAM-D were used to evaluate the efficacy data for all the studies included in the review. The data reporting of most studies were incomplete even after supplementing the provided data from contacted two authors (Lee 2002b; Shinkai 2004). Therefore, with three exceptions (Tignol 1998; Sechter 2000; Shinkai 2004), the number of patients with response and remission were imputed. In terms of acceptability, except for Leinonen 1997, all studies reported the total number of participants who dropped out prematurely during the trial. Yang 2003 did not provide the specific number of participants who dropped out during the study due to inefficacy or side effects. Annseau 1989a also did not provide the number of participants who dropped out during the study due to side effects. Outcome data concerning tolerability were extractable for the majority of studies but were not available for four (Annseau 1994; Leinonen 1997; Shinkai 2004; Yang 2003).

No data were obtained for social adjustment, social functioning, health-related quality of life or costs to health care services from the included studies.

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#### **Excluded studies**

Of the 25 studies considered for inclusion, 3 studies were excluded because they were additional publications of trials already included (Onodera 1992; Baek 2002b; Lee 2004). Two studies did not use other antidepressant as a comparator drug (Macher 1989; Kanemoto 2004). One study was not randomised (Wyeth 2006). Another study did not use relevant operational diagnostic criteria (Baek 2002a). One study looked at response to drugs by gender (Naito 2007). Finally, one study did not include acute

phase treatment (Dardennes 1998). No study was excluded due to having more than 20% of the participants with bipolar depression as defined in our exclusion criteria. One study remains awaiting assessment (Yoshimura 2007).

### **Risk of bias in included studies**

See Figure 1 and Figure 2 for a graphical summary of methodological quality for the 16 included studies, based on the six risk of bias domains.

# Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.





Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.





#### Allocation

All trials were described as randomised. Using the Cochrane criteria which rate the adequacy of the random allocation concealment, most of the trials were rated as "unclear" or *moderate* risk of bias except Endo 1995, Shinkai 2004 and Yamashita 1995, in which risk of bias was rated as low.

#### Blinding

The outcome assessment was blind to treatment allocation in most of the studies except Shinkai 2004, in which the adequacy of the blinding was rated as "unclear" or *moderate* risk of bias, and Lee 2002b where the design was 'open label'.

#### Incomplete outcome data

Five studies were incomplete in outcome reporting (Annseau 1994;Guelfi 1998a;Tignol 1998; Van Amerongen 2002;Yang 2003).

# Selective reporting

The study protocol was not available for all studies. Two studies lacked reporting of adverse events (Yang 2003; Shinkai 2004), one did not report the number of participants experiencing at least some side effects (Annseau 1994) and one (Tignol 1998) failed to report the MADRS scores indicated in the methods section of the published trial report. One study did not report the number of participants who dropped out from the trial due to any reason (Leinonen 1997) and other did not report the number of participants who dropped out from the trial due to side effects (Annseau 1989a).

Standard deviations were not reported In five studies (Annseau 1991c; Guelfi 1998a; Tignol 1998;Sechter 2000; Van Amerongen 2002). Two studies were rated as "unclear" due to insufficient information (Lee 2002b; Lopez-Ibor 2004).

#### Other potential sources of bias

Except for Shinkai 2004, all the studies were sponsored by a pharmaceutical company marketing milnacipran.

#### **Effects of interventions**

The results are reported comparison by comparison (TCAs, Heterocyclics, SSRIs and newer antidepressants) and the forest plots are organised according to the relevance of outcomes, as reported in the review protocol. Some significant differences in efficacy, acceptability and tolerability were found and details are listed below.

#### 1. Milnacipran versus TCAs

Efficacy outcomes were obtained from 7 studies (n=820) ([dichotomous outcomes] acute phase: 4 studies, n=537, early phase: 6 studies, n=820; [continuous outcomes] acute phase: 7 studies, n=820, early phase: 6 studies, n=765). Acceptability outcomes were obtained from 7 studies (n=902) (due to any reason: 6 studies (n=795), due to inefficacy: 7 studies (n=902), due to side effects: 6 studies (n=756)). Tolerability outcomes were obtained from 6 studies (n=795).

#### A. Milnacipran versus Imipramine

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

#### a) Acute phase treatment (6 to 12 weeks)

There was no evidence that milnacipran was more efficacious than imipramine (OR1.05, 95%CI: 0.71 to 1.54) (see Analysis 1.1, Figure 3).

#### Figure 3. Forest plot of comparison: 1 Response at acute phase (6-12 weeks), outcome: 1.1 Milnacipran vs TCAs.

	Milnacipran		Milnacipran TCAs			Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
1.1.1 Milnacipran vs Ir	nipramine	2							
Lopez-Ibor 2004	20	51	20	49	20.2%	0.94 [0.42, 2.08]			
Tignol 1998	67	112	64	109	37.4%	1.05 [0.61, 1.79]	<b>_</b>		
Van Amerongen 2002 Subtotal (95% CI)	35	53 216	35	56 214	20.9% <b>78.6%</b>	1.17 [0.53, 2.56] 1.05 [0.71, 1.54]	•		
Total events	122		119						
Heterogeneity: $Tau^2 = 0$	0.00; Chi <sup>2</sup>	= 0.15	. df = 2	P = 0.9	$(93); I^2 = ($	0%			
Test for overall effect: Z	2 = 0.23 (F	P = 0.8	2)						
1.1.2 Milancipran vs C	lomipram	ine							
Leinonen 1997	22	52	34	55	21.4%	0.45 [0.21, 0.98]			
Subtotal (95% CI)		52		55	21.4%	0.45 [0.21, 0.98]			
Total events	22		34						
Heterogeneity: Not app	licable								
Test for overall effect: Z	z = 2.01 (F	P = 0.0	4)						
Total (95% CI)		268		269	100.0%	0.87 [0.59, 1.30]	-		
Total events	144		153						
Heterogeneity: Tau <sup>2</sup> = (	0.03; Chi <sup>2</sup>	= 3.75	, df = 3	(P = 0.2)	29); I <sup>2</sup> = 2	20%	0102 05 1 2 5 1		
Test for overall effect: Z	r = 0.66 (F	P = 0.5	1)				Favours TCAs Favours Milnacir		
Test for subaroup differ	rences: Ch	$i^2 = 3.6$	0 df = 1	1 (P = 0)	$(06) I^2 =$	= 72 2%	ravours rens ravours minucip		

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to imipramine (OR1.11,95%CI: 0.73 to 1.69) (see Analysis 2.1, Figure 4).

#### Figure 4. Forest plot of comparison: 2 Response at early phase (1-4 weeks), outcome: 2.1 Milnacipran vs TCAs.

	Milnaci	pran	TCA	s		Odds Ratio	Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl				
2.1.1 Milancipran vs Imipramine											
Tignol 1998	23	112	16	109	19.4%	1.50 [0.75, 3.03]					
Van Amerongen 2002	24	53	30	56	17.5%	0.72 [0.34, 1.52]					
Yamashita 1995	28	66	25	66	19.6%	1.21 [0.60, 2.43]					
Subtotal (95% CI)		231		231	56.5%	1.11 [0.73, 1.69]					
Total events	75		71								
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 2.06	, df = 2	(P = 0.3)	36); I <sup>2</sup> = 3	3%					
Test for overall effect: Z	c = 0.50 (F	<b>P</b> = 0.6	2)								
2.1.2 Milnacipran vs C	lomipram	ine									
Leinonen 1997	. 7	52	14	55	11.1%	0.46 [0.17, 1.24]	<b>_</b>				
Subtotal (95% CI)		52		55	11.1%	0.46 [0.17, 1.24]					
Total events	7		14								
Heterogeneity: Not appl	licable										
Test for overall effect: Z	= 1.54  (F	<b>P</b> = 0.1	2)								
2.1.3 Milnacipran vs A	mitriptyli	ne									
Annseau 1989a	29	97	21	49	19.0%	0.57 [0.28, 1.16]	<b>_</b>				
Annseau 1989c	13	44	16	43	13.4%	0.71 [0.29, 1.73]	<b>_</b>				
Subtotal (95% CI)		141		92	32.3%	0.62 [0.35, 1.08]					
Total events	42		37								
Heterogeneity: Tau <sup>2</sup> = 0	0.00; Chi <sup>2</sup>	= 0.14	, df = 1	(P = 0.2)	71); $I^2 = ($	0%					
Test for overall effect: Z	1 = 1.68 (F	<b>P</b> = 0.0	9)								
Total (95% CI)		424		378	100.0%	0.83 [0.58, 1.20]	•				
Total events	124		122								
Heterogeneity: $Tau^2 = 0$	0.05; Chi <sup>2</sup>	= 6.58	, df = 5	(P = 0.2)	25); I <sup>2</sup> = 2	24%					
Test for overall effect: Z	= 0.98 (F	P = 0.3	3)				Favours TCAs Favours Milpacipra				
Test for subgroup differ	rences: Ch	$i^2 = 4.3$	2, df = 2	2 (P = 0)	0.12), I <sup>2</sup> =	= 53.7%	ravours reas ravours miniacipra				

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

# 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

2-1. EFFICACY - Number of patients who achieved remission

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to imipramine (see Analysis 4.1).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to imipramine (see Analysis 5.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to imipramine (see Analysis 7.1).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to imipramine (see Analysis 8.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-3 to -5. EFFICACY- Social adjustment, social functioning, healthrelated quality of life, costs to health care services

No data available.

#### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to any cause compared to imipramine (see Analysis 9.1).

#### b) Due to inefficacy

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to inefficacy compared to imipramine (see Analysis 10.1).



#### c) Due to adverse events

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to adverse events compared to imipramine (see Analysis 11.1).

#### 2-7. TOLERABILITY

#### a) Total number of patients experiencing at least one adverse event

There was evidence that milnacipran was associated with a lower rate of patients experiencing adverse events than imipramine (OR 0.43, 95%CI 0.28 to 0.66) (see Analysis 12.1, Figure 5).

# Figure 5. Forest plot of comparison: 12 Patients with at least some adverse events (Tolerability), outcome: 12.1 Milnacipran vs TCAs.



#### b) Total number of patients experiencing a specific adverse event

#### 1. sleepiness/drowsiness

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing sleepiness/ drowsiness than imipramine (see Analysis 13.1).

#### 2. insomnia

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than imipramine (see Analysis 14.1).

#### 3. dry mouth

There was evidence that milnacipran was associated with a lower rate of participants experiencing dry mouth than imipramine (OR 0.57, 95%CI 0.37 to 0.86) (see Analysis 15.1).

#### 4. constipation

There was evidence that milnacipran was associated with a lower rate of participants experiencing constipation than imipramine (OR 0.64, 95%CI 0.41 to 0.98) (see Analysis 16.1).

5. urination problems

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing urination problems than imipramine (see Analysis 17.1).

#### 6. hypotension

There was no evidence that milnacipran was associated with a lower rate of participants experiencing hypotension than imipramine (see Analysis 18.1).

#### 7. agitation/ anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/ anxiety than imipramine (see Analysis 19.1).

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

10. vomiting/ nausea

There was evidence that milnacipran was associated with a higher rate of participants experiencing vomiting/ nausea than imipramine (OR 2.31, 95%CI 1.13 to 4.72) (see Analysis 22.1).

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#### 11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than imipramine (see Analysis 23.1).

#### B. Milnacipran versus Clomipramine

Only Leinonen 1997 provided the data.

#### 1.PRIMARY OUTCOME

1-1. EFFICACY - Number of patients who responded to treatment

#### a) Acute phase treatment (6 to 12 weeks)

There was evidence that clomipramine was more efficacious than milnacipran (OR0.45, 95%CI: 0.21 to 0.98) (see Analysis 1.1, Figure 3).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to clomipramine (OR0.46, 95%CI: 0.17 to 1.24) (see Analysis 2.1, Figure 4).

#### c) Follow-up phase treatment (16 to 24 weeks)

No substantial effect was found with milnacipran compared to clomipramine (OR0.72, 95%CI: 0.33 to 1.55) (see Analysis 3.1, Figure 6).

# Figure 6. Forest plot of comparison: 3 Response at follow-up phase (4-6 months), outcome: 3.1 Milnacipran vs TCAs.

	Milnacipran		n TCAs			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M–H, Random, 95% CI
3.1.1 Milnacipran vs	Clomipra	mine					
Leinonen 1997	27	52	33	55	100.0%	0.72 [0.33, 1.55]	
Subtotal (95% CI)		52		55	100.0%	0.72 [0.33, 1.55]	
Total events	27		33				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.84	(P = 0.	40)				
T . 1/050/ CD							
Total (95% CI)		52		55	100.0%	0.72 [0.33, 1.55]	
Total events	27		33				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.84	(P = 0.	40)				Eavours TCAs Eavours Milnacionar
Test for subgroup diffe	erences: N	ravours reas ravours minacipiar					

# 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

#### 2-1. EFFICACY - Number of patients who achieved remission

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to clomipramine (see Analysis 4.1).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to clomipramine (see Analysis 5.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

No substantial effect was found with milnacipran compared to clomipramine (see Analysis 6.1).

#### 2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

There was evidence that clomipramine was more efficacious than milnacipran (SMD 0.44, 95%C:I 0.03 to 0.85) (see Analysis 7.1).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to clomipramine (see Analysis 8.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

#### No data available.

<u>2-3 to -5. EFFICACY- Social adjustment, social functioning, health-</u> related quality of life, costs to health care services

No data available.

2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to any cause compared to clomipramine (see Analysis 9.1).

#### b) Due to inefficacy

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to inefficacy compared to clomipramine (see Analysis 10.1).

#### c) Due to adverse events

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to adverse events compared to clomipramine (see Analysis 11.1).

#### 2-7. TOLERABILITY

#### a) Total number of patients experiencing at least one adverse event

No data available.

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/drowsiness



There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing sleepiness/ drowsiness than clomipramine (see Analysis 13.1).

#### 2. insomnia

There was evidence that milnacipran was associated with a higher rate of participants experiencing insomnia than clomipramine (OR 5.55, 95%CI 1.14 to 27.04) (see Analysis 14.1).

#### 3. dry mouth

There was evidence that milnacipran was associated with a lower rate of participants experiencing dry mouth than clomipramine (OR 0.45, 95%CI 0.21 to 0.97) (see Analysis 15.1).

4. constipation

No data available.

5. urination problems

No data available.

6. hypotension

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing hypotension than clomipramine (see Analysis 18.1).

#### 7. agitation/anxiety

No data available.

8. suicide wishes / gestures/ attempts

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing suicide wishes/ gestures/ attempts than clomipramine (see Analysis 20.1).

9. completed suicide

No data available.

#### 10. vomiting/ nausea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing vomiting/ nausea than clomipramine (see Analysis 22.1).

#### 11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than clomipramine (see Analysis 23.1).

#### C. Milnacipran versus Amitriptyline

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

#### a) Acute phase treatment (6 to 12 weeks)

No data available.

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to amitriptyline (OR 0.62, 95%CI: 0.35 to 1.08) (see Analysis 2.1, Figure 4).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

#### 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

2-1. EFFICACY - Number of patients who achieved remission

#### a) Acute phase treatment (6 to 12 weeks)

No data available.

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to amitriptyline (see Analysis 5.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to amitriptyline (see Analysis 7.1).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to amitriptyline (see Analysis 8.1).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-3 to -5. EFFICACY- Social adjustment, social functioning, healthrelated quality of life, costs to health care services

No data available.

# 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with smaller or larger rate of drop out rate due to any cause compared to amitriptyline (see Analysis 9.1).

#### b) Due to inefficacy

There was no evidence that milnacipran was associated with smaller or larger rate of drop out rate due to inefficacy compared to amitriptyline (see Analysis 10.1).

#### c) Due to adverse events

There was no evidence that milnacipran was associated with smaller or larger rate of drop out rate due to adverse events compared to amitriptyline (see Analysis 11.1).

# 2-7. TOLERABILITY

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#### a) Total number of patients experiencing at least one adverse event

There was evidence that milnacipran was associated with smaller rate of patients experiencing adverse events than amitriptyline (OR 0.23, 95%CI 0.13 to 0.40) (see Analysis 12.1, Figure 5).

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/ drowsiness

There was evidence that milnacipran was associated with a lower rate of participants experiencing sleepiness/drowsiness than amitriptyline (OR 0.07, 95%CI 0.02 to 0.22) (see Analysis 13.1).

#### 2. insomnia

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than amitriptyline (see Analysis 14.1).

#### 3. dry mouth

There was evidence that milnacipran was associated with a lower rate of participants experiencing dry mouth than amitriptyline (OR 0.22, 95%CI 0.12 to 0.39) (see Analysis 15.1).

#### 4. constipation

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than amitriptyline (see Analysis 16.1).

5. urination problems

No data available.

6. hypotension

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing hypotension than amitriptyline (see Analysis 18.1).

7. agitation/ anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/anxiety than amitriptyline (see Analysis 19.1).

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

10. vomiting/ nausea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing vomiting/ nausea than amitriptyline (see Analysis 22.1).

11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than amitriptyline (see Analysis 23.1).

#### 2. Milnacipran versus Heterocyclics

Only Endo 1995 (n=179) that compared milnacipran with mianserin provided efficacy, acceptability and tolerability outcomes.

#### A. Milnacipran versus Mianserin

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

# a) Acute phase treatment (6 to 12 weeks)

No data available.

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to mianserin (OR1.10, 95%CI: 0.54 to 2.23) (see Analysis 2.3, Figure 7).

# Figure 7. Forest plot of comparison: 2 Response at early phase (1-4 weeks), outcome: 2.3 Milnacipran vs Hererocyclics.

		Milnaci	pran	Heteroc	clics		Odds Ratio	Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
	2.3.1 Milancipran vs	Mianseriı	n					
	Endo 1995 Subtotal (95% CI)	19	84 <b>84</b>	20	95 95	100.0% 100.0%	1.10 [0.54, 2.23] 1.10 [0.54, 2.23]	
	Total events	19		20				
	Heterogeneity: Not ap	plicable						
	Test for overall effect:	Z = 0.25	(P = 0)	.80)				
	Total (95% CI)		84		95	100.0%	1.10 [0.54, 2.23]	
	Total events	19		20				
	Heterogeneity: Not ap	plicable						
	Test for overall effect:	Z = 0.25	(P = 0)	.80)				Eavours Heterocyclics Favours Milnacinran
	Test for subgroup diffe	erences: N	lot app	licable				
c) Fo	llow-up phase treatme	nt (16 to 2	4 week	s)			a) Acute phase treat	ment (6 to 12 weeks)

No data available.

No data available.

#### 2. SECONDARY OUTCOMES

2-1. EFFICACY - Number of patients who achieved remission

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to mianserin (see Analysis 5.3).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

#### 2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to mianserin (see Analysis 7.3).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to mianserin (see Analysis 8.3).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

<u>2-3 to -5. EFFICACY- Social adjustment, social functioning, health-</u> related quality of life, costs to health care services

No data available.

#### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with higher or lower rate of drop out rate due to any cause compared to mianserin (see Analysis 9.3).

### b) Due to inefficacy

There was no evidence that milnacipran was associated with higher or lower rate of drop out rate due to inefficacy compared to mianserin (see Analysis 10.3).

# c) Due to adverse events

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to adverse events compared to mianserin (see Analysis 11.3).

#### 2-7. TOLERABILITY

#### a) Total number of patients experiencing at least one adverse event

There was no evidence that milnacipran was associated with higher or lower rate of patients experiencing adverse events than mianserin (see Analysis 12.3).

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/ drowsiness

There was evidence that milnacipran was associated with a lower rate of participants experiencing sleepiness/drowsiness than mianserin (OR 0.21, 95%CI 0.08 to 0.58) (see Analysis 13.3).

#### 2. insomnia

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than mianserin (see Analysis 14.3).

#### 3. dry mouth

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing dry mouth than mianserin (see Analysis 15.3).

#### 4. constipation

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than mianserin (see Analysis 16.3).

5. urination problems

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than mianserin (see Analysis 17.3).

#### 6. hypotension

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing hypotension than mianserin (see Analysis 18.3).

7. agitation/ anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/anxiety than mianserin (see Analysis 19.3).

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

10. vomiting/ nausea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing vomiting/nausea than mianserin (see Analysis 22.3).

11. diarrhoea

No data reported.

#### 3. Milnacipran versus SSRIs

Efficacy and acceptability outcomes were obtained from two studies comparing milnacipran with fluvoxamine (Annseau 1991c; Clerc 2001), three with fluoxetine (Annseau 1994; Guelfi 1998a; Lee 2002b), two with paroxetine (Sechter 2000; Shinkai 2004), and the remaining one with sertraline (Yang 2003). Outcome concerning tolerability were extractable from two studies comparing milnacipran with fluvoxamine (Annseau 1991c; Clerc 2001), two with fluoxetine (Guelfi 1998a; Lee 2002b), one with paroxetine (Sechter 2000) and none with sertraline.

#### A. Milnacipran versus Fluvoxamine

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment



#### a) Acute phase treatment (6 to 12 weeks)

There was no evidence that milnacipran was more efficacious than fluvoxamine (OR1.76, 95%CI: 0.81 to 3.83) (see Analysis 1.2, Figure 8).

# Figure 8. Forest plot of comparison: 1 Response at acute phase (6-12 weeks), outcome: 1.2 Milnacipran vs SSRIs.

	Milnacip	ran	SSRI	s		Odds Ratio	Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl			
1.2.1 Milnacipran vs Fluvoxamine										
Clerc 2001 Subtotal (95% CI)	40	57 57	32	56 <b>56</b>	14.9% <b>14.9%</b>	1.76 [0.81, 3.83] 1.76 [0.81, 3.83]	-			
Total events	40		32							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 1.43	(P = 0.	15)							
1.2.2 Milnacipran vs	Fluoxetine	e								
Annseau 1994	32	97	43	93	20.0%	0.57 [0.32, 1.03]				
Guelfi 1998a	109	200	51	100	23.6%	1.15 [0.71, 1.86]	<b>_</b>			
Lee 2002b	17	39	11	31	11.1%	1.40 [0.53, 3.71]	•			
Subtotal (95% CI)		336		224	54.7%	0.93 [0.55, 1.58]				
Total events	158		105							
Heterogeneity: Tau <sup>2</sup> =	0.11; Chi	$^{2} = 4.0$	)7, df = 2	2 (P = 0)	0.13); I <sup>2</sup> =	= 51%				
Test for overall effect:	Z = 0.27	(P = 0.	79)							
1.2.3 Milnacipran vs	Paroxetine	e								
Sechter 2000	86	149	91	153	24.4%	0.93 [0.59, 1.47]				
Subtotal (95% CI)		149		153	24.4%	0.93 [0.59, 1.47]	-			
Total events	86		91							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 0.31	(P = 0.	76)							
1.2.4 Milnacipran vs	Sertraline									
Yang 2003	9	27	3	26	6.0%	3.83 [0.90, 16.26]				
Subtotal (95% CI)		27		26	6.0%	3.83 [0.90, 16.26]				
Total events	9		3							
Heterogeneity: Not ap	plicable	(B 0	07)							
lest for overall effect:	Z = 1.82	(P = 0.	.07)							
Total (95% CI)		569		459	100.0%	1.11 [0.76, 1.64]	+			
Total events	293		231							
Heterogeneity: Tau <sup>2</sup> =	0.10; Chi	° = 9.6	5, df = !	5 (P = 0)	0.09); l <sup>2</sup> =	= 48%	0.10.2 0.5 1 2 5 10			
Test for overall effect:	Z = 0.54	(P = 0.)	.59)			12.20	Favours SSRIs Favours Milnacipra			
lest for subgroup diff	erences: C	nı* = 5	.20, df =	= 3 (P =	= 0.16), l'	= 42.3%				

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluvoxamine (OR1.54, 95%CI: 0.87 to 2.72) (see Analysis 2.2, Figure 9).



# Figure 9. Forest plot of comparison: 2 Response at early phase (1-4 weeks), outcome: 2.2 Milancipran vs SSRIs.

	Milnaci	pran	SSR	s		Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl	
2.2.1 Milnacipran vs	s Fluvoxan	line						
Annseau 1991c	32	86	10	41	11.9%	1.84 [0.80, 4.24]		
Clerc 2001	22	57	18	56	13.9%	1.33 [0.61, 2.88]		
Subtotal (95% CI)		143		97	25.8%	1.54 [0.87, 2.72]		
Total events	54		28					
Heterogeneity: Tau <sup>4</sup>	= 0.00; Ch	$i^2 = 0.3$	31, df =	1 (P = 0)	0.58); l <sup>2</sup> =	= 0%		
Test for overall effect	t: $Z = 1.49$	(P = 0)	.14)					
2.2.2 Milnacipran vs	s Fluoxetin	e						
Guelfi 1998a	83	200	31	100	32.2%	1.58 [0.95, 2.63]		
Lee 2002b	8	39	6	31	6.0%	1.08 [0.33, 3.51]		
Subtotal (95% CI)		239		131	38.2%	1.49 [0.93, 2.37]		
Total events	91		37				-	
Heterogeneity: Tau <sup>2</sup>	= 0.00; Ch	$i^2 = 0.3$	34, df =	1 (P =	0.56); l <sup>2</sup> =	= 0%		
Test for overall effect	t: Z = 1.66	(P = 0	.10)					
2.2.3 Milnacipran vs	s Paroxetin	e						
Sechter 2000	38	149	37	153	30.6%	1.07 [0.64, 1.81]	<b>_</b>	
Shinkai 2004	10	20	13	21	5.4%	0.62 [0.18, 2.13]		
Subtotal (95% CI)		169		174	36.0%	0.99 [0.61, 1.60]		
Total events	48		50					
Heterogeneity: Tau <sup>2</sup>	= 0.00; Ch	$i^2 = 0.6$	55, df =	1 (P = )	0.42); I <sup>2</sup> =	= 0%		
Test for overall effect	t: $Z = 0.05$	(P = 0	.96)					
Total (95% CI)		551		402	100.0%	1.30 [0.97, 1.73]	◆	
Total events	193		115					
Heterogeneity: Tau <sup>2</sup>	= 0.00; Ch	$i^2 = 3.2$	23, df =	5 (P = )	0.66); I <sup>2</sup> =	= 0%		
Test for overall effect	t: Z = 1.76	(P = 0)	.08)				U.IU.2 U.S I Z S IO	
Test for subgroup di	fferences: O	$chi^2 = 1$	.92, df =	= 2 (P =	= 0.38), I	<sup>2</sup> = 0%	ravours sorts ravours minacipra	
llow-up phase treatme	nt (16 to 24	weeks)			c) Follow-up phase treat	ment (16 to 24 weeks)		
ata available.					No data available.			
	(only figu	ros for	cubstant	ial		2 2 to 5 FEELCACY So	cial adjustment social functioning he	
vences were reported in the text)						related quality of life, costs to health care services		
rences were reported	пп спе сехо	/			related quality of life, costs to health care services			

2-1. EFFICACY - Number of patients who achieved remission

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to fluvoxamine (see Analysis 4.2).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluvoxamine (see Analysis 5.2).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

# 2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to fluvoxamine (see Analysis 7.2).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluvoxamine (see Analysis 8.2).

lthrelated quality of life, costs to health care services

No data available.

#### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to any cause compared to fluvoxamine (see Analysis 9.2).

#### b) Due to inefficacy

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to inefficacy compared to fluvoxamine (see Analysis 10.2).

#### c) Due to adverse events

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to adverse events compared to fluvoxamine (see Analysis 11.2).

#### 2-7. TOLERABILITY



#### a) Total number of patients experiencing at least one adverse event

There was evidence that milnacipran was associated with lower rate of patients experiencing adverse events than fluvoxamine (OR 0.51, 95%CI 0.28 to 0.94) (see Analysis 12.2).

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/drowsiness

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing sleepiness/ drowsiness than fluvoxamine (see Analysis 13.2).

#### 2. insomnia

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than fluvoxamine (see Analysis 14.2).

#### 3. dry mouth

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing dry mouth than fluvoxamine (see Analysis 15.2).

#### 4. constipation

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing constipation than fluvoxamine (see Analysis 16.2).

#### 5. urination problems

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing urination problems than fluvoxamine (see Analysis 17.2).

#### 6. hypotension

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing hypotension than fluvoxamine (see Analysis 18.2).

#### 7. agitation/anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/anxiety than fluvoxamine (see Analysis 19.2).

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

10. vomiting/ nausea

There was evidence that milnacipran was associated with a lower rate of participants experiencing vomiting/nausea than fluvoxamine (OR 0.51, 95%CI 0.28 to 0.94)(see Analysis 22.2).

11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than fluvoxamine (see Analysis 23.2).

#### B. Milnacipran versus Fluoxetine

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

#### a) Acute phase treatment (6 to 12 weeks)

There was no evidence that milnacipran was more efficacious than fluoxetine (OR0.93, 95%CI: 0.55 to 1.58) (see Analysis 1.2, Figure 8).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluoxetine (OR1.49, 95%CI: 0.93 to 2.37) (see Analysis 2.2, Figure 9).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

#### 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

2-1. EFFICACY - Number of patients who achieved remission

# a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to fluoxetine (see Analysis 4.2).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluoxetine (see Analysis 5.2).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to fluoxetine (see Analysis 7.2).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to fluoxetine (see Analysis 8.2).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-3 to -5. EFFICACY- Social adjustment, social functioning, healthrelated quality of life, costs to health care services

No data available.

#### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to any cause compared to fluoxetine (see Analysis 9.2).

Milnacipran versus other antidepressive agents for depression (Review)



#### b) Due to inefficacy

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to inefficacy compared to fluoxetine (see Analysis 10.2).

#### c) Due to adverse events

There was no evidence that milnacipran was associated with higher or lower rate of drop out due to adverse events compared to fluoxetine (see Analysis 11.2).

#### 2-7. TOLERABILITY

#### a) Total number of patients experiencing at least one adverse event

There was no evidence that milnacipran was associated with higher or lower rate of patients experiencing adverse events than fluoxetine (see Analysis 12.2).

#### b) Total number of patients experiencing a specific adverse event

#### 1. sleepiness/drowsiness

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing sleepiness/ drowsiness than fluoxetine (see Analysis 13.2).

#### 2. insomnia

There was evidence that milnacipran was associated with a lower rate of participants experiencing insomnia than fluoxetine (OR 0.41, 95%CI: 0.20 to 0.87) (see Analysis 14.2).

# 3. dry mouth

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing dry mouth than fluoxetine (see Analysis 15.2).

#### 4. constipation

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing constipation than fluoxetine (see Analysis 16.2).

#### 5. urination problems

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing urination problems than fluoxetine (see Analysis 17.2).

#### 6. hypotension

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing hypotension than fluoxetine (see Analysis 18.2).

#### 7. agitation/ anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/ anxiety than fluoxetine (see Analysis 19.2).

8. suicide wishes/ gestures/ attempts

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing suicide wishes/ gestures/ attempts than fluoxetine (see Analysis 20.2).

#### 9. completed suicide

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing completed suicide than fluoxetine (see Analysis 21.1).

#### 10. vomiting/ nausea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing vomiting/nausea than fluoxetine (see Analysis 22.2).

#### 11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than fluoxetine (see Analysis 23.2).

#### C. Milnacipran versus Paroxetine

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

# a) Acute phase treatment (6 to 12 weeks)

There was no evidence that milnacipran was more efficacious than paroxetine (OR0.93, 95%CI: 0.59 to 1.47) (see Analysis 1.2, Figure 8).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to paroxetine (OR 0.99, 95%CI: 0.61 to 1.60) (see Analysis 2.2, Figure 9).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

# 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

2-1. EFFICACY - Number of patients who achieved remission

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to paroxetine (see Analysis 4.2).

#### b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to paroxetine (see Analysis 5.2).

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

#### 2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to paroxetine (see Analysis 7.2).

# b) Early phase treatment (1 to 4 weeks)

No substantial effect was found with milnacipran compared to paroxetine (see Analysis 8.2).

# c) Follow-up phase treatment (16 to 24 weeks)

No data available.

<u>2-3 to -5. EFFICACY- Social adjustment, social functioning, health-related quality of life, costs to health care services</u>

No data available.

### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to any cause compared to paroxetine (see Analysis 9.2).

#### b) Due to inefficacy

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to inefficacy compared to paroxetine (see Analysis 10.2).

#### c) Due to adverse events

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to adverse events compared to paroxetine (see Analysis 11.2).

#### 2-7. TOLERABILITY

#### a) Total number of patients experiencing at least one adverse event

There was no evidence that milnacipran was associated with a higher or lower rate of patients experiencing adverse events than paroxetine (see Analysis 12.2).

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/ drowsiness

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing sleepiness/ drowsiness than paroxetine (see Analysis 13.2).

2. insomnia

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing insomnia than paroxetine (see Analysis 14.2).

3. dry mouth

No data available.

4. constipation

No data available.

5. urination problems

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing urination problem than paroxetine (see Analysis 17.2).

#### 6. hypotension

No data available.

7. agitation/ anxiety

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing agitation/ anxiety than paroxetine (see Analysis 19.2).

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

10. vomiting/ nausea

There was evidence that milnacipran was associated with a higher or lower rate of participants experiencing vomiting/nausea than paroxetine (see Analysis 22.2).

11. diarrhoea

There was no evidence that milnacipran was associated with a higher or lower rate of participants experiencing diarrhoea than paroxetine (see Analysis 23.2).

#### D. Milnacipran versus Sertraline

#### **1.PRIMARY OUTCOME**

1-1. EFFICACY - Number of patients who responded to treatment

#### a) Acute phase treatment (6 to 12 weeks)

There was no evidence that milnacipran was more efficacious than sertraline (OR 3.83, 95%CI: 0.90 to 16.26) (see Analysis 1.2, Figure 8).

#### b) Early phase treatment (1 to 4 weeks)

No data available.

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

# 2. SECONDARY OUTCOMES (only figures for substantial differences were reported in the text)

2-1. EFFICACY - Number of patients who achieved remission

a) Acute phase treatment (6 to 12 weeks)

Not estimable.

b) Early phase treatment (1 to 4 weeks)

No data available.

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-2. EFFICACY - Severity of depression at treatment phase

#### a) Acute phase treatment (6 to 12 weeks)

No substantial effect was found with milnacipran compared to sertraline (see Analysis 7.2).



#### b) Early phase treatment (1 to 4 weeks)

No data available.

#### c) Follow-up phase treatment (16 to 24 weeks)

No data available.

2-3 to -5. EFFICACY- Social adjustment, social functioning, healthrelated quality of life, costs to health care services

#### No data available.

#### 2-6. ACCEPTABILITY - Drop out rate

#### a) Due to any cause

There was no evidence that milnacipran was associated with a higher or lower rate of drop out due to any cause compared to sertraline (see Analysis 9.2).

#### b) Due to inefficacy

No data available.

#### c) Due to adverse events

No data available.

2-7. TOLERABILITY

a) Total number of patients experiencing at least one adverse event No data available.

#### b) Total number of patients experiencing a specific adverse event

1. sleepiness/drowsiness

No data available.

2. insomnia

No data available.

3. dry mouth

No data available.

4. constipation

No data available.

5. urination problems

No data available.

6. hypotension

No data available.

7. agitation/anxiety

No data available.

8. suicide wishes/ gestures/ attempts

No data available.

9. completed suicide

No data available.

#### 10. vomiting/nausea

No data available.

11. diarrhoea

No data available.

# Subgroup analysis

#### 1. Milnacipran dosing

When we limited to participants treated with high dose milnacipran, no difference was found for response at early phase compared with TCAs (see Analysis 24.1). Response at acute phase was not analysed because only Leinonen 1997 provided relevant data. In terms of SSRIs, all studies were within the therapeutic range with the exception of Annseau 1991c, in which a higher dose was used. Due to the small number of trials without the therapeutic range, it was not considered meaningful to carry out this preplanned subgroup analysis.

Participants treated with low dose (<100mg/day) milnacipran were compared with TCAs (Yamashita 1995), with heterocyclics (Endo 1995) and with SSRIs (Shinkai 2004). Due to the small number of trials without the therapeutic range for each comparison, it was not considered meaningful to carry out this pre-planned subgroup analysis.

Four studies (Yamashita 1995, Endo 1995, Leinonen 1997, Tignol 1998) involved a flexible-dose scheduling design. When we limited to studies involving a flexible-dose scheduling design, no difference was found for response compared with TCAs (see Analysis 25.1, Analysis 26.1).

#### 2. Comparator dosing

All comparator doses were within the therapeutic range, with the exception of Clerc 2001, which used a higher dose, and Yamashita 1995, which used a lower dose. Due to the small number of trials without the therapeutic range, it was not considered meaningful to carry out this pre-planned subgroup analysis.

#### 3. Depression severity

All studies reported a mean baseline score corresponding to moderate major depression, with the exception of Guelfi 1998a where the mean baseline score corresponded to a severe major depression. Therefore, it was not meaningful to carry out this preplanned subgroup analysis.

#### 4. Treatment settings

Among subgroups by the study settings, we did not find difference for response between milnacipran and TCAs or SSRIs based on seven studies for inpatients (comparing TCAs: Annseau 1989a; Annseau 1989c; Van Amerongen 2002; Lopez-Ibor 2004, comparing SSRIs: Annseau 1991c; Guelfi 1998a; Shinkai 2004) and four studies for outpatients (comparing SSRIs only:Annseau 1994; Sechter 2000; Lee 2002b; Yang 2003). Among subgroups by the study settings, we did not find difference for response in each settings (see Analysis 27.1, Analysis 28.1, Analysis 29.1, Analysis 29.2, Analysis 30.1).



#### 5. Elderly patients

As only one study specifically recruited elderly patients (Tignol 1998), it was not meaningful to carry out this pre-planned subgroup analysis.

#### Sensitivity analysis

# 1. Excluding trials with unclear concealment of random allocation and/or unclear double blinding

Although technically possible to carry out these sensitivity analyses, they were not performed, because they would not have contributed useful information due to the small number of studies (only three trials) reporting clear details on concealment of random allocation (Endo 1995, Yamashita 1995, Shinkai 2004).

#### 2. Excluding trials whose dropout rate was greater than 20%

Referring to TCAs, a dropout rate greater than 20% was found for four studies comparing milnacipran with imipramine (Yamashita 1995, Tignol 1998, Van Amerongen 2002, Lopez-Ibor 2004) and one with amitriptyline (Annseau 1989a). In terms of heterocyclics, the only study (Endo 1995) comparing milnacipran with mianserin reported a dropout rate greater than 20%. Among SSRIs, a dropout rate greater than 20% was found for two studies comparing milnacipran with fluoxetine (Guelfi 1998a, Lee 2002b), one with fluvoxamine (Clerc 2001), one with paroxetine (Sechter 2000) and one with sertraline (Yang 2003). Therefore, these pre-planned sensitivity analyses were not carried out because there were insufficient trials to allow meaningful formal assessment.

#### 3. Performing the worst and best-case scenario analysis

Results from these sensitivity analyses did not materially change the main findings (full details available on request from authors)

#### 4. Excluding trials for which the imputation methods were used

#### a) Imputed response rate

Excluding trials for which the response rate had to be calculated based on the imputation method, results for all comparisons did not materially change the main findings.

#### b) Borrowed SDs

Excluding trials for which the SD had to be borrowed from other trials, results from these sensitivity analyses did not materially change the main findings.

# 5. Examination of "wish bias" and exclusion of studies funded by the pharmaceutical company marketing milnacipran

These pre-planned sensitivity analyses were not carried out because there were insufficient trials run by manufacturers other than the pharmaceutical company marketing milnacipran to allow meaningful formal assessment. All the studies were sponsored by a pharmaceutical company marketing milnacipran except for Shinkai 2004.

#### **Funnel plot analysis**

There was no evidence of publication bias or other small study effects based on visual inspections of the funnel-plots with regard to the outcome variables.

#### DISCUSSION

#### Summary of main results

A total of 16 randomised controlled trials (n=2277) were included in this review. Milnacipran does not seem to provide a significant advantage in efficacy over other antidepressive agents for the acute phase treatment of major depression. However, the data from one trial suggest that milnacipran may be inferior in terms of response compared to clomipramine (OR0.45, 95%CI: 0.21 to 0.98). Further, compared with TCAs, intervention groups including patients taking milnacipran were associated with fewer patients leaving the trial early due to adverse events as compared to patients taking TCAs (OR 0.55; 95%CI 0.35 to 0.85) (Analysis 11.1). There was also small amount of evidence that patients taking milnacipran experienced fewer adverse events of sleepiness/ drowsiness, dry mouth or constipation, as compared with those taking TCAs.

The included studies did not report on all the outcomes that were pre-specified in the protocol of this review. Outcomes of clear relevance to patients and clinicians, in particular, patients' and their carers' attitudes to treatment, their ability to return to work and resume normal social functioning, were not reported in the included studies. Also ,only a small number of trials per comparison were found for most of the antidepressants. This limits the power of the review to detect moderate but clinically meaningful differences between the antidepressive agents.

#### **Overall completeness and applicability of evidence**

It has long been argued that placebo controlled trials are required to adequately demonstrate the efficacy of novel antidepressant drugs (Kupfer 2002), however, in the present review we focused only on the comparison between milnacipran and other active treatments for two reasons. First, in this review we focused on the following important clinical matter: "When an milnacipran is to be prescribed, would it constitute the better choice ?"

To answer this question within a clinically sound perspective, we included studies with active treatment comparisons. Second, placebo-controlled studies are different from active comparator trials in terms of design, conduct and population, and furthermore it has been shown that placebo response in published trials of antidepressant drug for major depressive disorder is highly variable and often substantial (Walsh 2002). Retrieved randomised evidence compared milnacipran with a small selection of possible comparator antidepressants and no trials comparing milnacipran with escitalopram or citalopram (amongst SSRIs), or with venlafaxine, duloxetine, mirtazapine, bupropion, reboxetine or hypericum (amongst the newer antidepressive agents), or with some of the first generation antidepressants (such as MAOIs) were found. Although the search was comprehensive and thorough, it is still possible that there are unpublished studies that have not been identified but the small number of trials identified per comparison hinders the detection of any publication bias.

As in all systematic reviews and meta-analyses, in the present study the main concern is about assessing the studies which were identified. The more information that is pooled together, the more precise and accurate is the estimate (Higgins 2005). We are realistically aware that a possibly significant piece of information has not been published and thus is not contributing to the true treatment estimate we were seeking. Although we

did our very best to retrieve as many data as possible, through asking pharmaceutical companies and study authors to supply all available information, we can assume that data from some trials are still lacking, most of which are likely to be studies with negative findings. We are also aware of the possibility that a number of further randomised controlled trials comparing milnacipran with other antidepressant drugs are currently being conducted and these will be included in future updates of the review.

# Potential biases in the review process

Some possible limitations of this review should be noted. Firstly, we had to impute the response and remission rates, our primary outcome, for most of the included trials. However, we consider that this is hardly rare, since incomplete reporting of outcome (i.e. an outcome reporting bias) is common within published articles of randomised trials (Chan 2004, Chan 2005). Further, imputation of response and remission rates by a validated statistical method (Furukawa 2006) in our review should minimize those biases. Nevertheless, we regret that we were unable to do a sensitivity analysis excluding trials with imputed response rates. As we update this review and assemble more trials involving milnacipran, we hope to conduct such a sensitivity analysis and be able to examine if our conclusions are robust.

Secondly, high dropout rates reduce the reliability of the assessment of other outcomes. Further, by making multiple comparisons we might have committed a type 1 error, that is, identifying and reporting a spurious association. Thirdly, all but one of the included trials had been funded by the drug company marketing milnacipran. There is nothing inherently wrong or biasing in this but, in view of the overwhelming evidence that sponsorship bias exists not only in psychiatry (Heres 2006) but also in medicine overall (Bekelman 2003), we should pay special attention that we may not inadvertently fall prey to such a bias. Therefore, these associations should be made clear to let anyone judge the relevance of the current findings.

# Agreements and disagreements with other studies or reviews

Venlafaxine, another dual serotonin-norepinephrine reuptake inhibitor, has been the first new generation antidepressant to be claimed to have differential effectiveness vis-a-vis the other antidepressants. The superiority of venlafaxine was first demonstrated in a drug company sponsored meta-analysis (Thase 2001), and subsequently confirmed in an independently conducted meta-analysis (Smith 2002). In addition, duloxetine, another SNRI, is also reported to be efficacious for the treatment of major depressive disorder and is well tolerated, safe and effective for the treatment of core depressive symptoms (Goldstein 2002, Cowen 2005, Frampton 2007). In keeping with these findings, milnacipran has been reported to be superior to SSRIs and equal to TCAs in two drug company sponsored meta-analyses (Puech 1997, Lopez-Ibor 1996). However, this superiority was not replicated in a subsequent independently-conducted meta-analysis (Papakostas 2007a). Our current review, which has included two additional trials involving SSRIs (Shinkai 2004, Yang 2003), and seven TCAs trials (Tignol 1998, Van Amerongen 2002, Lopez-Ibor 2004, Leinonen 1997, Annseau 1989a, Annseau 1989c, Yamashita 1995) and one heterocyclic trial (Endo 1995) since Papakostas 2007a, confirms its findings.

The methodological limitation of standard systematic reviews is that they can rely only on evidence from direct comparisons. However, given the wide spectrum of available comparisons for the treatment of major depression, the use of the methodology of multiple treatments meta-analysis (MTM, also known as network meta-analysis) may help overcome this limitation (Lumley 2002; Lu 2004: Lu 2006; Salanti 2008). MTM is a statistical method that enables to integrate data from direct comparisons (when treatments are compared within a randomised trial) and indirect comparisons (when treatments are compared between trials by combining results on how effective they are against a common comparator treatment) involving diverse regimens, and to assess the strength and consistency of the evidence. MTM has already been used in other fields of medicine (Psaty 2003; Elliott 2007), and these comparisons may provide a clinically useful summary that can be used to guide treatment decisions. In the field of major depression, we have recently published a MTM including our data for milnacipran to compare both direct and indirect effects of 12 new-generation antidepressants (Cipriani 2009a). The corresponding OR with 95%CI for efficacy (response rate) and acceptability (total dropout rate) are shown in Table 1. All of the confidence intervals overlap widely between MTM and direct comparisons, mainly because the confidence intervals of the direct comparisons are wide, generally indicating that the network of evidence is consistent. When the relative ratio of ORs was smaller than 0.59 (vs fluvoxamine and vs sertraline for response), the ORs of the MTM were revealed to be more conservative (i.e. closer to the null result) than the direct comparisons. It is possible that including indirect evidence may have 'cancelled out' the potential biases such as sponsorship and publication biases. The value of MTMs are increasingly acknowledged (Santaguida 2005) along with their pitfalls (Ioannidis 2006). Further methodological work is needed to confirm the relevance and validity of the review.

# AUTHORS' CONCLUSIONS

# **Implications for practice**

The results of this review suggest that milnacipran is no more or less effective than other antidepressants in the acute phase treatment of major depression. There is also inadequate evidence to detect a substantial difference between milnacipran and other antidepressive agents in terms of acceptability and tolerability. However, there is some evidence in favour of milnacipran over TCAs in terms of dropouts due to adverse events and the rates of experiencing adverse events.

#### **Implications for research**

More randomised controlled trials comparing milnacipran with other antidepressants are needed to generate more precise and accurate information about the drug. Also, randomised controlled trials comparing milnacipran with other comparator such as escitalopram, venlafaxine, duloxetine, mirtazapine, or hypericum are needed. Furthermore, future studies should focus to a greater extent on outcomes of clear relevance to patients and clinicians, in particular, patients' and their carers' attitudes to treatment, their ability to return to work and resume normal social functioning. Cost-effectiveness also need to be assessed.



# ACKNOWLEDGEMENTS

This review is one publication of the Meta-Analyses of New Generation Antidepressants (MANGA) project in which a group of researchers within the Cochrane Collaboration Depression, Anxiety and Neurosis Group agreed to conduct a systematic review of all available evidence for 12 new generation antidepressants to inform clinical practice and mental health policies.

As of April 2009, we have completed an individual review for fluoxetine (Cipriani 2005), sertraline (Cipriani 2009b) and escitalopram (Cipriani 2009c), and published the protocols for fluvoxamine (Omori 2006), citalopram (Imperadore 2007), paroxetine (Cipriani 2007a), venlafaxine (Cipriani 2007b), duloxetine (Nose 2007) and mirtazapine (Watanabe 2006).

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\* Indicates the major publication for the study

Annseau 1989a	
Methods	4 week randomised double blind study.
Participants	Diagnosis: Inpatients with RDC major depressive disorder
	Male and Female.
	Threshold of baseline severity: MADRS>=25, CGI<=4, Raskin Scale for Depression>Covi Anxiety Scale Total number of all allocated participants: N=146



Annseau 1989a (Continued)	Age: mean 48.6 (SD 10.8) y, range 20-70y.	
Interventions	Milnacipran 50/100mg: N=97 (50mg: N=47, 100mg: N=48) Amitriptyline 150mg: N=49	
	Fixed dosing schedule	
Outcomes	Hamilton Depression R	ating Scale-24 item, MADRS,CGI-I, CGI-S
Notes	Funding: by industry	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomly assigned". Probably done.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind". Probably done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (re- porting bias)	High risk	Did not provide number of participants who dropped out during the study due to side effects.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

#### Annseau 1989c

Methods	4 week randomised double blind study	
Participants	Diagnosis: Inpatients with RDC major depressive disorder	
	Male and Female.	
	Threshold of baseline severity: MADRS>=25, CGI<=5, Raskin Scale for Depression>Covi Anxiety Scale Total number of all allocated participants: N=87 Age: mean 49.6 (SD 11.6) y, range 23-68y.	
Interventions	Milnacipran 200mg: N=44 Amitriptyline 150mg: N=43	
	Fixed dosing schedule.	
Outcomes	Hamilton Depression Rating Scale-24 item, MADRS,CGI-I, CGI-S	
Notes	Funding: by industry	
Risk of bias		



#### Annseau 1989c (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomly assigned". Probably done.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (re- porting bias)	Low risk	The study protocol is not available but it is clear that the published reports in- clude all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

#### Annseau 1991c

Methods	4 week randomised double blind study		
Participants	Diagnosis: Inpatients with RDC major depressive disorder		
	Male and Female.		
	Threshold of baseline s Total number of all allo Age: mean 43.7 (SD 12.	severity: MADRS>=25, CGI<=5, Raskin Scale for Depression>Covi Anxiety Scale ocated participants: N=127 4)y, range 20-70y.	
Interventions	Milnacipran 150-300/200mg: N=86 (150-300mg:N=42, 200mg:N=44) Fluvoxamine 200mg: N=41		
	Fixed dosing schedule.		
Outcomes	Hamilton Depression Rating Scale-24 item, MADRS,CGI-I, CGI-S		
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomly assigned". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	



#### Annseau 1991c (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (re- porting bias)	High risk	Some missing standard deviations.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

#### Annseau 1994

Methods	6 week randomised double blind study		
Participants	Diagnosis: Outpatients with DSM-III-R major depressive episode		
	Male and Female.		
	Threshold of baseline severity: MADRS>=25, CGI-S<=4, Raskin Scale for Depression>Covi Anxiety Scale Total number of all allocated participants: N=190 Age: mean 44.9 (SD 11.2)y, range 19-68y.		
Interventions	Milnacipran 100mg: N=97 Fluoxetine 20mg: N=93		
	Fixed dosing schedule.		
Outcomes	Hamilton Depression Rating Scale-24 item, MADRS,CGI-I, CGI-S, CGI-E, 100mm VAS for depressed mood, psychomotor retardation, anxiety and insomnia		
Notes	Funding: by industry	Funding: by industry	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Bias Random sequence genera- tion (selection bias)	Authors' judgement	Support for judgement Quote: "randomly assigned". Probably done.	
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias)	Authors' judgement Low risk Unclear risk	Support for judgement Quote: "randomly assigned". Probably done. Insufficient information.	
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes	Authors' judgement Low risk Unclear risk Low risk	Support for judgement         Quote: "randomly assigned". Probably done.         Insufficient information.         Quote: "double-blind"	
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes Incomplete outcome data (attrition bias) All outcomes	Authors' judgement Low risk Unclear risk Low risk High risk	Support for judgement         Quote: "randomly assigned". Probably done.         Insufficient information.         Quote: "double-blind"         Some of actual figures of outcome data are missing. Incoherence between denominators.	
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes Incomplete outcome data (attrition bias) All outcomes Selective reporting (re- porting bias)	Authors' judgement         Low risk         Unclear risk         Low risk         High risk         High risk	Support for judgement         Quote: "randomly assigned". Probably done.         Insufficient information.         Quote: "double-blind"         Some of actual figures of outcome data are missing. Incoherence between denominators.         No data of participants who experienced at least some side effects.	



Clerc 2001			
Methods	6 week randomised double blind study		
Participants	Diagnosis: Outpatients with DSM-III-R major depressive episode		
	Male and Female.		
	Threshold of baseline s Total number of all allo Age: mean 48.7 (SD 15.)	everity: MADRS>=25, Raskin Scale for Depression ocated participants: N=113 1)y for milnacipran, mean 51.2 (SD 12.6)y for fluvoxamine	
Interventions	Milnacipran 100mg: N=57 Fluvoxamine 200mg: N=56		
	Fixed dosing schedule.	Fixed dosing schedule.	
Outcomes	Hamilton Depression R	Hamilton Depression Rating Scale-24 item, MADRS,CGI-I, CGI-S, CGI-E	
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.	
Selective reporting (re- porting bias)	Low risk	The study protocol is not available but it is clear that the published reports in- clude all expected outcomes, including those that were pre-specified.	
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.	

Endo 1995	
Methods	4 week randomised double blind study
Participants	Diagnosis: In- and Out-patients with DSM-III-R major depressive episode
	Male and Female.
	Threshold of baseline severity: Not reported.
	Total number of all allocated participants: N=179
	Age: range 20-65y
Interventions	Milnacipran 50-150mg (mean: 68.6mg): N=84 Mianserine 30- 60mg : N=95



Endo 1995 (Continued)	Flexible dosing schedu	le.
Outcomes	Hamilton Depression R	ating Scale-21 item, CGI-I, CPRG
Notes	Funding: by industry	
	Article in Japanese.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.
Allocation concealment (selection bias)	Low risk	Central allocation used.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (re- porting bias)	Low risk	The study protocol is not available but it is clear that the published reports in- clude all expected outcomes, including those that were pre-specified.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

### Guelfi 1998a

Methods	12 week randomised double blind study	
Participants	Diagnosis: Inpatients with DSM-III-R major depression	
	Male and Female.	
	Threshold of baseline severity: HDRS-17>=22, Newcastle scale>=6, HDRS specific endogenous sub- scale>=8 Total number of all allocated participants: N=300 Age: mean 45.6 (SD 12.8)y for milnacipran 100mg, mean 45.2 (SD 12.5)y for milnacipran 200mg, mean 45.8 (SD 12.8)y for fluoxetine; range 18-70y	
 Interventions	Milnacipran 100/200mg; N=200 (100mg;N=100, 200mg;N=100)	
	Fluoxetine 20mg: N=100	
	Fixed dosing schedule.	
Outcomes	Hamilton Depression Rating Scale-17 item, MADRS, CGI-S	
Notes	Funding: by industry	
Risk of bias		



#### Guelfi 1998a (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing primary outcome data at early phase.
Selective reporting (re- porting bias)	High risk	Some missing standard deviations.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

#### Lee 2002b

Methods	6 week randomised op	en-label study	
Participants	Diagnosis: Outpatients with DSM-IV major depressive disorder		
	Male and Female.		
	Threshold of baseline severity: HDRS-17>=17, MADRS>=21 Total number of all allocated participants: N=70 Age: mean 49 (SD 15)y for milnacipran , mean 51 (SD 12)y for fluoxetine; range 17-70y		
Interventions	Milnacipran 100mg: N= Fluoxetine 20mg: N=31	-39	
	Fixed dosing schedule.		
Outcomes	Hamilton Depression R	Rating Scale-17 item, MADRS, CGI-I, Covi Anxiety Scale	
Notes	Funding: by industry		
	Article in Korean.		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Blinding (performance bias and detection bias)	High risk	Open-label study	



#### Lee 2002b (Continued) All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.
Selective reporting (re- porting bias)	Unclear risk	Insufficient information.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

#### Leinonen 1997

Methods	26 week randomised double blind study		
Participants	Diagnosis: In- and Out-patients with DSM-III-R major depressive episode		
	Male and Female.		
	Threshold of baseline severity: HDRS-17>=18, CGI>=moderately ill Total number of all allocated participants: N=107 Age: mean 49.2 (SD 9.8)y for milnacipran, mean 47.1 (SD 10.6)y for clomipramine; range 18-70y		
Interventions	Milnacipran 100-200mg: N=52 Clomipramine 75-150mg: N=55		
	Flexible dosing schedu	Flexible dosing schedule.	
Outcomes	Hamilton Depression Rating Scale-17 item, MADRS, CGI-S		
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes	Unclear risk Low risk	Insufficient information. Quote: "double-blind"	
Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes Incomplete outcome data (attrition bias) All outcomes	Unclear risk Low risk Low risk	Insufficient information. Quote: "double-blind" No missing primary outcome.	
Allocation concealment (selection bias) Blinding (performance bias and detection bias) All outcomes Incomplete outcome data (attrition bias) All outcomes Selective reporting (re- porting bias)	Unclear risk Low risk Low risk High risk	Insufficient information. Quote: "double-blind" No missing primary outcome. Number of participants who dropped out the trial is missing.	



### Lopez-Ibor 2004

Methods	6 week randomised double blind study		
Participants	Diagnosis: Inpatients with DSM-III-R major depressive episode		
	Male and Female.		
	Threshold of baseline severity: MADRS>=25 Total number of all allocated participants: N=100 Age: range 18-70y		
Interventions	Milnacipran 100mg: N=51 Imipramine 150mg: N=49		
	Fixed dosing schedule.	Fixed dosing schedule.	
Outcomes	Hamilton Depression R	Hamilton Depression Rating Scale-21 item, MADRS, 100mm VAS for subjective depression	
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised"	
Allocation concealment (selection bias)	Unclear risk	Unclear	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome data.	
Selective reporting (re- porting bias)	Unclear risk	Number of patient receiving each intervention at the early phase is unclear.	
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.	

Sechter 2000	
Methods	6 week randomised double blind study
Participants	Diagnosis: Outpatients with DSM-IV major depressive disorder
	Male and Female.
	Threshold of baseline severity: MADRS>=20
	Total number of all allocated participants: N=302
	Age: mean 44.8 (SD 11.6)y for milnacipran, mean 42.8 (SD 11.2)y for paroxetine; range 18-70y
Interventions	Milnacipran 100mg: N=149
	Imipramine 20mg: N=153

Milnacipran versus other antidepressive agents for depression (Review)

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Sechter 2000 (Continued)	Fixed dosing schedule.		
Outcomes	Hamilton Depression Rating Scale-17 item, MADRS, CGI-I, CGI-S		
Notes	Funding: by industry	Funding: by industry	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised"	
Allocation concealment (selection bias)	Unclear risk	Unclear	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome.	
Selective reporting (re- porting bias)	High risk	Missing standard deviations.	
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.	

# Shinkai 2004

Methods	4 week randomised double blind study			
Participants	Diagnosis: Inpatients with DSM-IV major depressive disorder without psychotic features			
	Male and Female.	Male and Female.		
	Threshold of baseline severity: HDRS-17>=15 Total number of all allocated participants: N=41 Age: mean 53 (SD 17)y; range 20-78y			
Interventions	Milnacipran mean 80.25mg: N=20 Paroxetine mean 34.28mg: N=21			
	Flexible dosing schedule.			
Outcomes	Hamilton Depression Rating Scale-17 item			
Notes	Funding: independent from industry			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomly"		



#### Shinkai 2004 (Continued)

Allocation concealment (selection bias)	Low risk	Quote: "randomly divided into either milnacipran or the paroxetine group us- ing StatView, a computerized statistical package"
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing primary outcome.
Selective reporting (re- porting bias)	High risk	Adverse events were not reported so that could not be entered in to the meta- analysis.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

### Tignol 1998

Methods	8 week randomised double blind study		
Participants	Diagnosis: In- and Out-patients with DSM-III-R major depressive episode		
	Male and Female.		
	Threshold of baseline severity: HDRS-17>=17, MADRS>=25, improvement during washout phase less than 25% of the initial score, MMSE>=20 Total number of all allocated participants: N=221 Age: mean 74.0 (SD 6.2)y for milnacipran, mean 74.2 (SD 6.8)y for imipramine; range 65-93y		
Interventions	Milnacipran 75-100mg N=112 Imipramine 75-100mg N=109		
	Flexible dosing schedule.		
Outcomes	Hamilton Depression Rating Scale-17 item, MADRS, CGI-I, CGI-S, Covi Anxiety Scale, WAIS, Digit Symbol Substitution Test (DSST), Word-paired test, MMSE, Functional Status Questionnaire (FSQ)		
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing primary outcome at early phase.	



### Tignol 1998 (Continued)

Selective reporting (re- porting bias)	High risk	MADRS scores were reported incompletely. Missing standard deviations.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

### Van Amerongen 2002

Methods	6 week randomised double blind study		
Participants	Diagnosis: Inpatients with DSM-III major depression		
	Male and Female.		
	Threshold of baseline severity: HDRS-17>=17, MADRS>=25, improvement during washout phase less than 25% of the initial score, MMSE>=20 Total number of all allocated participants: N=109 Age: mean 46.7y (range 23-70y) for milnacipran, mean 45.9 y (range 20-71y) for imipramine; range 18-70y for total sample		
Interventions	Milnacipran 100mg N=53 Imipramine 150mg N=56		
	Fixed dosing schedule.	Fixed dosing schedule.	
Outcomes	Hamilton Depression Rating Scale-21 item, MADRS, CGI-3, 100mm VAS for subjective depression		
Notes	Funding: by industry		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.	
Allocation concealment (selection bias)	Unclear risk	Insufficient information.	
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"	
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing primary outcome at early phase.	
Selective reporting (re- porting bias)	High risk	Missing standard deviations.	
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.	

#### Yamashita 1995

Methods	4 week randomised double blind study	
Milnacipran versus other antid	epressive agents for depression (Review)	44
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Yamashita 1995 (Continued)								
Participants	Diagnosis: In- and Out- patients with DSM-III-R major depressive episode							
	Male and Female.							
	Threshold of baseline severity: Not reported. Total number of all allocated participants: N=132 Age: range 20-65y for total sample							
Interventions	Milnacipran 50-150mg (mean:77.2mg) N=66 Imipramine 50-150mg (mean:89.1mg) N=66							
	Flexible dosing schedu	le						
Outcomes	Hamilton Depression R	ating Scale-21 item, CGI-I, CPRG						
Notes	Funding: by industry							
	Article in Japanese.							
Risk of bias								
Bias	Authors' judgement	Support for judgement						
Bias Random sequence genera- tion (selection bias)	Authors' judgement	Support for judgement Quote: "randomised". Probably done.						
Bias Random sequence genera- tion (selection bias) Allocation concealment (selection bias)	Authors' judgement Low risk Low risk	Support for judgement         Quote: "randomised". Probably done.         Cental allocation used.						
BiasRandom sequence generation (selection bias)Allocation concealment (selection bias)Blinding (performance bias and detection bias) All outcomes	Authors' judgement Low risk Low risk Low risk	Support for judgement         Quote: "randomised". Probably done.         Cental allocation used.         Quote: "double-blind"						
BiasRandom sequence generation (selection bias)Allocation concealment (selection bias)Blinding (performance bias and detection bias) All outcomesIncomplete outcome data (attrition bias) All outcomes	Authors' judgement Low risk Low risk Low risk Low risk Low risk	Support for judgement         Quote: "randomised". Probably done.         Cental allocation used.         Quote: "double-blind"         No missing primary outcome data.						
BiasRandom sequence generation (selection bias)Allocation concealment (selection bias)Blinding (performance bias and detection bias) All outcomesIncomplete outcome data (attrition bias) All outcomesSelective reporting (re- porting bias)	Authors' judgement Low risk Low risk Low risk Low risk Low risk Low risk	Support for judgement         Quote: "randomised". Probably done.         Cental allocation used.         Quote: "double-blind"         No missing primary outcome data.         The study protocol is not available but it is clear that the published reports in-clude all expected outcomes, including those that were pre-specified.						
BiasRandom sequence generation (selection bias)Allocation concealment (selection bias)Blinding (performance bias and detection bias) All outcomesIncomplete outcome data (attrition bias) All outcomesSelective reporting (re- porting bias)Other bias	Authors' judgement Low risk Low risk Low risk Low risk Low risk Unclear risk	Support for judgementQuote: "randomised". Probably done.Cental allocation used.Quote: "double-blind"No missing primary outcome data.The study protocol is not available but it is clear that the published reports in- clude all expected outcomes, including those that were pre-specified.Insufficient information to assess whether an important risk of bias exists.						

# Yang 2003

Methods	8 week randomised double blind study
Participants	Diagnosis: Outpatients with DSM-IV major depressive disorder
	Male and Female.
	Threshold of baseline severity: HDRS-17>=17 Total number of all allocated participants: N=53 Age: not shown
Interventions	Milnacipran 100mg N=27 Sertraline 100mg N=26



Yang 2003 (Continued)	Flexible dosing schedu	le							
Outcomes	Hamilton Depression R								
Notes	Funding: by industry	Funding: by industry							
	Article in Korean.								
Risk of bias									
Bias	Authors' judgement	Support for judgement							
Random sequence genera- tion (selection bias)	Low risk	Quote: "randomised". Probably done.							
Allocation concealment (selection bias)	Unclear risk	Insufficient information.							
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "double-blind"							
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcome data missing.							
Selective reporting (re- porting bias)	High risk	Adverse events are not reported so that could not be entered in a meta-analy- sis.							
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.							

# Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baek 2002a	Did not use relevant operational diagnostic criteria.
Baek 2002b	Additional publication of trial already included.
Dardennes 1998	Did not include acute phase treatment.
Kanemoto 2004	Did not use other antidepressant as a comparator drug.
Lee 2004	Additional publication of trial already included.
Macher 1989	Did not use other antidepressant as a comparator drug.
Naito 2007	Secondary analysis of separate two studies (Ito 2002; Yoshida 2002), thus not a concurrent comparison study
Onodera 1992	Additional publication of trial already included.
Wyeth 2006	Method of allocation was not randomised (e.g. controlled clinical trial).



# **Characteristics of studies awaiting assessment** [ordered by study ID]

Yoshimura 2007	
Methods	RCT
Participants	42 Japanese adults
Interventions	paroxetine vs milnacipran
Outcomes	Serum BDNF levels, response and remission rates
Notes	

# DATA AND ANALYSES

# Comparison 1. Response at acute phase (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	4	537	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.59, 1.30]
1.1 Milnacipran vs Imipramine	3	430	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.71, 1.54]
1.2 Milancipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.45 [0.21, 0.98]
2 Milnacipran vs SSRIs	6	1028	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.76, 1.64]
2.1 Milnacipran vs Fluvoxam- ine	1	113	Odds Ratio (M-H, Random, 95% Cl)	1.76 [0.81, 3.83]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.55, 1.58]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.59, 1.47]
2.4 Milnacipran vs Sertraline	1	53	Odds Ratio (M-H, Random, 95% CI)	3.83 [0.90, 16.26]

# Analysis 1.1. Comparison 1 Response at acute phase (6-12 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs		Odds Ratio			Weight	Odds Ratio			
	n/N	n/N		M-H, Random, 95% Cl				M-H, Random, 95% CI			
1.1.1 Milnacipran vs Imipramine											
Lopez-Ibor 2004	20/51	20/49				•				20.24%	0.94[0.42,2.08]
Tignol 1998	67/112	64/109					_			37.44%	1.05[0.61,1.79]
Van Amerongen 2002	35/53	35/56				+•				20.91%	1.17[0.53,2.56]
Subtotal (95% CI)	216	214		1		$\blacklozenge$				78.59%	1.05[0.71,1.54]
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	



<b>a</b> , 1, 1									
Study or subgroup	Milnacipran	TCAS			Od	ids Ratio		Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom, 95% Cl			M-H, Random, 95% Cl
Total events: 122 (Milnacipran), 119	(TCAs)								
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.15, df	f=2(P=0.93); I <sup>2</sup> =0%								
Test for overall effect: Z=0.23(P=0.82	2)								
1.1.2 Milancipran vs Clomipramine	e								
Leinonen 1997	22/52	34/55			•			21.41%	0.45[0.21,0.98]
Subtotal (95% CI)	52	55						21.41%	0.45[0.21,0.98]
Total events: 22 (Milnacipran), 34 (To	CAs)								
Heterogeneity: Not applicable									
Test for overall effect: Z=2.01(P=0.04	1)								
	200	200						100%	
18tal (95% CI)	268	269						100%	0.87[0.59,1.3]
Total events: 144 (Milnacipran), 153	(TCAs)								
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =3.75	, df=3(P=0.29); l <sup>2</sup> =20.010	%							
Test for overall effect: Z=0.66(P=0.51	.)								
Test for subgroup differences: Chi <sup>2</sup> =	3.6, df=1 (P=0.06), l <sup>2</sup> =72.	23%							
		Favours TCAs	0.1	0.2	0.5	1 2	5 10	Favours Milnacipran	

# Analysis 1.2. Comparison 1 Response at acute phase (6-12 weeks), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
1.2.1 Milnacipran vs Fluvoxamine					
Clerc 2001	40/57	32/56	+	14.87%	1.76[0.81,3.83]
Subtotal (95% CI)	57	56		14.87%	1.76[0.81,3.83]
Total events: 40 (Milnacipran), 32 (SSF	RIS)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					
1.2.2 Milnacipran vs Fluoxetine					
Annseau 1994	32/97	43/93		19.99%	0.57[0.32,1.03]
Guelfi 1998a	109/200	51/100	<b>_</b>	23.61%	1.15[0.71,1.86]
Lee 2002b	17/39	11/31		11.1%	1.4[0.53,3.71]
Subtotal (95% CI)	336	224		54.71%	0.93[0.55,1.58]
Total events: 158 (Milnacipran), 105 (S	SSRIs)				
Heterogeneity: Tau <sup>2</sup> =0.11; Chi <sup>2</sup> =4.07, o	df=2(P=0.13); I <sup>2</sup> =50.83	3%			
Test for overall effect: Z=0.27(P=0.79)					
1.2.3 Milnacipran vs Paroxetine					
Sechter 2000	86/149	91/153	<b>-</b>	24.44%	0.93[0.59,1.47]
Subtotal (95% CI)	149	153		24.44%	0.93[0.59,1.47]
Total events: 86 (Milnacipran), 91 (SSF	RIS)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P	<0.0001); l <sup>2</sup> =100%				
Test for overall effect: Z=0.31(P=0.76)					
1.2.4 Milnacipran vs Sertraline					
Yang 2003	9/27	3/26	+ + +	5.99%	3.83[0.9,16.26]
Subtotal (95% CI)	27	26		5.99%	3.83[0.9,16.26]
Total events: 9 (Milnacipran), 3 (SSRIs	)				
		Favours SSRIs 0.1	0.2 0.5 1 2 5 1	.0 Favours Milnaciprar	1



Study or subgroup	Milnacipran	SSRIs			00	dds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	I			M-H, Random, 95% Cl
Heterogeneity: Not applicable											
Test for overall effect: Z=1.82(P=0.	07)										
Total (95% CI)	569	459				-	►			100%	1.11[0.76,1.64]
Total events: 293 (Milnacipran), 23	1 (SSRIs)										
Heterogeneity: Tau <sup>2</sup> =0.1; Chi <sup>2</sup> =9.6	5, df=5(P=0.09); l <sup>2</sup> =48.19 <sup>0</sup>	%									
Test for overall effect: Z=0.54(P=0.	59)										
Test for subgroup differences: Chi <sup>4</sup>	<sup>2</sup> =5.2, df=1 (P=0.16), l <sup>2</sup> =42	2.29%									
		Favours SSRIs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Comparison 2. Response at early phase (1-4 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	802	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.58, 1.20]
1.1 Milancipran vs Imipramine	3	462	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.73, 1.69]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.46 [0.17, 1.24]
1.3 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% Cl)	0.62 [0.35, 1.08]
2 Milancipran vs SSRIs	6	953	Odds Ratio (M-H, Random, 95% Cl)	1.30 [0.97, 1.73]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	1.54 [0.87, 2.72]
2.2 Milnacipran vs Fluoxetine	2	370	Odds Ratio (M-H, Random, 95% CI)	1.49 [0.93, 2.37]
2.3 Milnacipran vs Paroxetine	2	343	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.61, 1.60]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	1.10 [0.54, 2.23]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.54, 2.23]

# Analysis 2.1. Comparison 2 Response at early phase (1-4 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
2.1.1 Milancipran vs Imipramine					
Tignol 1998	23/112	16/109		19.45%	1.5[0.75,3.03]
Van Amerongen 2002	24/53	30/56	+	17.48%	0.72[0.34,1.52]
Yamashita 1995	28/66	25/66		19.62%	1.21[0.6,2.43]
Subtotal (95% CI)	231	231	-	56.55%	1.11[0.73,1.69]
Total events: 75 (Milnacipran), 71 (TCA	s)				
		Favours TCAs	0.2 0.5 1 2 5	Favours Milnaciprar	1

Milnacipran versus other antidepressive agents for depression (Review)

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Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95%	6 CI	M-H, Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.06, df=	=2(P=0.36); I <sup>2</sup> =2.96%			-	
Test for overall effect: Z=0.5(P=0.62)					
2.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	7/52	14/55	+	11.12%	0.46[0.17,1.24]
Subtotal (95% CI)	52	55		11.12%	0.46[0.17,1.24]
Total events: 7 (Milnacipran), 14 (TCA	(s)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.54(P=0.12)	)				
2.1.3 Milnacipran vs Amitriptyline					
Annseau 1989a	29/97	21/49		18.96%	0.57[0.28,1.16]
Annseau 1989c	13/44	16/43	+	13.37%	0.71[0.29,1.73]
Subtotal (95% CI)	141	92		32.33%	0.62[0.35,1.08]
Total events: 42 (Milnacipran), 37 (TC	CAs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.14, df=	=1(P=0.71); I <sup>2</sup> =0%				
Test for overall effect: Z=1.68(P=0.09)	1				
Total (95% CI)	424	378	-	100%	0.83[0.58,1.2]
Total events: 124 (Milnacipran), 122 (	TCAs)				
Heterogeneity: Tau <sup>2</sup> =0.05; Chi <sup>2</sup> =6.58,	df=5(P=0.25); I <sup>2</sup> =23.99	%			
Test for overall effect: Z=0.98(P=0.33)	1				
Test for subgroup differences: Chi <sup>2</sup> =4	.32, df=1 (P=0.12), l <sup>2</sup> =5	3.68%			
		Favours TCAs	0.2 0.5 1 2	5 Favours Milnacipra	n

# Analysis 2.2. Comparison 2 Response at early phase (1-4 weeks), Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs		Odds Ratio				Weight	Odds Ratio	
	n/N	n/N		Ν	1-H, Ran	dom, 95% Cl				M-H, Random, 95% CI
2.2.1 Milnacipran vs Fluvoxamine										
Annseau 1991c	32/86	10/41			-	+ +	_		11.92%	1.84[0.8,4.24]
Clerc 2001	22/57	18/56				++			13.92%	1.33[0.61,2.88]
Subtotal (95% CI)	143	97							25.84%	1.54[0.87,2.72]
Total events: 54 (Milnacipran), 28 (SS	SRIs)									
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.31, df	=1(P=0.58); I <sup>2</sup> =0%									
Test for overall effect: Z=1.49(P=0.14	)									
2.2.2 Milnacipran vs Fluoxetine										
Guelfi 1998a	83/200	31/100							32.22%	1.58[0.95,2.63]
Lee 2002b	8/39	6/31				+			5.96%	1.08[0.33,3.51]
Subtotal (95% CI)	239	131							38.18%	1.49[0.93,2.37]
Total events: 91 (Milnacipran), 37 (SS	SRIs)									
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.34, df	=1(P=0.56); I <sup>2</sup> =0%									
Test for overall effect: Z=1.66(P=0.1)										
2.2.3 Milnacipran vs Paroxetine										
Sechter 2000	38/149	37/153			_	<b>•</b> •			30.58%	1.07[0.64,1.81]
Shinkai 2004	10/20	13/21			+-	+			5.4%	0.62[0.18,2.13]
Subtotal (95% CI)	169	174			<				35.97%	0.99[0.61,1.6]
		Favours SSRIs	0.1	0.2	0.5	1 2	5	<sup>10</sup> Favo	ours Milnacipran	



Study or subgroup	Milnacipran	SSRIs			00	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% CI	l			M-H, Random, 95% Cl
Total events: 48 (Milnacipran), 50 (	SSRIs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.65, o	df=1(P=0.42); I <sup>2</sup> =0%										
Test for overall effect: Z=0.05(P=0.9	96)										
Total (95% CI)	551	402								100%	1.3[0.97,1.73]
Total events: 193 (Milnacipran), 11	5 (SSRIs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =3.23, o	df=5(P=0.66); I <sup>2</sup> =0%										
Test for overall effect: Z=1.76(P=0.0	08)										
Test for subgroup differences: Chi <sup>2</sup>	=1.92, df=1 (P=0.38), I <sup>2</sup> =0%										
	F	avours SSRIs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Analysis 2.3. Comparison 2 Response at early phase (1-4 weeks), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Od	lds Rat	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% Cl
2.3.1 Milancipran vs Mianserin											
Endo 1995	19/84	20/95				-				100%	1.1[0.54,2.23]
Subtotal (95% CI)	84	95				$\blacklozenge$				100%	1.1[0.54,2.23]
Total events: 19 (Milnacipran), 20 (Het	erocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.25(P=0.8)											
Total (95% CI)	84	95								100%	1.1[0.54,2.23]
Total events: 19 (Milnacipran), 20 (Het	erocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.25(P=0.8)											
	Fav	ours Heterocyclics	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Comparison 3. Response at follow-up phase (4-6 months)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	1	107	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.55]
1.1 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.33, 1.55]

# Analysis 3.1. Comparison 3 Response at follow-up phase (4-6 months), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs		Odds Ratio					Weight	Odds Ratio
	n/N	n/N		M-H, Ra	ndom,	95% CI				M-H, Random, 95% Cl
3.1.1 Milnacipran vs Clomipramine										
Leinonen 1997	27/52	33/55				-			100%	0.72[0.33,1.55]
Subtotal (95% CI)	52	55				-	1		100%	0.72[0.33,1.55]
		Favours TCAs 0.	.1 0.2	0.5	1	2	5	10	Favours Milnacipran	



Study or subgroup	Milnacipran	TCAs			Oc	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	I			M-H, Random, 95% Cl
Total events: 27 (Milnacipran), 33 (TC/	As)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.84(P=0.4)											
Total (95% CI)	52	55					-			100%	0.72[0.33,1.55]
Total events: 27 (Milnacipran), 33 (TC/	As)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.84(P=0.4)											
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Comparison 4. Remission at acute phase (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	4	537	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.57, 1.19]
1.1 Milnacipran vs Imipramine	3	430	Odds Ratio (M-H, Random, 95% CI)	0.94 [0.62, 1.41]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.43 [0.17, 1.07]
2 Milnacipran vs SSRIs	6	1028	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.73, 1.32]
2.1 Milnacipran vs Fluvoxam- ine	1	113	Odds Ratio (M-H, Random, 95% Cl)	1.48 [0.66, 3.30]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.91 [0.56, 1.46]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% Cl)	0.92 [0.57, 1.49]
2.4 Milnacipran vs Sertraline	1	53	Odds Ratio (M-H, Random, 95% Cl)	0.0 [0.0, 0.0]

# Analysis 4.1. Comparison 4 Remission at acute phase (6-12 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weig	nt Odds Ratio
	n/N	n/N	M-H, Random, 95	% CI	M-H, Random, 95% Cl
4.1.1 Milnacipran vs Imipramine					
Lopez-Ibor 2004	10/51	11/49	+	- :	.4.91% 0.84[0.32,2.21]
Tignol 1998	36/112	38/109	<b>_</b>		44.3% 0.89[0.51,1.55]
Van Amerongen 2002	24/53	24/56		- 2	4.17% 1.1[0.52,2.35]
Subtotal (95% CI)	216	214	•	8	3.39% 0.94[0.62,1.41]
Total events: 70 (Milnacipran), 73 (	TCAs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.27,	df=2(P=0.88); I <sup>2</sup> =0%				
Test for overall effect: Z=0.32(P=0.7	75)				
4.1.2 Milnacipran vs Clomiprami	ne				
Leinonen 1997	9/52	18/55			.6.61% 0.43[0.17,1.07]
		Favours TCAs	0.1 0.2 0.5 1 2	<sup>5</sup> <sup>10</sup> Favours M	Inacipran

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Study or subgroup	Milnacipran	TCAs			Od	ds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	1			M-H, Random, 95% Cl
Subtotal (95% CI)	52	55								16.61%	0.43[0.17,1.07]
Total events: 9 (Milnacipran), 18 (T	CAs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=	D(P<0.0001); I <sup>2</sup> =100%										
Test for overall effect: Z=1.81(P=0.0	07)										
Total (95% CI)	268	269								100%	0.82[0.57,1.19]
Total events: 79 (Milnacipran), 91 (	TCAs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.58, o	df=3(P=0.46); I <sup>2</sup> =0%										
Test for overall effect: Z=1.03(P=0.3	3)										
Test for subgroup differences: Chi <sup>2</sup>	=2.32, df=1 (P=0.13), I <sup>2</sup> =56.	85%									
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	I

# Analysis 4.2. Comparison 4 Remission at acute phase (6-12 weeks), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio	
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI	
4.2.1 Milnacipran vs Fluvoxamine						
Clerc 2001	20/57	15/56		13.6%	1.48[0.66,3.3]	
Subtotal (95% CI)	57	56		13.6%	1.48[0.66,3.3]	
Total events: 20 (Milnacipran), 15 (SSI	RIs)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.95(P=0.34)						
4.2.2 Milnacipran vs Fluoxetine						
Annseau 1994	15/97	22/93		16.52%	0.59[0.28,1.22]	
Guelfi 1998a	47/200	20/100		25.31%	1.23[0.68,2.21]	
Lee 2002b	7/39	6/31		6%	0.91[0.27,3.05]	
Subtotal (95% CI)	336	224		47.83%	0.91[0.56,1.46]	
Total events: 69 (Milnacipran), 48 (SSI	RIs)					
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =2.35,	df=2(P=0.31); I <sup>2</sup> =14.88	%				
Test for overall effect: Z=0.4(P=0.69)						
4.2.3 Milnacipran vs Paroxetine						
Sechter 2000	49/149	53/153		38.57%	0.92[0.57,1.49]	
Subtotal (95% CI)	149	153		38.57%	0.92[0.57,1.49]	
Total events: 49 (Milnacipran), 53 (SSI	RIs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P	P<0.0001); I²=100%					
Test for overall effect: Z=0.32(P=0.75)						
4.2.4 Milnacipran vs Sertraline						
Yang 2003	0/27	0/26			Not estimable	
Subtotal (95% CI)	27	26			Not estimable	
Total events: 0 (Milnacipran), 0 (SSRIs	5)					
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)	569	459	•	100%	0.98[0.73,1.32]	
Total events: 138 (Milnacipran), 116 (S	SSRIs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =3.5, df=4	(P=0.48); I <sup>2</sup> =0%					
		Favours SSRIs 0.1	0.2 0.5 1 2 5	<sup>10</sup> Favours Milnacipran	l	



Study or subgroup	Milnacipran n/N	SSRIs n/N			Od M-H, Rar	ds Ra ndon	atio 1, 95% Cl			Weight	Odds Ratio M-H, Random, 95% Cl
Test for overall effect: Z=0.12(P=0.91)											
Test for subgroup differences: Chi <sup>2</sup> =1	.16, df=1 (P=0.56), I <sup>2</sup> =	-0%									
		Favours SSRIs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Comparison 5. Remission at early phase (1-4 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	802	Odds Ratio (M-H, Random, 95% CI)	0.89 [0.56, 1.40]
1.1 Milnacipran vs Imipramine	3	462	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.59, 1.79]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.11, 4.33]
1.3 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.25, 1.54]
2 Milnacipran vs SSRIs	6	953	Odds Ratio (M-H, Random, 95% CI)	1.28 [0.77, 2.14]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.52, 3.58]
2.2 Milnacipran vs Fluoxetine	2	370	Odds Ratio (M-H, Random, 95% CI)	1.72 [0.71, 4.17]
2.3 Milnacipran vs Paroxetine	2	343	Odds Ratio (M-H, Random, 95% CI)	0.95 [0.42, 2.17]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.57, 3.67]
3.1 Milnacipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.57, 3.67]

# Analysis 5.1. Comparison 5 Remission at early phase (1-4 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
5.1.1 Milnacipran vs Imipramine					
Tignol 1998	3/112	2/109			1.47[0.24,8.99]
Van Amerongen 2002	13/53	18/56		29.67%	0.69[0.3,1.59]
Yamashita 1995	18/66	14/66		32.64%	1.39[0.63,3.1]
Subtotal (95% CI)	231	231	-	68.71%	1.03[0.59,1.79]
Total events: 34 (Milnacipran), 34 (	TCAs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.59,	df=2(P=0.45); l <sup>2</sup> =0%				
Test for overall effect: Z=0.11(P=0.9	91)				
5.1.2 Milnacipran vs Clomiprami	ne				
Leinonen 1997	2/52	3/55	+	6.25%	0.69[0.11,4.33]
Subtotal (95% CI)	52	55		6.25%	0.69[0.11,4.33]
		Favours TCAs	0.1 0.2 0.5 1 2 5	<sup>10</sup> Favours Milnaciprar	1



Study or subgroup	Milnacinran	TCAc	Odde Patio	Waight	Odds Patio
Study of subgroup	Milliacipran		Mul Bandam 05% Cl	weight	
	n/N	n/N	M-H, Random, 95% Ci		M-H, Random, 95% CI
Total events: 2 (Milnacipran), 3 (TCAs)	)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
5.1.3 Milnacipran vs Amitriptyline					
Annseau 1989a	9/97	7/49		18.86%	0.61[0.21,1.76]
Annseau 1989c	2/44	3/43 -		6.18%	0.63[0.1,4]
Subtotal (95% CI)	141	92		25.04%	0.62[0.25,1.54]
Total events: 11 (Milnacipran), 10 (TC	As)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1(P	P=0.97); I <sup>2</sup> =0%				
Test for overall effect: Z=1.03(P=0.3)					
Total (95% CI)	424	379		100%	0 89[0 56 1 4]
	- 27	510		100%	0.05[0.50,1.4]
Total events: 47 (Milnacipran), 47 (TC	As)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.55, df=	5(P=0.77); I <sup>2</sup> =0%				
Test for overall effect: Z=0.52(P=0.6)					
Test for subgroup differences: Chi <sup>2</sup> =0.	.95, df=1 (P=0.62), I <sup>2</sup> =0	%			
		Favours TCAs 0	0.1 0.2 0.5 1 2 5	<sup>10</sup> Favours Milnacipran	

# Analysis 5.2. Comparison 5 Remission at early phase (1-4 weeks), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
5.2.1 Milnacipran vs Fluvoxamine					
Annseau 1991c	9/86	3/41	+	14.05%	1.48[0.38,5.79]
Clerc 2001	5/57	4/56	+	13.92%	1.25[0.32,4.92]
Subtotal (95% CI)	143	97		27.97%	1.36[0.52,3.58]
Total events: 14 (Milnacipran), 7 (SS	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.03, d	f=1(P=0.86); I <sup>2</sup> =0%				
Test for overall effect: Z=0.63(P=0.53	3)				
5.2.2 Milnacipran vs Fluoxetine					
Guelfi 1998a	20/200	6/100		29.2%	1.74[0.68,4.48]
Lee 2002b	2/39	1/31		4.36%	1.62[0.14,18.76]
Subtotal (95% CI)	239	131		33.56%	1.72[0.71,4.17]
Total events: 22 (Milnacipran), 7 (SS	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1	.(P=0.96); l <sup>2</sup> =0%				
Test for overall effect: Z=1.21(P=0.23	3)				
5.2.3 Milnacipran vs Paroxetine					
Sechter 2000	9/149	9/153		28.77%	1.03[0.4,2.67]
Shinkai 2004	3/20	4/21		9.7%	0.75[0.15,3.87]
Subtotal (95% CI)	169	174		38.47%	0.95[0.42,2.17]
Total events: 12 (Milnacipran), 13 (S	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.11, d	f=1(P=0.74); I <sup>2</sup> =0%				
Test for overall effect: Z=0.12(P=0.9)	)				
Total (95% CI)	551	402	-	100%	1.28[0.77,2.14]
Total events: 48 (Milnacipran), 27 (S	SRIs)				
		Favours SSRIs 0.1	0.2 0.5 1 2 5 1	<sup>0</sup> Favours Milnacipra	n



Study or subgroup	Milnacipran n/N	SSRIs n/N			Od M-H, Ra	lds Ra ndon	atio n, 95% Cl			Weight	Odds Ratio M-H, Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.1, df=	5(P=0.95); I <sup>2</sup> =0%										
Test for overall effect: Z=0.96(P=0.34	1)										
Test for subgroup differences: Chi <sup>2</sup> =	0.96, df=1 (P=0.62), l <sup>2</sup> =0	%									
		Favours SSRIs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

# Analysis 5.3. Comparison 5 Remission at early phase (1-4 weeks), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Od	lds Rat	io			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom,	95% CI				M-H, Random, 95% CI
5.3.1 Milnacipran vs Mianserin											
Endo 1995	11/84	9/95						-		100%	1.44[0.57,3.67]
Subtotal (95% CI)	84	95			-					100%	1.44[0.57,3.67]
Total events: 11 (Milnacipran), 9 (Hete	rocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.76(P=0.44)											
Total (95% CI)	84	95			-					100%	1.44[0.57,3.67]
Total events: 11 (Milnacipran), 9 (Hete	rocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.76(P=0.44)											
	Fa	vours Heterocyclic	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

### Comparison 6. Remission at follow-up phase (4-6 months)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	1	107	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.28, 1.31]
1.1 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	0.61 [0.28, 1.31]

# Analysis 6.1. Comparison 6 Remission at follow-up phase (4-6 months), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs			Ode	ds Rat	io			Weight	Odds Ratio
	n/N	n/N			M-H, Rar	ndom,	95% CI				M-H, Random, 95% CI
6.1.1 Milnacipran vs Clomipramine											
Leinonen 1997	21/52	29/55		-						100%	0.61[0.28,1.31]
Subtotal (95% CI)	52	55		-						100%	0.61[0.28,1.31]
Total events: 21 (Milnacipran), 29 (TCA	s)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.28(P=0.2)											
Total (95% CI)	52	55		-						100%	0.61[0.28,1.31]
Total events: 21 (Milnacipran), 29 (TCA	s)										
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

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Study or subgroup	Milnacipran n/N	TCAs n/N	Odds Ratio M-H, Random, 95% Cl				Weight	Odds Ratio M-H, Random, 95% Cl			
Heterogeneity: Not applicable											
Test for overall effect: Z=1.28(P=0.2)					1				1		
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnaciprar	1

# Comparison 7. Depression scale-end point score at acute phase (6-12 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	7	820	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.07, 0.21]
1.1 Milnacipran vs Imipramine	4	509	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.15, 0.20]
1.2 Milnacipran vs Clomipramine	1	93	Std. Mean Difference (IV, Random, 95% CI)	0.44 [0.03, 0.85]
1.3 Milancipran vs Amitriptyline	2	218	Std. Mean Difference (IV, Random, 95% CI)	-0.00 [-0.42, 0.42]
2 Milnacipran vs SSRIs	8	963	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.11, 0.19]
2.1 Milnacipran vs Fluvox- amine	2	224	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.45, 0.17]
2.2 Milnacipran vs Fluoxe- tine	3	372	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.21, 0.42]
2.3 Milnacipran vs Paroxe- tine	2	340	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.09, 0.33]
2.4 Milnacipran vs Sertraline	1	27	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.91, 0.61]
3 Milnacipran vs Hetero- cyclics	1	167	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.43, 0.18]
3.1 Milnacipran vs Mianserin	1	167	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.43, 0.18]

# Analysis 7.1. Comparison 7 Depression scale-end point score at acute phase (6-12 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Mil	nacipran	TCAs			Std. Mean Difference				Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	Random, 95% CI					Random, 95% Cl	
7.1.1 Milnacipran vs Imipramine											
Lopez-Ibor 2004	28	8.7 (9.1)	27	7.8 (8.6)			+			7.08%	0.1[-0.43,0.63]
			Favour	s Milnacipran	-1	-0.5	0	0.5	1	Favours TCAs	

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Study or subgroup	Miln	acipran	TCAs		Std. Mean Difference	Weight	Std. Mean Difference
	Ν	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Tignol 1998	112	8.9 (5.9)	107	8.9 (5.9)		26.27%	0[-0.26,0.26]
Van Amerongen 2002	53	9.2 (9.7)	56	9.8 (9.7)	+	13.7%	-0.06[-0.44,0.31]
Yamashita 1995	62	11.5 (10.7)	64	10.4 (9.3)		15.71%	0.11[-0.24,0.46]
Subtotal ***	255		254		-	62.76%	0.02[-0.15,0.2]
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.54, df=3	3(P=0.91	); I <sup>2</sup> =0%					
Test for overall effect: Z=0.28(P=0.78)							
7.1.2 Milnacipran vs Clomipramine							
Leinonen 1997	47	12 (9.5)	46	8 (8.5)	+	11.51%	0.44[0.03,0.85]
Subtotal ***	47		46			11.51%	0.44[0.03,0.85]
Heterogeneity: Not applicable							
Test for overall effect: Z=2.09(P=0.04)							
7.1.3 Milancipran vs Amitriptyline							
Annseau 1989a	86	13.6 (10.8)	45	11.6 (8.5)		14.75%	0.2[-0.16,0.56]
Annseau 1989c	44	14.1 (10)	43	16.7 (12.4)	+	10.98%	-0.23[-0.65,0.19]
Subtotal ***	130		88			25.73%	-0[-0.42,0.42]
Heterogeneity: Tau <sup>2</sup> =0.05; Chi <sup>2</sup> =2.26, c	df=1(P=0	.13); I <sup>2</sup> =55.84%					
Test for overall effect: Z=0.01(P=0.99)							
Total ***	432		388		•	100%	0.07[-0.07.0.21]
Heterogeneity: $Tau^2=0$ : $Chi^2=6$ 31 df=6	5(P=0.39	)· 1 <sup>2</sup> =4.9%			-		[
Test for overall effect: 7=0 97(P=0 33)	s	,,,.					
Test for subgroup differences: $Chi^2-3$	47 df=1	(P=0.18) 12=42 3	240%				
rescror subgroup unterences. Clil -3.4	+i, ui=1	(1 -0.10), 1 -42.3	U T				
			Favour	s Milnacipran	-1 -0.5 0 0.5	<ul> <li>Favours TC</li> </ul>	CAs

# Analysis 7.2. Comparison 7 Depression scale-end point score at acute phase (6-12 weeks), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Miln	acipran	:	SSRIs	Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	Random, 95% Cl		Random, 95% Cl
7.2.1 Milnacipran vs Fluvoxamine							
Annseau 1991c	76	14.2 (10.8)	35	13.9 (8.5)	+	11.72%	0.03[-0.37,0.43]
Clerc 2001	57	12.1 (11.1)	56	15.5 (12.4)	+	13.22%	-0.29[-0.66,0.08]
Subtotal ***	133		91			24.95%	-0.14[-0.45,0.17]
Heterogeneity: Tau <sup>2</sup> =0.01; Chi <sup>2</sup> =1.29, o	lf=1(P=0	.26); l <sup>2</sup> =22.62%					
Test for overall effect: Z=0.88(P=0.38)							
7.2.2 Milnacipran vs Fluoxetine							
Annseau 1994	74	17.2 (11.1)	75	14.2 (11.6)	+	16.27%	0.26[-0.06,0.59]
Guelfi 1998a	105	7.9 (5.9)	54	9 (6.5)		15.82%	-0.18[-0.51,0.15]
Lee 2002b	38	14.5 (7.4)	26	12.5 (5.9)		8.07%	0.29[-0.21,0.79]
Subtotal ***	217		155			40.16%	0.1[-0.21,0.42]
Heterogeneity: Tau <sup>2</sup> =0.04; Chi <sup>2</sup> =4.28, o	lf=2(P=0	.12); I <sup>2</sup> =53.3%					
Test for overall effect: Z=0.64(P=0.52)							
7.2.3 Milnacipran vs Paroxetine							
Sechter 2000	148	11.9 (5.9)	151	11.4 (5.9)		25.51%	0.08[-0.14,0.31]
Shinkai 2004	20	13.1 (5.9)	21	11 (5)		5.58%	0.38[-0.24,1]
			Favour	s Milnacipran	-1 -0.5 0 0.5 1	Favours SS	SRIs



Study or subgroup	Miln	acipran	9	SSRIs	Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	Random, 95% CI		Random, 95% CI
Subtotal ***	168		172		-	31.08%	0.12[-0.09,0.33]
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.76, df=	1(P=0.38	); I <sup>2</sup> =0%					
Test for overall effect: Z=1.1(P=0.27)							
7.2.4 Milnacipran vs Sertraline							
Yang 2003	12	13.5 (2.1)	15	13.8 (1.8)		3.81%	-0.15[-0.91,0.61]
Subtotal ***	12		15			3.81%	-0.15[-0.91,0.61]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.39(P=0.7)							
Total ***	530		433		<b>•</b>	100%	0.04[-0.11,0.19]
Heterogeneity: Tau <sup>2</sup> =0.01; Chi <sup>2</sup> =9.01, o	df=7(P=0	.25); I <sup>2</sup> =22.33%					
Test for overall effect: Z=0.51(P=0.61)							
Test for subgroup differences: Chi <sup>2</sup> =2.	2, df=1 (F	P=0.53), I <sup>2</sup> =0%					
			_			1	

Favours Milnacipran <sup>-1</sup> <sup>-0.5</sup> <sup>0</sup> <sup>0.5</sup> <sup>1</sup> Favours SSRIs

# Analysis 7.3. Comparison 7 Depression scale-end point score at acute phase (6-12 weeks), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Miln	acipran	Hete	ocyclics	Std. Mea	n Difference	Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	Rando	om, 95% Cl		Random, 95% CI
7.3.1 Milnacipran vs Mianserin								
Endo 1995	78	14.3 (9.9)	89	15.5 (9.8)			100%	-0.12[-0.43,0.18]
Subtotal ***	78		89				100%	-0.12[-0.43,0.18]
Heterogeneity: Not applicable								
Test for overall effect: Z=0.78(P=0.43)								
Total ***	78		89				100%	-0.12[-0.43,0.18]
Heterogeneity: Not applicable								
Test for overall effect: Z=0.78(P=0.43)								
			Favours	Milnacipran	-1 -0.5	0 0.5	<sup>1</sup> Favours He	eterocyclic

# Comparison 8. Depression scale-end point score at early phase (1-4 weeks)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	765	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.11, 0.38]
1.1 Milnacipran vs Imipramine	3	454	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.25, 0.21]
1.2 Milnacipran vs Clomipramine	1	93	Std. Mean Difference (IV, Random, 95% CI)	0.66 [0.25, 1.08]
1.3 Milancipran vs Amitriptyline	2	218	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.22, 0.48]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 Milnacipran vs SSRIs	5	824	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.25, 0.14]
2.1 Milnacipran vs Fluvox- amine	2	233	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.31, 0.22]
2.2 Milnacipran vs Fluoxe- tine	2	292	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.69, 0.67]
2.3 Milnacipran vs Paroxe- tine	1	299	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-0.23, 0.23]
3 Milnacipran vs Hetero- cyclics	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.51, 0.21]
3.1 Milnacipran vs Mianserin	1	121	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.51, 0.21]

# Analysis 8.1. Comparison 8 Depression scale-end point score at early phase (1-4 weeks), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Mil	nacipran		TCAs	Std. Mean Difference	Weight	Std. Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	Random, 95% CI		Random, 95% CI
8.1.1 Milnacipran vs Imipramine							
Tignol 1998	112	17.4 (5.5)	107	18.3 (5.5)		20.22%	-0.16[-0.43,0.1]
Van Amerongen 2002	53	14.2 (9.1)	56	12 (9.1)		16.22%	0.24[-0.14,0.62]
Yamashita 1995	62	13.6 (10.2)	64	14 (7.6)	+	17.17%	-0.04[-0.39,0.3]
Subtotal ***	227		227		-	53.6%	-0.02[-0.25,0.21]
Heterogeneity: Tau <sup>2</sup> =0.01; Chi <sup>2</sup> =2.94,	df=2(P=	0.23); l <sup>2</sup> =32.02%					
Test for overall effect: Z=0.16(P=0.87	)						
8.1.2 Milnacipran vs Clomipramine	1						
Leinonen 1997	47	18.3 (6.1)	46	14.5 (5.2)		14.88%	0.66[0.25,1.08]
Subtotal ***	47		46			14.88%	0.66[0.25,1.08]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.11(P=0)							
8.1.3 Milancipran vs Amitriptyline							
Annseau 1989a	86	20.8 (10.8)	45	17.7 (9.6)		16.71%	0.3[-0.07,0.66]
Annseau 1989c	44	29.8 (6.8)	43	30.3 (8.9)		14.8%	-0.06[-0.48,0.36]
Subtotal ***	130		88			31.52%	0.13[-0.22,0.48]
Heterogeneity: Tau <sup>2</sup> =0.02; Chi <sup>2</sup> =1.61,	df=1(P=	0.21); l <sup>2</sup> =37.71%					
Test for overall effect: Z=0.75(P=0.46	)						
Total ***	404		361			100%	0.14[-0.11,0.38]
Heterogeneity: Tau <sup>2</sup> =0.06; Chi <sup>2</sup> =13.6	6, df=5(P	=0.02); I <sup>2</sup> =63.4%					
Test for overall effect: Z=1.11(P=0.27	)						
Test for subgroup differences: Chi <sup>2</sup> =7	.9, df=1	(P=0.02), I <sup>2</sup> =74.69	9%				
			Favour	s Milnacipran <sup>-1</sup>	-0.5 0 0.5	<sup>1</sup> Favours TC	As

# Analysis 8.2. Comparison 8 Depression scale-end point score at early phase (1-4 weeks), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Miln	acipran	9	SSRIs	Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	Random, 95% CI		Random, 95% CI
8.2.1 Milnacipran vs Fluvoxamine							
Annseau 1991c	83	20.5 (10.8)	37	21.1 (9.7)	-+-	16.54%	-0.06[-0.44,0.33]
Clerc 2001	57	20.2 (9)	56	20.5 (8.8)	-+-	17.66%	-0.03[-0.4,0.34]
Subtotal ***	140		93		<b>+</b>	34.2%	-0.04[-0.31,0.22]
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.01, df=	1(P=0.93	); I <sup>2</sup> =0%					
Test for overall effect: Z=0.33(P=0.74)							
8.2.2 Milnacipran vs Fluoxetine							
Guelfi 1998a	151	13.2 (5.5)	77	15 (5.5)		24.76%	-0.33[-0.6,-0.05]
Lee 2002b	38	17.9 (6.6)	26	15.6 (5.2)	++	11.3%	0.37[-0.13,0.88]
Subtotal ***	189		103		<b>•</b>	36.06%	-0.01[-0.69,0.67]
Heterogeneity: Tau <sup>2</sup> =0.2; Chi <sup>2</sup> =5.72, df	=1(P=0.0	02); I <sup>2</sup> =82.5%					
Test for overall effect: Z=0.03(P=0.98)							
8.2.3 Milnacipran vs Paroxetine							
Sechter 2000	148	15.5 (5.5)	151	15.5 (5.5)	+	29.74%	0[-0.23,0.23]
Subtotal ***	148		151		<b>♦</b>	29.74%	0[-0.23,0.23]
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	477		347		<b>+</b>	100%	-0.05[-0.25,0.14]
Heterogeneity: Tau <sup>2</sup> =0.02; Chi <sup>2</sup> =6.7, df	=4(P=0.1	L5); I <sup>2</sup> =40.34%					
Test for overall effect: Z=0.55(P=0.58)							
Test for subgroup differences: Chi <sup>2</sup> =0.	06, df=1	(P=0.97), I <sup>2</sup> =0%					
			Favour	s Milnacipran	-4 -2 0 2	4 Favours SS	RIs

# Analysis 8.3. Comparison 8 Depression scale-end point score at early phase (1-4 weeks), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Miln	acipran	Hete	Heteocyclics		Std. Mean Difference			Weight	Std. Mean Difference	
	Ν	Mean(SD)	Ν	Mean(SD)		Rando	m, 95% C	I			Random, 95% CI
8.3.1 Milnacipran vs Mianserin											
Endo 1995	55	15.4 (9.7)	66	16.8 (8.8)		-				100%	-0.15[-0.51,0.21]
Subtotal ***	55		66							100%	-0.15[-0.51,0.21]
Heterogeneity: Not applicable											
Test for overall effect: Z=0.83(P=0.41)											
Total ***	55		66							100%	-0.15[-0.51,0.21]
Heterogeneity: Not applicable											
Test for overall effect: Z=0.83(P=0.41)									т		
			Favours	Milnacipran	-2	-1	0	1	2	Favours Hete	erocyclic

# Comparison 9. Total dropouts (any reason)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	795	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.62, 1.33]
1.1 Milnacipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.52, 1.48]
1.2 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% Cl)	0.97 [0.47, 1.97]
2 Milnacipran vs SSRIs	8	1196	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.26]
2.1 Milancipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	0.80 [0.42, 1.54]
2.2 Milancipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.71, 1.46]
2.3 Milnacipran vs Paroxetine	2	343	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.49, 1.48]
2.4 Milancipran vs Sertraline	1	53	Odds Ratio (M-H, Random, 95% CI)	1.70 [0.57, 5.05]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.57, 1.87]
3.1 Milacipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.57, 1.87]

# Analysis 9.1. Comparison 9 Total dropouts (any reason), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
9.1.1 Milnacipran vs Imipramine					
Lopez-Ibor 2004	23/51	22/49		17.09%	1.01[0.46,2.22]
Tignol 1998	39/112	35/109		26.67%	1.13[0.65,1.98]
Van Amerongen 2002	11/53	24/56		15.31%	0.35[0.15,0.82]
Yamashita 1995	22/66	19/66		18.73%	1.24[0.59,2.59]
Subtotal (95% CI)	282	280		77.8%	0.88[0.52,1.48]
Total events: 95 (Milnacipran), 100 (TC	As)				
Heterogeneity: Tau <sup>2</sup> =0.14; Chi <sup>2</sup> =6.19, c	lf=3(P=0.1); I <sup>2</sup> =51.53%	Ď			
Test for overall effect: Z=0.49(P=0.62)					
9.1.2 Milnacipran vs Amitriptyline					
Annseau 1989a	24/97	11/49		16.29%	1.14[0.5,2.56]
Annseau 1989c	3/44	5/43 -	+	5.91%	0.56[0.12,2.49]
Subtotal (95% CI)	141	92		22.2%	0.97[0.47,1.97]
Total events: 27 (Milnacipran), 16 (TCA	As)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.67, df=	1(P=0.41); I <sup>2</sup> =0%				
Test for overall effect: Z=0.1(P=0.92)					
Total (95% CI)	423	372	-	100%	0.9[0.62,1.33]
Total events: 122 (Milnacipran), 116 (T	CAs)				
Heterogeneity: Tau <sup>2</sup> =0.06; Chi <sup>2</sup> =6.88, c	df=5(P=0.23); I <sup>2</sup> =27.3%	Ď			
Test for overall effect: Z=0.52(P=0.6)					
	Favo	urs Milnacipran 0.1	0.2 0.5 1 2 5	<sup>10</sup> Favours TCAs	

Milnacipran versus other antidepressive agents for depression (Review)

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Study or subgroup	Milnacipran n/N	TCAs n/N			Ode M-H, Rar	ds Ra ndon	atio n, 95% Cl			Weight	Odds Ratio M-H, Random, 95% Cl
Test for subgroup differences: Chi <sup>2</sup> =0.04, df=1 (P=0.83), I <sup>2</sup> =0%					I						
	[ev.		0.1	0.2	0.5	1	2	5	10	Cause TCAs	

Favours Milnacipran 0.1 0.2 0.5 1 2 5 10 Favours TCAs

# Analysis 9.2. Comparison 9 Total dropouts (any reason), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
9.2.1 Milancipran vs Fluvoxamine					
Annseau 1991c	10/86	6/41		6.04%	0.77[0.26,2.28]
Clerc 2001	15/57	17/56		10.64%	0.82[0.36,1.86]
Subtotal (95% CI)	143	97		16.68%	0.8[0.42,1.54]
Total events: 25 (Milnacipran), 23 (SS	RIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.01, df=	=1(P=0.93); I <sup>2</sup> =0%				
Test for overall effect: Z=0.67(P=0.5)					
9.2.2 Milancipran vs Fluoxetine					
Annseau 1994	23/97	18/93		14.79%	1.3[0.65,2.6]
Guelfi 1998a	99/200	50/100	_ <b>+</b> _	31.03%	0.98[0.61,1.58]
Lee 2002b	16/39	15/31		7.92%	0.74[0.29,1.92]
Subtotal (95% CI)	336	224	•	53.74%	1.02[0.71,1.46]
Total events: 138 (Milnacipran), 83 (S	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.91, df=	=2(P=0.63); I <sup>2</sup> =0%				
Test for overall effect: Z=0.08(P=0.93)					
9.2.3 Milnacipran vs Paroxetine					
Sechter 2000	29/149	33/153		22.86%	0.88[0.5,1.54]
Shinkai 2004	0/20	1/21	+	- 0.67%	0.33[0.01,8.67]
Subtotal (95% CI)	169	174		23.53%	0.85[0.49,1.48]
Total events: 29 (Milnacipran), 34 (SS	RIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.33, df=	=1(P=0.57); I <sup>2</sup> =0%				
Test for overall effect: Z=0.56(P=0.58)					
9.2.4 Milancipran vs Sertraline					
Yang 2003	15/27	11/26	+	6.05%	1.7[0.57,5.05]
Subtotal (95% CI)	27	26		6.05%	1.7[0.57,5.05]
Total events: 15 (Milnacipran), 11 (SS	RIs)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.96(P=0.34)					
Total (95% CI)	675	521	•	100%	0.97[0.74,1.26]
Total events: 207 (Milnacipran), 151 (	SSRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.88, df=	7(P=0.9); l <sup>2</sup> =0%				
Test for overall effect: Z=0.24(P=0.81)					
Test for subgroup differences: Chi <sup>2</sup> =1.	.63, df=1 (P=0.65), I <sup>2</sup> =0	)%		_1	
	Favo	ours Milnacipran <sup>0.</sup>	1 0.2 0.5 1 2 5	<sup>10</sup> Favours SSRIs	

# Analysis 9.3. Comparison 9 Total dropouts (any reason), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odds Ratio		Weight	Odds Ratio
	n/N	n/N	М-Н	, Random, 95% Cl			M-H, Random, 95% Cl
9.3.1 Milacipran vs Mianserin							
Endo 1995	37/84	41/95				100%	1.04[0.57,1.87]
Subtotal (95% CI)	84	95		-		100%	1.04[0.57,1.87]
Total events: 37 (Milnacipran), 41 (Het	erocyclics)						
Heterogeneity: Not applicable							
Test for overall effect: Z=0.12(P=0.9)							
Total (95% CI)	84	95		-		100%	1.04[0.57,1.87]
Total events: 37 (Milnacipran), 41 (Het	erocyclics)						
Heterogeneity: Not applicable							
Test for overall effect: Z=0.12(P=0.9)							
	Fa	avours Milnacipran	0.1 0.2 0	.5 1 2	5 10 F	Favours Heterocyclic	

### Comparison 10. Dropouts due to inefficacy

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	7	902	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.82, 1.99]
1.1 Milnacipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	1.14 [0.66, 1.95]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	3.04 [0.89, 10.38]
1.3 Milnacipran vs Amitrypty- line	2	233	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.42, 2.90]
2 Milnacipran vs SSRIs	7	1143	Odds Ratio (M-H, Random, 95% Cl)	0.99 [0.66, 1.48]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	1.39 [0.53, 3.63]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.42, 1.70]
2.3 Millnacipran vs Paroxetine	2	343	Odds Ratio (M-H, Random, 95% CI)	1.58 [0.55, 4.54]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.57 [0.22, 1.51]
3.1 Milnacipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.57 [0.22, 1.51]

### Analysis 10.1. Comparison 10 Dropouts due to inefficacy, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran n/N	TCAs n/N	Odds Ratio M-H, Random, 95% Cl				Weight	Odds Ratio M-H, Random, 95% Cl			
10.1.1 Milnacipran vs Imipramine											
		Favours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours TCAs	



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Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
Lopez-Ibor 2004	12/51	11/49		19.91%	1.06[0.42,2.7]
Tignol 1998	16/112	8/109	+	21.43%	2.1[0.86,5.14]
Van Amerongen 2002	5/53	9/56	+	13.37%	0.54[0.17,1.74]
Yamashita 1995	7/66	7/66		14.64%	1[0.33,3.03]
Subtotal (95% CI)	282	280	-	69.36%	1.14[0.66,1.95]
Total events: 40 (Milnacipran), 35 (TCAs	s)				
Heterogeneity: Tau <sup>2</sup> =0.04; Chi <sup>2</sup> =3.43, di	f=3(P=0.33); l <sup>2</sup> =12.58	%			
Test for overall effect: Z=0.47(P=0.64)					
10.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	10/52	4/55	++	12.11%	3.04[0.89,10.38]
Subtotal (95% CI)	52	55		- 12.11%	3.04[0.89,10.38]
Total events: 10 (Milnacipran), 4 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.77(P=0.08)					
10.1.3 Milnacipran vs Amitryptyline					
Annseau 1989a	15/97	7/49		18.53%	1.1[0.42,2.9]
Annseau 1989c	0/44	0/43			Not estimable
Subtotal (95% CI)	141	92		18.53%	1.1[0.42,2.9]
Total events: 15 (Milnacipran), 7 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
Total (95% CI)	475	427	•	100%	1.27[0.82,1.99]
Total events: 65 (Milnacipran), 46 (TCAs	s)				
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =5.6, df=	=5(P=0.35); I <sup>2</sup> =10.7%				
Test for overall effect: Z=1.06(P=0.29)					
Test for subgroup differences: Chi <sup>2</sup> =2.1	8, df=1 (P=0.34), I <sup>2</sup> =8	.09%			
	Favo	ours Milnacipran 0.1	0.2 0.5 1 2 5 1	<sup>.0</sup> Favours TCAs	

# Analysis 10.2. Comparison 10 Dropouts due to inefficacy, Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs		Odds	Ratio		Weight	Odds Ratio
	n/N	n/N		M-H, Rand	om, 95% Cl		-	M-H, Random, 95% Cl
10.2.1 Milnacipran vs Fluvoxamine	•							
Annseau 1991c	2/86	1/41	◀—				2.81%	0.95[0.08,10.82]
Clerc 2001	10/57	7/56			+		15.16%	1.49[0.52,4.24]
Subtotal (95% CI)	143	97					17.97%	1.39[0.53,3.63]
Total events: 12 (Milnacipran), 8 (SSF	RIs)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.11, df	=1(P=0.74); I <sup>2</sup> =0%							
Test for overall effect: Z=0.67(P=0.5)								
10.2.2 Milnacipran vs Fluoxetine								
Annseau 1994	9/97	5/93			+	_	12.92%	1.8[0.58,5.59]
Guelfi 1998a	37/200	24/100			<u> </u>		49.03%	0.72[0.4,1.29]
Lee 2002b	2/39	4/31	←	+			5.3%	0.36[0.06,2.14]
Subtotal (95% CI)	336	224					67.25%	0.84[0.42,1.7]
Total events: 48 (Milnacipran), 33 (SS	SRIs)							
	Favo	ours Milnacipran	0.1	0.2 0.5	1 2	5 <sup>10</sup> Fa	wours SSRIs	



Study or subgroup	Milnacipran	SSRIs	Odds	Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Rand	om, 95% Cl		M-H, Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> =0.13; Chi <sup>2</sup> =2.85,	df=2(P=0.24); I <sup>2</sup> =29.93	%				
Test for overall effect: Z=0.47(P=0.64)						
10.2.3 Millnacipran vs Paroxetine						
Sechter 2000	9/149	6/153		+	14.79%	1.58[0.55,4.54]
Shinkai 2004	0/20	0/21				Not estimable
Subtotal (95% CI)	169	174			14.79%	1.58[0.55,4.54]
Total events: 9 (Milnacipran), 6 (SSRIs	5)					
Heterogeneity: Not applicable						
Test for overall effect: Z=0.84(P=0.4)						
Total (95% CI)	648	495			100%	0.99[0.66,1.48]
Total events: 69 (Milnacipran), 47 (SS	RIs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =4.79, df=	5(P=0.44); I <sup>2</sup> =0%					
Test for overall effect: Z=0.06(P=0.95)						
Test for subgroup differences: Chi <sup>2</sup> =1.	.21, df=1 (P=0.55), l <sup>2</sup> =0	9%				
	Favo	ours Milnacipran	0.1 0.2 0.5	1 2 5 10	<sup>0</sup> Favours SSRIs	

# Analysis 10.3. Comparison 10 Dropouts due to inefficacy, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95	5% CI	M-H, Random, 95% Cl
10.3.1 Milnacipran vs Mianserin					
Endo 1995	7/84	13/95		100%	0.57[0.22,1.51]
Subtotal (95% CI)	84	95		100%	0.57[0.22,1.51]
Total events: 7 (Milnacipran), 13 (Heter	ocyclics)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					
Total (95% CI)	84	95		100%	0.57[0.22,1.51]
Total events: 7 (Milnacipran), 13 (Heter	ocyclics)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.12(P=0.26)					
	Fa	avours Milnacipran	0.1 0.2 0.5 1	2 <sup>5</sup> <sup>10</sup> Favours Heterocyc	clic

### Comparison 11. Dropouts due to adverse events

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	756	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.35, 0.85]
1.1 Milnacipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.35, 1.04]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.18, 1.03]



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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.3 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% Cl)	0.56 [0.12, 2.49]
2 Milnacipran vs SSRIs	7	1143	Odds Ratio (M-H, Random, 95% CI)	0.71 [0.48, 1.04]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.17, 1.47]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.41, 1.19]
2.3 Milancipran vs Paroxetine	2	343	Odds Ratio (M-H, Random, 95% CI)	0.82 [0.42, 1.62]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.33, 1.87]
3.1 Milnacipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.33, 1.87]

# Analysis 11.1. Comparison 11 Dropouts due to adverse events, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
11.1.1 Milnacipran vs Imipramine					
Lopez-Ibor 2004	5/51	7/49	+	13.04%	0.65[0.19,2.21]
Tignol 1998	15/112	23/109		38.35%	0.58[0.28,1.18]
Van Amerongen 2002	1/53	5/56	+	4.09%	0.2[0.02,1.74]
Yamashita 1995	4/66	4/66		9.52%	1[0.24,4.18]
Subtotal (95% CI)	282	280		64.99%	0.6[0.35,1.04]
Total events: 25 (Milnacipran), 39 (TCA	ls)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.54, df=3	8(P=0.67); I <sup>2</sup> =0%				
Test for overall effect: Z=1.83(P=0.07)					
11.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	11/52	21/55	<b>e</b>	26.34%	0.43[0.18,1.03]
Subtotal (95% CI)	52	55		26.34%	0.43[0.18,1.03]
Total events: 11 (Milnacipran), 21 (TCA	ls)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.9(P=0.06)					
11.1.3 Milnacipran vs Amitriptyline					
Annseau 1989c	3/44	5/43 —		8.67%	0.56[0.12,2.49]
Subtotal (95% CI)	44	43 -		8.67%	0.56[0.12,2.49]
Total events: 3 (Milnacipran), 5 (TCAs)					- / -
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
	370	370		100%	
Total (35% CI)	510	516		100%	0.55[0.55,0.65]
I otal events: 39 (Milhacipran), 65 (TCA	$(D = 0, 0, C) + 1^2 = 0.0($				
Test for everall effects 7=2 (2/D=0.01)	0(1-0.86);1-=0%				
Test for overall effect: Z=Z.68(P=0.01)	$1 + 1 = 0 + 0 + 1^2$	AD/			
lest for subgroup differences: Chi <sup>2</sup> =0.3	s9, at=1 (P=0.82), P=0	J%			
	Favo	ours Milnacipran <sup>0.1</sup>	0.2 0.5 1 2 5	10 Favours TCAs	

### Analysis 11.2. Comparison 11 Dropouts due to adverse events, Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Rati	o Weight	Odds Ratio
	n/N	n/N	M-H, Random, S	35% CI	M-H, Random, 95% Cl
11.2.1 Milnacipran vs Fluvoxamine	•				
Annseau 1991c	7/86	5/41	+	— 10.3%	0.64[0.19,2.15]
Clerc 2001	1/57	4/56	↓		0.23[0.03,2.15]
Subtotal (95% CI)	143	97		13.37%	0.51[0.17,1.47]
Total events: 8 (Milnacipran), 9 (SSRI	s)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.62, df	=1(P=0.43); I <sup>2</sup> =0%				
Test for overall effect: Z=1.25(P=0.21)	)				
11.2.2 Milnacipran vs Fluoxetine					
Annseau 1994	6/97	7/93	+	11.88%	0.81[0.26,2.51]
Guelfi 1998a	28/200	19/100		37.06%	0.69[0.37,1.32]
Lee 2002b	2/39	3/31	<b>←</b> +	4.41%	0.5[0.08,3.23]
Subtotal (95% CI)	336	224		53.35%	0.7[0.41,1.19]
Total events: 36 (Milnacipran), 29 (SS	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.18, df	=2(P=0.91); I <sup>2</sup> =0%				
Test for overall effect: Z=1.31(P=0.19)	)				
11.2.3 Milancipran vs Paroxetine					
Sechter 2000	17/149	20/153		- 31.85%	0.86[0.43,1.71]
Shinkai 2004	0/20	1/21	← +	1.43%	0.33[0.01,8.67]
Subtotal (95% CI)	169	174		33.28%	0.82[0.42,1.62]
Total events: 17 (Milnacipran), 21 (SS	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.31, df	=1(P=0.58); I <sup>2</sup> =0%				
Test for overall effect: Z=0.57(P=0.57)	)				
Total (95% CI)	648	495	•	100%	0.71[0.48,1.04]
Total events: 61 (Milnacipran), 59 (SS	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.68, df	=6(P=0.95); I <sup>2</sup> =0%				
Test for overall effect: Z=1.74(P=0.08)	)				
Test for subgroup differences: Chi <sup>2</sup> =0	0.57, df=1 (P=0.75), I <sup>2</sup> =0	0%			
	Fave	ours Milnacipran	0.1 0.2 0.5 1	2 5 <sup>10</sup> Favours SSRIs	

# Analysis 11.3. Comparison 11 Dropouts due to adverse events, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics	Od	Odds Ratio		Odds Ratio
	n/N	n/N	M-H, Rar	1dom, 95% Cl		M-H, Random, 95% CI
11.3.1 Milnacipran vs Mianserin						
Endo 1995	10/84	14/95		<b>_</b>	100%	0.78[0.33,1.87]
Subtotal (95% CI)	84	95			100%	0.78[0.33,1.87]
Total events: 10 (Milnacipran), 14 (He	eterocyclics)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(I	P<0.0001); I²=100%					
Test for overall effect: Z=0.55(P=0.58)						
Total (95% CI)	84	95			100%	0.78[0.33,1.87]
Total events: 10 (Milnacipran), 14 (He	eterocyclics)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(I	P<0.0001); l <sup>2</sup> =100%					
	Fa	vours Milnacipran	0.1 0.2 0.5	1 2 5	<sup>10</sup> Favours Heterocycl	ic


Study or subgroup	Milnacipran n/N	Heterocyclics n/N			Od M-H, Ra	lds Ra ndon	atio 1, 95% Cl			Weight Odds Ratio M-H, Random, 95%	CI
Test for overall effect: Z=0.55(P=0.58)			_		1						
		Favours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclic	

### Comparison 12. Patients with at least some adverse events (Tolerability)

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	795	Odds Ratio (M-H, Random, 95% CI)	0.35 [0.24, 0.53]
1.1 Milnacipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.66]
1.2 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% CI)	0.23 [0.13, 0.40]
2 Milnacipran vs SSRIs	5	912	Odds Ratio (M-H, Random, 95% Cl)	0.86 [0.55, 1.34]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.28, 0.94]
2.2 Milnacipran vs Fluoxetine	2	370	Odds Ratio (M-H, Random, 95% CI)	0.90 [0.49, 1.67]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	1.45 [0.87, 2.43]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.62 [0.34, 1.15]
3.1 Milnacipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.34, 1.15]

# Analysis 12.1. Comparison 12 Patients with at least some adverse events (Tolerability), Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
12.1.1 Milnacipran vs Imipramine					
Lopez-Ibor 2004	17/51	34/49	<b>←</b> →──	14.37%	0.22[0.1,0.51]
Tignol 1998	65/112	81/109	<b>-</b>	21.67%	0.48[0.27,0.85]
Van Amerongen 2002	16/53	30/56		15.58%	0.37[0.17,0.82]
Yamashita 1995	27/66	33/66	+	18.11%	0.69[0.35,1.38]
Subtotal (95% CI)	282	280	•	69.74%	0.43[0.28,0.66]
Total events: 125 (Milnacipran), 178 (TC	As)				
Heterogeneity: Tau <sup>2</sup> =0.07; Chi <sup>2</sup> =4.49, df	=3(P=0.21); I <sup>2</sup> =33.249	6			
Test for overall effect: Z=3.82(P=0)					
12.1.2 Milnacipran vs Amitriptyline					
Annseau 1989a	25/97	32/49	<b>←→</b>	16.64%	0.18[0.09,0.39]
Annseau 1989c	15/44	27/43		13.62%	0.31[0.13,0.74]
Subtotal (95% CI)	141	92		30.26%	0.23[0.13,0.4]
Total events: 40 (Milnacipran), 59 (TCAs	)			1	
	Favo	urs Milnacipran	0.1 0.2 0.5 1 2 5 10	<sup>0</sup> Favours TCAs	



Study or subgroup	Milnacipran	TCAs			Od	lds Ra	atio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndon	n, 95%	CI			M-H, Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.75	5, df=1(P=0.39); I <sup>2</sup> =0%										
Test for overall effect: Z=5.11(P<	0.0001)										
Total (95% CI)	423	372								100%	0.35[0.24,0.53]
Total events: 165 (Milnacipran), 2	237 (TCAs)										
Heterogeneity: Tau <sup>2</sup> =0.11; Chi <sup>2</sup> =8	3.95, df=5(P=0.11); l <sup>2</sup> =44.14%										
Test for overall effect: Z=5.04(P<	0.0001)										
Test for subgroup differences: Ch	ni <sup>2</sup> =3, df=1 (P=0.08), l <sup>2</sup> =66.72%										
	Favours M	Iilnacipran	0.1	0.2	0.5	1	2	5	10	Favours TCAs	

Analysis 12.2. Comparison 12 Patients with at least some adverse events (Tolerability), Outcome 2 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
12.2.1 Milnacipran vs Fluvoxamin	e				
Annseau 1991c	32/86	22/41		20.86%	0.51[0.24,1.09]
Clerc 2001	7/57	12/56	+	14.03%	0.51[0.19,1.42]
Subtotal (95% CI)	143	97		34.9%	0.51[0.28,0.94]
Total events: 39 (Milnacipran), 34 (S	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1	(P=1); I <sup>2</sup> =0%				
Test for overall effect: Z=2.17(P=0.03	3)				
12.2.2 Milnacipran vs Fluoxetine					
Guelfi 1998a	20/200	11/100		20.07%	0.9[0.41,1.96]
Lee 2002b	13/39	11/31		14.53%	0.91[0.34,2.45]
Subtotal (95% CI)	239	131		34.6%	0.9[0.49,1.67]
Total events: 33 (Milnacipran), 22 (S	SRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1	(P=0.99); I <sup>2</sup> =0%				
Test for overall effect: Z=0.33(P=0.74	1)				
12.2.3 Milnacipran vs Paroxetine					
Sechter 2000	115/149	107/153	+	30.51%	1.45[0.87,2.43]
Subtotal (95% CI)	149	153		30.51%	1.45[0.87,2.43]
Total events: 115 (Milnacipran), 107	(SSRIs)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0	(P<0.0001); I <sup>2</sup> =100%				
Test for overall effect: Z=1.42(P=0.15	5)				
Total (95% CI)	531	381		100%	0.86[0.55,1.34]
Total events: 187 (Milnacipran), 163	(SSRIs)				
Heterogeneity: Tau <sup>2</sup> =0.1; Chi <sup>2</sup> =6.62,	df=4(P=0.16); I <sup>2</sup> =39.6%				
Test for overall effect: Z=0.68(P=0.5)					
Test for subgroup differences: Chi <sup>2</sup> =	6.62, df=1 (P=0.04), I <sup>2</sup> =6	9.8%			
	Favo	ours Milnacipran 0.1	0.2 0.5 1 2 5	<sup>10</sup> Favours SSRIs	

# Analysis 12.3. Comparison 12 Patients with at least some adverse events (Tolerability), Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Od	ds Rati	io			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom,	95% CI				M-H, Random, 95% Cl
12.3.1 Milnacipran vs Mianserin											
Endo 1995	27/84	41/95				$\vdash$				100%	0.62[0.34,1.15]
Subtotal (95% CI)	84	95								100%	0.62[0.34,1.15]
Total events: 27 (Milnacipran), 41 (He	terocyclics)					ĺ					
Heterogeneity: Not applicable						İ					
Test for overall effect: Z=1.51(P=0.13)						ļ					
Total (95% CI)	84	95								100%	0.62[0.34,1.15]
Total events: 27 (Milnacipran), 41 (He	terocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.51(P=0.13)											
	Fa	avours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclic	

## Comparison 13. Adverse events: Sleepiness/ Drowsiness

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	5	693	Odds Ratio (M-H, Random, 95% CI)	0.22 [0.07, 0.73]
1.1 Milancipran vs Imipramine	2	353	Odds Ratio (M-H, Random, 95% CI)	0.68 [0.19, 2.45]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.20 [0.01, 4.35]
1.3 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% Cl)	0.07 [0.02, 0.22]
2 Milancipran vs SSRIs	6	1102	Odds Ratio (M-H, Random, 95% CI)	0.56 [0.26, 1.17]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	0.43 [0.10, 1.85]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.15, 2.71]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.69]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.21 [0.08, 0.58]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	0.21 [0.08, 0.58]

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
13.1.1 Milancipran vs Imipramine					
Tignol 1998	3/112	7/109		24.61%	0.4[0.1,1.59]
Yamashita 1995	3/66	2/66		19.63%	1.52[0.25,9.43]
Subtotal (95% CI)	178	175		44.24%	0.68[0.19,2.45]
Total events: 6 (Milnacipran), 9 (TCAs)					
Heterogeneity: Tau <sup>2</sup> =0.21; Chi <sup>2</sup> =1.31, d	lf=1(P=0.25); l <sup>2</sup> =23.7%				
Test for overall effect: Z=0.59(P=0.56)					
13.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	0/52	2/55	<b>←</b>	10.55%	0.2[0.01,4.35]
Subtotal (95% CI)	52	55		10.55%	0.2[0.01,4.35]
Total events: 0 (Milnacipran), 2 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
13.1.3 Milnacipran vs Amitriptyline					
Annseau 1989a	2/97	11/49	<b>•</b>	22.56%	0.07[0.02,0.34]
Annseau 1989c	2/44	17/43	<b>•</b>	22.65%	0.07[0.02,0.34]
Subtotal (95% CI)	141	92		45.21%	0.07[0.02,0.22]
Total events: 4 (Milnacipran), 28 (TCAs	)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1(P=	=1); l²=0%				
Test for overall effect: Z=4.69(P<0.0001	L)				
Total (95% CI)	371	322		100%	0.22[0.07,0.73]
Total events: 10 (Milnacipran), 39 (TCA	ls)				
Heterogeneity: Tau <sup>2</sup> =0.96; Chi <sup>2</sup> =9.02, d	lf=4(P=0.06); l <sup>2</sup> =55.64%				
Test for overall effect: Z=2.5(P=0.01)					
Test for subgroup differences: Chi <sup>2</sup> =6.7	77, df=1 (P=0.03), l <sup>2</sup> =70.4	46%			
	Favour	rs Milnacipran	0.02 0.1 1 10 50	Favours TCAs	

## Analysis 13.1. Comparison 13 Adverse events: Sleepiness/ Drowsiness, Outcome 1 Milnacipran vs TCAs.

# Analysis 13.2. Comparison 13 Adverse events: Sleepiness/ Drowsiness, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odd	s Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Rand	dom, 95% CI		M-H, Random, 95% Cl
13.2.1 Milnacipran vs Fluvoxamine						
Annseau 1991c	11/86	7/41		+	52.07%	0.71[0.25,2]
Clerc 2001	1/57	6/56		+	11.95%	0.15[0.02,1.28]
Subtotal (95% CI)	143	97			64.03%	0.43[0.1,1.85]
Total events: 12 (Milnacipran), 13 (SSF	RIS)					
Heterogeneity: Tau <sup>2</sup> =0.53; Chi <sup>2</sup> =1.71, c	lf=1(P=0.19); l <sup>2</sup> =41.49%	6				
Test for overall effect: Z=1.13(P=0.26)						
13.2.2 Milnacipran vs Fluoxetine						
Annseau 1994	2/97	2/93		+	14.1%	0.96[0.13,6.94]
Guelfi 1998a	0/200	1/100	<b>+</b> +		5.37%	0.17[0.01,4.1]
Lee 2002b	1/39	1/31	+	+	6.99%	0.79[0.05,13.15]
Subtotal (95% CI)	336	224			26.46%	0.64[0.15,2.71]
Total events: 3 (Milnacipran), 4 (SSRIs)						
	Favou	urs Milnacipran	0.1 0.2 0.5	1 2 5 10	Favours SSRIs	

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Study or subgroup	Milnacipran	SSRIs			Od	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N		I	M-H, Ra	ndom	, 95% CI				M-H, Random, 95% CI
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.87, df	f=2(P=0.65); I <sup>2</sup> =0%										
Test for overall effect: Z=0.61(P=0.54	4)										
13.2.3 Milnacipran vs Paroxetine											
Sechter 2000	1/149	2/153	-		•					9.51%	0.51[0.05,5.69]
Subtotal (95% CI)	149	153								9.51%	0.51[0.05,5.69]
Total events: 1 (Milnacipran), 2 (SSR	ls)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.55(P=0.58	3)										
Total (95% CI)	628	474								100%	0.56[0.26.1.17]
Total events: 16 (Milnacipran), 19 (St	SRIs)									200,0	0.00[0.20,2.21]
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.61, df	f=5(P=0.76); I <sup>2</sup> =0%										
Test for overall effect: Z=1.55(P=0.12	2)										
Test for subgroup differences: Chi <sup>2</sup> =	0.14, df=1 (P=0.93), I <sup>2</sup> =0	%									
	Favo	urs Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	

## Analysis 13.3. Comparison 13 Adverse events: Sleepiness/ Drowsiness, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odd	ls Ratio			Weight	Odds Ratio
	n/N	n/N		M-H, Ran	dom, 95% CI				M-H, Random, 95% Cl
13.3.1 Milancipran vs Mianserin									
Endo 1995	5/84	22/95	←					100%	0.21[0.08,0.58]
Subtotal (95% CI)	84	95						100%	0.21[0.08,0.58]
Total events: 5 (Milnacipran), 22 (Heter	ocyclics)								
Heterogeneity: Not applicable									
Test for overall effect: Z=2.99(P=0)									
Total (95% CI)	84	95						100%	0.21[0.08,0.58]
Total events: 5 (Milnacipran), 22 (Heter	ocyclics)								
Heterogeneity: Not applicable									
Test for overall effect: Z=2.99(P=0)									
	Fa	avours Milnacipran	0.1	0.2 0.5	1 2	5	10	Favours Heterocyclic	S

### Comparison 14. Adverse events: Insomnia

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	756	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.57, 2.22]
1.1 Milancipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.49, 1.53]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	5.55 [1.14, 27.04]
1.3 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% Cl)	1.5 [0.24, 9.45]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2 Milancipran vs SSRIs	6	1102	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.29, 0.90]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	0.73 [0.28, 1.92]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.20, 0.87]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.05, 5.69]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.07, 18.39]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.07, 18.39]

# Analysis 14.1. Comparison 14 Adverse events: Insomnia, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
14.1.1 Milancipran vs Imipramine					
Lopez-Ibor 2004	11/51	14/49	<b>_</b>	25.34%	0.69[0.28,1.71]
Tignol 1998	5/112	9/109		20.41%	0.52[0.17,1.6]
Van Amerongen 2002	16/53	12/56		26.47%	1.59[0.67,3.77]
Yamashita 1995	0/66	1/66		4.07%	0.33[0.01,8.21]
Subtotal (95% CI)	282	280	<b></b>	76.28%	0.86[0.49,1.53]
Total events: 32 (Milnacipran), 36 (TCA	As)				
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =3.26, c	df=3(P=0.35); I <sup>2</sup> =7.91%	6			
Test for overall effect: Z=0.5(P=0.62)					
14.1.2 Milnacipran vs Clomipramine	1				
Leinonen 1997	9/52	2/55	*	13.18%	5.55[1.14,27.04]
Subtotal (95% CI)	52	55		13.18%	5.55[1.14,27.04]
Total events: 9 (Milnacipran), 2 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.12(P=0.03)					
14.1.3 Milnacipran vs Amitriptvline					
Annseau 1989c	3/44	2/43		10 54%	1 5[0 24 9 45]
Subtotal (95% CI)	44	43		10.54%	1.5[0.24.9.45]
Total events: 3 (Milnacipran), 2 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					
	270	270		1000/	1 12[0 57 2 22]
	318	318		100%	1.12[0.57,2.22]
Total events: 44 (Milnacipran), 40 (TCA	AS)				
Heterogeneity: Tau <sup>2</sup> =0.26; Chi <sup>2</sup> =8.09, c	1t=5(P=0.15); l <sup>2</sup> =38.22	%			
Test for overall effect: Z=0.34(P=0.74)					
Test for subgroup differences: Chi <sup>2</sup> =4.8	8, df=1 (P=0.09), I <sup>2</sup> =58	.32%			
	Favo	ours Milnacipran <sup>0</sup>	.02 0.1 1 10 50	Favours TCAs	

Study or subgroup	Milnacipran	SSRIs		Odds Ratio	Weight	Odds Ratio
	n/N	n/N		M-H, Random, 95% Cl		M-H, Random, 95% CI
14.2.1 Milnacipran vs Fluvoxamine						
Annseau 1991c	12/86	7/41			31.63%	0.79[0.28,2.18]
Clerc 2001	0/57	1/56	◀—	+	- 3.15%	0.32[0.01,8.07]
Subtotal (95% CI)	143	97			34.78%	0.73[0.28,1.92]
Total events: 12 (Milnacipran), 8 (SSRIs	)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.27, df=1	(P=0.6); I <sup>2</sup> =0%					
Test for overall effect: Z=0.65(P=0.52)						
14.2.2 Milnacipran vs Fluoxetine						
Annseau 1994	5/97	7/93			23.3%	0.67[0.2,2.18]
Guelfi 1998a	7/200	10/100		<b>_</b>	32.84%	0.33[0.12,0.89]
Lee 2002b	0/39	2/31	-++		3.46%	0.15[0.01,3.23]
Subtotal (95% CI)	336	224			59.6%	0.41[0.2,0.87]
Total events: 12 (Milnacipran), 19 (SSRI	ls)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.27, df=2	(P=0.53); I <sup>2</sup> =0%					
Test for overall effect: Z=2.34(P=0.02)						
14.2.3 Milnacipran vs Paroxetine						
Sechter 2000	1/149	2/153	←	+	5.62%	0.51[0.05,5.69]
Subtotal (95% CI)	149	153			5.62%	0.51[0.05,5.69]
Total events: 1 (Milnacipran), 2 (SSRIs)						
Heterogeneity: Not applicable						
Test for overall effect: Z=0.55(P=0.58)						
Total (95% CI)	628	474			100%	0.51[0.29,0.9]
Total events: 25 (Milnacipran), 29 (SSRI	ls)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.36, df=5	(P=0.8); I <sup>2</sup> =0%					
Test for overall effect: Z=2.32(P=0.02)						
Test for subgroup differences: Chi <sup>2</sup> =0.8	2, df=1 (P=0.66), I <sup>2</sup> =0	0%				
	Favo	ours Milnacipran	0.1 0.	2 0.5 1 2 5	<sup>10</sup> Favours SSRIs	

## Analysis 14.2. Comparison 14 Adverse events: Insomnia, Outcome 2 Milancipran vs SSRIs.

## Analysis 14.3. Comparison 14 Adverse events: Insomnia, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odds Ratio			Weight	Odds Ratio			
	n/N	n/N		M-H, Random, 95% Cl			M-H, Random, 95% Cl				
14.3.1 Milancipran vs Mianserin											
Endo 1995	1/84	1/95	←						→	100%	1.13[0.07,18.39]
Subtotal (95% CI)	84	95								100%	1.13[0.07,18.39]
Total events: 1 (Milnacipran), 1 (Heter	rocyclics)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P	P<0.0001); I <sup>2</sup> =100%										
Test for overall effect: Z=0.09(P=0.93)											
Total (95% CI)	84	95								100%	1.13[0.07,18.39]
Total events: 1 (Milnacipran), 1 (Heter	rocyclics)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P	P<0.0001); I <sup>2</sup> =100%										
Test for overall effect: Z=0.09(P=0.93)				1							
	Fav	ours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclics	



## Comparison 15. Adverse events: Dry mouth

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	7	902	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.28, 0.65]
1.1 Milancipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.37, 0.86]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.45 [0.21, 0.97]
1.3 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% Cl)	0.22 [0.12, 0.39]
2 Milancipran vs SSRIs	4	500	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.60, 1.80]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	0.87 [0.42, 1.78]
2.2 Milnacipran vs Fluoxetine	2	260	Odds Ratio (M-H, Random, 95% CI)	1.34 [0.58, 3.13]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.15, 1.30]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	0.44 [0.15, 1.30]

# Analysis 15.1. Comparison 15 Adverse events: Dry mouth, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
15.1.1 Milancipran vs Imipramine					
Lopez-Ibor 2004	20/51	26/49	-+	14.05%	0.57[0.26,1.26]
Tignol 1998	19/112	38/109	_ <b>+</b> _	17.24%	0.38[0.2,0.72]
Van Amerongen 2002	14/53	14/56	<b>+</b>	12.94%	1.08[0.46,2.54]
Yamashita 1995	13/66	20/66	-+	13.91%	0.56[0.25,1.26]
Subtotal (95% CI)	282	280	•	58.15%	0.57[0.37,0.86]
Total events: 66 (Milnacipran), 98 (TCA	s)				
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =3.64, d	f=3(P=0.3); I <sup>2</sup> =17.6%				
Test for overall effect: Z=2.66(P=0.01)					
15.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	19/52	31/55	<b>+</b>	14.38%	0.45[0.21,0.97]
Subtotal (95% CI)	52	55	•	14.38%	0.45[0.21,0.97]
Total events: 19 (Milnacipran), 31 (TCA	s)				
Heterogeneity: Not applicable					
Test for overall effect: Z=2.04(P=0.04)					
15.1.3 Milnacipran vs Amitriptyline					
Annseau 1989a	23/97	32/49	<b>+</b>	14.83%	0.17[0.08,0.35]
Annseau 1989c	15/44	27/43	<b>_</b>	12.64%	0.31[0.13,0.74]
Subtotal (95% CI)	141	92	◆	27.47%	0.22[0.12,0.39]
	Favo	ours Milnacipran	0.02 0.1 1 10 50	Favours TCAs	



Study or subgroup	Milnacipran	TCAs			Odds	Ratio			Weight	Odds Ratio
	n/N	n/N		M-H	, Rando	om, 95% Cl				M-H, Random, 95% Cl
Total events: 38 (Milnacipran), 59	(TCAs)									
Heterogeneity: Tau <sup>2</sup> =0.02; Chi <sup>2</sup> =1.	1, df=1(P=0.29); I <sup>2</sup> =9.15%									
Test for overall effect: Z=5.01(P<0.	.0001)									
Total (95% CI)	475	427			$ \bullet $				100%	0.43[0.28,0.65]
Total events: 123 (Milnacipran), 18	88 (TCAs)									
Heterogeneity: Tau <sup>2</sup> =0.16; Chi <sup>2</sup> =12	2.23, df=6(P=0.06); l <sup>2</sup> =50.9	6%								
Test for overall effect: Z=3.95(P<0.	.0001)									
Test for subgroup differences: Chi	<sup>2</sup> =6.72, df=1 (P=0.03), l <sup>2</sup> =7	0.23%								
	Favo	urs Milnacipran	0.02	0.1	1	. 1	.0	50	Favours TCAs	

## Analysis 15.2. Comparison 15 Adverse events: Dry mouth, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs		Odds Ratio		Weight	Odds Ratio
	n/N	n/N		M-H, Random, 95% Cl			M-H, Random, 95% CI
15.2.1 Milnacipran vs Fluvoxamine							
Annseau 1991c	25/86	12/41				44.72%	0.99[0.44,2.24]
Clerc 2001	3/57	5/56				13.63%	0.57[0.13,2.49]
Subtotal (95% CI)	143	97				58.36%	0.87[0.42,1.78]
Total events: 28 (Milnacipran), 17 (SS	RIs)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.42, df=	=1(P=0.52); I <sup>2</sup> =0%						
Test for overall effect: Z=0.38(P=0.7)							
15.2.2 Milnacipran vs Fluoxetine							
Annseau 1994	13/97	10/93				38.78%	1.28[0.53,3.09]
Lee 2002b	1/39	0/31	◀──			2.86%	2.45[0.1,62.36]
Subtotal (95% CI)	136	124				41.64%	1.34[0.58,3.13]
Total events: 14 (Milnacipran), 10 (SS	RIs)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.14, df=	=1(P=0.7); I <sup>2</sup> =0%						
Test for overall effect: Z=0.68(P=0.5)							
	270	221				100%	1 04[0 6 1 8]
Total (95% CI)	219	221				100%	1.04[0.6,1.8]
Total events: 42 (Milnacipran), 27 (SS	RIS)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.15, df=	=3(P=0.76); I <sup>2</sup> =0%						
Test for overall effect: Z=0.15(P=0.88)	1						
Test for subgroup differences: Chi <sup>2</sup> =0	.59, df=1 (P=0.44), I <sup>2</sup> =0 <sup>0</sup>	%					
		Favours SSRIs	0.1 0.2	0.5 1 2	5 10	Favours Milnacipran	

## Analysis 15.3. Comparison 15 Adverse events: Dry mouth, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odds Ratio			Weight	Odds Ratio			
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% Cl
15.3.1 Milancipran vs Mianserin											
Endo 1995	5/84	12/95			+	+				100%	0.44[0.15,1.3]
Subtotal (95% CI)	84	95								100%	0.44[0.15,1.3]
Total events: 5 (Milnacipran), 12 (Het	erocyclics)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(F	P<0.0001); I²=100%										
	Fav	vours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclic	5

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Study or subgroup	Milnacipran	Heterocyclics			Od	ds Ra	ntio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	n, 95% Cl				M-H, Random, 95% Cl
Test for overall effect: Z=1.49(P=0.14)											
Total (95% CI)	84	95								100%	0.44[0.15,1.3]
Total events: 5 (Milnacipran), 12 (Hete	erocyclics)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=0(P	<0.0001); l <sup>2</sup> =100%										
Test for overall effect: Z=1.49(P=0.14)											
	Fi	avours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclic	s

### Comparison 16. Adverse events: Constipation

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	795	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.88]
1.1 Milancipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% Cl)	0.64 [0.41, 0.98]
1.2 Milnacipran vs Amitripty- line	2	233	Odds Ratio (M-H, Random, 95% CI)	0.60 [0.34, 1.06]
2 Milancipran vs SSRIs	5	800	Odds Ratio (M-H, Random, 95% CI)	1.19 [0.69, 2.06]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	1.30 [0.28, 6.01]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.67, 3.06]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.05, 1.29]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	0.27 [0.05, 1.29]

## Analysis 16.1. Comparison 16 Adverse events: Constipation, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds I	Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Rando	m, 95% Cl		M-H, Random, 95% Cl
16.1.1 Milancipran vs Imipramine						
Lopez-Ibor 2004	20/51	25/49	-++	-	18.56%	0.62[0.28,1.37]
Tignol 1998	14/112	22/109			21.95%	0.56[0.27,1.17]
Van Amerongen 2002	13/53	14/56	-+		15.43%	0.98[0.41,2.33]
Yamashita 1995	4/66	9/66	+-	_	7.71%	0.41[0.12,1.4]
Subtotal (95% CI)	282	280	•		63.64%	0.64[0.41,0.98]
Total events: 51 (Milnacipran), 70 (T	CAs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.53, d	f=3(P=0.68); I <sup>2</sup> =0%					
Test for overall effect: Z=2.06(P=0.04	1)					
16.1.2 Milnacipran vs Amitriptylin	e					
Annseau 1989a	25/97	20/49			21.98%	0.5[0.24,1.04]
Annseau 1989c	13/44	15/43			14.38%	0.78[0.32,1.93]
	Favo	urs Milnacipran	0.02 0.1 1	10 50	Favours TCAs	

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Study or subgroup	Milnacipran	TCAs		Odds Ratio	0	Weight	Odds Ratio
	n/N	n/N	М	-H, Random, 9	5% CI		M-H, Random, 95% CI
Subtotal (95% CI)	141	92		•		36.36%	0.6[0.34,1.06]
Total events: 38 (Milnacipran), 35	(TCAs)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.56,	df=1(P=0.46); I <sup>2</sup> =0%						
Test for overall effect: Z=1.77(P=0.	08)						
Total (95% CI)	423	372		•		100%	0.62[0.44,0.88]
Total events: 89 (Milnacipran), 105	5 (TCAs)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.11,	df=5(P=0.83); I <sup>2</sup> =0%						
Test for overall effect: Z=2.71(P=0.	01)						
Test for subgroup differences: Chi	<sup>2</sup> =0.03, df=1 (P=0.87), l <sup>2</sup> =00	%					
	Favo	urs Milnacipran	0.02 0.1	1	10 50	Favours TCAs	

## Analysis 16.2. Comparison 16 Adverse events: Constipation, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
16.2.1 Milnacipran vs Fluvoxamine					
Annseau 1991c	19/86	11/41	<b></b>	41.1%	0.77[0.33,1.82]
Clerc 2001	4/57	1/56		6.12%	4.15[0.45,38.35]
Subtotal (95% CI)	143	97		47.22%	1.3[0.28,6.01]
Total events: 23 (Milnacipran), 12 (SSR	RIS)				
Heterogeneity: Tau <sup>2</sup> =0.69; Chi <sup>2</sup> =1.93, d	If=1(P=0.16); I <sup>2</sup> =48.3%				
Test for overall effect: Z=0.33(P=0.74)					
16.2.2 Milnacipran vs Fluoxetine					
Annseau 1994	6/97	4/93		17.96%	1.47[0.4,5.37]
Guelfi 1998a	15/200	6/100		31.61%	1.27[0.48,3.38]
Lee 2002b	2/39	0/31		3.21%	4.2[0.19,90.76]
Subtotal (95% CI)	336	224		52.78%	1.43[0.67,3.06]
Total events: 23 (Milnacipran), 10 (SSR	RIS)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.53, df=2	2(P=0.77); I <sup>2</sup> =0%				
Test for overall effect: Z=0.93(P=0.35)					
Total (95% CI)	479	321		100%	1.19[0.69,2.06]
Total events: 46 (Milnacipran), 22 (SSR	lls)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.97, df=4	1(P=0.56); I <sup>2</sup> =0%				
Test for overall effect: Z=0.61(P=0.54)					
Test for subgroup differences: Chi <sup>2</sup> =0.0	01, df=1 (P=0.91), I <sup>2</sup> =09	6			
	Favo	urs Milnasinran 01	02 05 1 2 5 10		

Favours Milnacipran Favours SSRIs

## Analysis 16.3. Comparison 16 Adverse events: Constipation, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odds Ratio				Weight	Odds Ratio		
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% CI
16.3.1 Milancipran vs Mianserin											
Endo 1995	2/84	8/95	←	- +		+				100%	0.27[0.05,1.29]
Subtotal (95% CI)	84	95				-				100%	0.27[0.05,1.29]
	Fa	vours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclics	5

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Study or subgroup	Milnacipran	Heterocyclics			00	lds Ra	itio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	n, 95% C	I			M-H, Random, 95% Cl
Total events: 2 (Milnacipran), 8 (Heter	ocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.65(P=0.1)											
Total (95% CI)	84	95								100%	0.27[0.05,1.29]
Total events: 2 (Milnacipran), 8 (Heter	ocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.65(P=0.1)											
	F	avours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclic	S

## Comparison 17. Adverse events: Urination problems

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	2	232	Odds Ratio (M-H, Random, 95% CI)	1.81 [0.57, 5.73]
1.1 Milancipran vs Imipramine	2	232	Odds Ratio (M-H, Random, 95% Cl)	1.81 [0.57, 5.73]
2 Milancipran vs SSRIs	4	732	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.59, 3.90]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% Cl)	1.70 [0.39, 7.35]
2.2 Milnacipran vs Fluoxetine	1	190	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.31, 4.65]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	3.10 [0.13, 76.73]
3 Milnacipran vs Hetero- cyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	2.29 [0.20, 25.75]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	2.29 [0.20, 25.75]

# Analysis 17.1. Comparison 17 Adverse events: Urination problems, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio			Weight	Odds Ratio
	n/N	n/N	M-H, R	andom, 95% Cl			M-H, Random, 95% CI
17.1.1 Milancipran vs Imipramin	e						
Lopez-Ibor 2004	7/51	3/49				66.45%	2.44[0.59,10.03]
Yamashita 1995	2/66	2/66		<b>_</b>		33.55%	1[0.14,7.32]
Subtotal (95% CI)	117	115				100%	1.81[0.57,5.73]
Total events: 9 (Milnacipran), 5 (TC	CAs)						
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.51,	df=1(P=0.47); I <sup>2</sup> =0%						
Test for overall effect: Z=1.01(P=0.3	31)						
Total (95% CI)	117	115				100%	1.81[0.57,5.73]
Total events: 9 (Milnacipran), 5 (TC	CAs)						
	Favo	ours Milnacipran	0.02 0.1	1 10	50	Favours TCAs	

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Study or subgroup	Milnacipran n/N	TCAs n/N	Odds Ratio M-H, Random, 95% Cl					Weight	Odds Ratio M-H, Random, 95% Cl
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.51,	df=1(P=0.47); I <sup>2</sup> =0%								
Test for overall effect: Z=1.01(P=0.	31)			1					
	Fa	avours Milnacipran	0.02	0.1	1	10	50	Favours TCAs	

## Analysis 17.2. Comparison 17 Adverse events: Urination problems, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
17.2.1 Milnacipran vs Fluvoxamine					
Annseau 1991c	6/86	2/41		33.15%	1.46[0.28,7.58]
Clerc 2001	1/57	0/56	+	8.65%	3[0.12,75.22]
Subtotal (95% CI)	143	97		41.79%	1.7[0.39,7.35]
Total events: 7 (Milnacipran), 2 (SSRIs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.15, df=1	.(P=0.7); l <sup>2</sup> =0%				
Test for overall effect: Z=0.71(P=0.48)					
17.2.2 Milnacipran vs Fluoxetine					
Annseau 1994	5/97	4/93		49.49%	1.21[0.31,4.65]
Subtotal (95% CI)	97	93		49.49%	1.21[0.31,4.65]
Total events: 5 (Milnacipran), 4 (SSRIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
17.2.3 Milnacipran vs Paroxetine					
Sechter 2000	1/149	0/153	•	8.72%	3.1[0.13,76.73]
Subtotal (95% CI)	149	153		8.72%	3.1[0.13,76.73]
Total events: 1 (Milnacipran), 0 (SSRIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
Total (95% CI)	389	343		100%	1.51[0.59,3.9]
Total events: 13 (Milnacipran), 6 (SSRI	5)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.48, df=3	8(P=0.92); I <sup>2</sup> =0%				
Test for overall effect: Z=0.86(P=0.39)					
Test for subgroup differences: Chi <sup>2</sup> =0.3	82, df=1 (P=0.85), I <sup>2</sup> =0	%			
	Favo	ours Milnacipran (	0.1 0.2 0.5 1 2 5	10 Eavours SSRIs	

## Analysis 17.3. Comparison 17 Adverse events: Urination problems, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics		Odds Ratio				Weight	Odds Ratio		
	n/N	n/N			M-H, Ra	ndon	n, 95% Cl				M-H, Random, 95% CI
17.3.1 Milancipran vs Mianserin											
Endo 1995	2/84	1/95				-			→	100%	2.29[0.2,25.75]
Subtotal (95% CI)	84	95		_						100%	2.29[0.2,25.75]
Total events: 2 (Milnacipran), 1 (Heter	rocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.67(P=0.5)							1				
	Fa	vours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclics	5

Milnacipran versus other antidepressive agents for depression (Review)



Study or subgroup	Milnacipran	Heterocyclics			Od	ds Ra	atio			Weight	Odds Ratio
	n/N	n/N			M-H, Rar	ndon	n, 95% Cl				M-H, Random, 95% CI
Total (95% CI)	84	95								100%	2.29[0.2,25.75]
Total events: 2 (Milnacipran), 1 (Heter	ocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.67(P=0.5)				1							
	Fa	vours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours Heterocyclics	5

## Comparison 18. Adverse events: Hypotention

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	5	656	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.16, 1.45]
1.1 Milancipran vs Imipramine	3	462	Odds Ratio (M-H, Random, 95% CI)	0.17 [0.04, 0.76]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.74, 3.62]
1.3 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.14, 1.21]
2 Milancipran vs SSRIs	4	687	Odds Ratio (M-H, Random, 95% Cl)	1.50 [0.73, 3.08]
2.1 Milnacipran vs Fluvoxam- ine	1	127	Odds Ratio (M-H, Random, 95% CI)	1.42 [0.57, 3.53]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	1.51 [0.38, 5.95]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	3.43 [0.14, 85.37]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% Cl)	3.43 [0.14, 85.37]

## Analysis 18.1. Comparison 18 Adverse events: Hypotention, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs		Oc	lds Ratio			Weight	Odds Ratio
	n/N	n/N		M-H, Ra	ndom, 95%	5 CI			M-H, Random, 95% CI
18.1.1 Milancipran vs Imipramine	2								
Tignol 1998	1/112	6/109		•				16.41%	0.15[0.02,1.31]
Van Amerongen 2002	0/53	1/56		•		_		9.26%	0.35[0.01,8.68]
Yamashita 1995	0/66	4/66	◀—	+	<u> </u>			10.63%	0.1[0.01,1.98]
Subtotal (95% CI)	231	231	-		-			36.3%	0.17[0.04,0.76]
Total events: 1 (Milnacipran), 11 (T	CAs)								
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.3, df	=2(P=0.86); I <sup>2</sup> =0%								
Test for overall effect: Z=2.31(P=0.0	2)								
18.1.2 Milnacipran vs Clomipram	ine								
Leinonen 1997	22/52	17/55			+	i.		34.11%	1.64[0.74,3.62]
	Favou	urs Milnacipran	0.02	0.1	1	10	50	Favours TCAs	



Study or subgroup	Milnacipran	TCAs	Odds R	latio	Weight	Odds Ratio
	n/N	n/N	M-H, Rando	m, 95% Cl		M-H, Random, 95% CI
Subtotal (95% CI)	52	55			34.11%	1.64[0.74,3.62]
Total events: 22 (Milnacipran), 17 (TC	As)					
Heterogeneity: Not applicable						
Test for overall effect: Z=1.22(P=0.22)						
18.1.3 Milnacipran vs Amitriptyline						
Annseau 1989c	6/44	12/43			29.59%	0.41[0.14,1.21]
Subtotal (95% CI)	44	43			29.59%	0.41[0.14,1.21]
Total events: 6 (Milnacipran), 12 (TCA	.s)					
Heterogeneity: Not applicable						
Test for overall effect: Z=1.61(P=0.11)						
Total (95% CI)	327	329		-	100%	0.48[0.16,1.45]
Total events: 29 (Milnacipran), 40 (TC	As)					
Heterogeneity: Tau <sup>2</sup> =0.78; Chi <sup>2</sup> =9.14,	df=4(P=0.06); I <sup>2</sup> =56.22	%				
Test for overall effect: Z=1.31(P=0.19)						
Test for subgroup differences: Chi <sup>2</sup> =8	.67, df=1 (P=0.01), l <sup>2</sup> =7	5.94%				
	Favo	urs Milnacipran	0.02 0.1 1	10 50	Eavours TCAs	

# Analysis 18.2. Comparison 18 Adverse events: Hypotention, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs		Odds Ratio	<b>b</b>		Weight	Odds Ratio
	n/N	n/N		M-H, Random, 9	5% CI			M-H, Random, 95% Cl
18.2.1 Milnacipran vs Fluvoxamine								
Annseau 1991c	22/86	8/41					62.73%	1.42[0.57,3.53]
Subtotal (95% CI)	86	41					62.73%	1.42[0.57,3.53]
Total events: 22 (Milnacipran), 8 (SSRI	s)							
Heterogeneity: Not applicable								
Test for overall effect: Z=0.75(P=0.45)								
18.2.2 Milnacipran vs Fluoxetine								
Annseau 1994	7/97	3/93			-		27.23%	2.33[0.58,9.31]
Guelfi 1998a	0/200	1/100	<b>↓</b> →				5.06%	0.17[0.01,4.1]
Lee 2002b	1/39	0/31	◀		+		4.98%	2.45[0.1,62.36]
Subtotal (95% CI)	336	224				-	37.27%	1.51[0.38,5.95]
Total events: 8 (Milnacipran), 4 (SSRIs	)							
Heterogeneity: Tau <sup>2</sup> =0.24; Chi <sup>2</sup> =2.28, o	df=2(P=0.32); I <sup>2</sup> =12.36	%						
Test for overall effect: Z=0.59(P=0.56)								
Total (95% CI)	422	265					100%	1.5[0.73,3.08]
Total events: 30 (Milnacipran), 12 (SSF	RIs)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2.31, df=	3(P=0.51); I <sup>2</sup> =0%							
Test for overall effect: Z=1.1(P=0.27)								
Test for subgroup differences: Chi <sup>2</sup> =0.	01, df=1 (P=0.94), I <sup>2</sup> =0	%						
	Favo	ours Milnacipran	0.1 0.2	0.5 1	2 !	5 10	Favours SSRIs	

## Analysis 18.3. Comparison 18 Adverse events: Hypotention, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Odds I	Ratio			Weight	Odds Ratio
	n/N	n/N		M-H	I, Rando	m, 95%	% CI			M-H, Random, 95% Cl
18.3.1 Milancipran vs Mianserin										
Endo 1995	1/84	0/95	_				-	$\rightarrow$	100%	3.43[0.14,85.37]
Subtotal (95% CI)	84	95	_						100%	3.43[0.14,85.37]
Total events: 1 (Milnacipran), 0 (Hetero	ocyclics)									
Heterogeneity: Not applicable										
Test for overall effect: Z=0.75(P=0.45)										
Total (95% CI)	84	95							100%	3.43[0.14,85.37]
Total events: 1 (Milnacipran), 0 (Hetero	ocyclics)									
Heterogeneity: Not applicable										
Test for overall effect: Z=0.75(P=0.45)				ī	.					
	Fa	vours Heterocyclic	0.1	0.2	0.5 1	2	5	5 10	Favours Milnacipran	

### Comparison 19. Adverse events: Agitaion/ anxiety

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	4	549	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.30, 1.37]
1.1 Milancipran vs Imipramine	3	462	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.23, 1.94]
1.2 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% CI)	0.62 [0.21, 1.83]
2 Milancipran vs SSRIs	6	1102	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.37, 1.30]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	0.55 [0.10, 3.04]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% Cl)	0.82 [0.43, 1.56]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.30, 6.27]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.37 [0.01, 9.27]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% Cl)	0.37 [0.01, 9.27]

## Analysis 19.1. Comparison 19 Adverse events: Agitaion/ anxiety, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds	Ratio		Weight	Odds Ratio
	n/N	n/N	M-H, Rand	om, 95% Cl			M-H, Random, 95% CI
19.1.1 Milancipran vs Imipramine							
Tignol 1998	5/112	6/109				38.9%	0.8[0.24,2.71]
Van Amerongen 2002	0/53	1/56	+			5.55%	0.35[0.01,8.68]
Yamashita 1995	0/66	1/66	+			5.56%	0.33[0.01,8.21]
	Favo	ours Milnacipran	0.02 0.1	10	50	Favours TCAs	



Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Subtotal (95% CI)	231	231	-	50.01%	0.66[0.23,1.94]
Total events: 5 (Milnacipran), 8 (TCAs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.44, df=2	2(P=0.8); I <sup>2</sup> =0%				
Test for overall effect: Z=0.75(P=0.45)					
19.1.2 Milnacipran vs Amitriptyline					
Annseau 1989c	7/44	10/43		49.99%	0.62[0.21,1.83]
Subtotal (95% CI)	44	43		49.99%	0.62[0.21,1.83]
Total events: 7 (Milnacipran), 10 (TCAs	5)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.86(P=0.39)					
Total (95% CI)	275	274	-	100%	0.64[0.3,1.37]
Total events: 12 (Milnacipran), 18 (TCA	As)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.44, df=3	B(P=0.93); I <sup>2</sup> =0%				
Test for overall effect: Z=1.14(P=0.25)					
Test for subgroup differences: Chi <sup>2</sup> =0.0	01, df=1 (P=0.94), l <sup>2</sup> =0 <sup>0</sup>	%			
	Favo	urs Milnacipran	0.02 0.1 1 10 50	Favours TCAs	

### Favours Milnacipran

# Analysis 19.2. Comparison 19 Adverse events: Agitaion/ anxiety, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
19.2.1 Milnacipran vs Fluvoxamine					
Annseau 1991c	14/86	16/41		26.57%	0.3[0.13,0.71]
Clerc 2001	2/57	1/56		5.81%	2[0.18,22.7]
Subtotal (95% CI)	143	97		32.38%	0.55[0.1,3.04]
Total events: 16 (Milnacipran), 17 (SSR	ls)				
Heterogeneity: Tau <sup>2</sup> =0.92; Chi <sup>2</sup> =2.07, d	f=1(P=0.15); I <sup>2</sup> =51.73	%			
Test for overall effect: Z=0.69(P=0.49)					
19.2.2 Milnacipran vs Fluoxetine					
Annseau 1994	13/97	10/93		25.68%	1.28[0.53,3.09]
Guelfi 1998a	12/200	10/100		25.76%	0.57[0.24,1.38]
Lee 2002b	0/39	1/31 •	+	3.44%	0.26[0.01,6.54]
Subtotal (95% CI)	336	224		54.88%	0.82[0.43,1.56]
Total events: 25 (Milnacipran), 21 (SSR	ls)				
Heterogeneity: Tau <sup>2</sup> =0.02; Chi <sup>2</sup> =2.13, d	f=2(P=0.34); I <sup>2</sup> =6.09%	6			
Test for overall effect: Z=0.61(P=0.54)					
19.2.3 Milnacipran vs Paroxetine					
Sechter 2000	4/149	3/153		12.74%	1.38[0.3,6.27]
Subtotal (95% CI)	149	153		12.74%	1.38[0.3,6.27]
Total events: 4 (Milnacipran), 3 (SSRIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.68)					
Total (95% CI)	628	474	-	100%	0.7[0.37,1.3]
Total events: 45 (Milnacipran), 41 (SSR	ls)				
	Favo	ours Milnacipran (	0.1 0.2 0.5 1 2 5 10	<sup>)</sup> Favours SSRIs	



Study or subgroup	Milnacipran n/N	SSRIs n/N			Od M-H. Ra	lds Ra ndom	itio 1. 95% Cl			Weight	Odds Ratio M-H. Random. 95% Cl
Heterogeneity: Tau <sup>2</sup> =0.19; Chi <sup>2</sup> =7.5	55, df=5(P=0.18); l <sup>2</sup> =33.77	%			,		,				
Test for overall effect: Z=1.14(P=0.	25)										
Test for subgroup differences: Chi <sup>4</sup>	<sup>2</sup> =0.66, df=1 (P=0.72), I <sup>2</sup> =0	%									
	Favo	urs Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	

## Analysis 19.3. Comparison 19 Adverse events: Agitaion/ anxiety, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Od	lds Rat	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% CI
19.3.1 Milancipran vs Mianserin											
Endo 1995	0/84	1/95	←		+					100%	0.37[0.01,9.27]
Subtotal (95% CI)	84	95								100%	0.37[0.01,9.27]
Total events: 0 (Milnacipran), 1 (Heter	ocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.6(P=0.55)											
Total (95% CI)	84	95								100%	0.37[0.01,9.27]
Total events: 0 (Milnacipran), 1 (Heter	ocyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.6(P=0.55)											
	Fav	vours Heterocyclic	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

### Comparison 20. Adverse events: Suicide wishes/ gestures/ attempts

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.51 [0.09, 2.91]
1.1 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.51 [0.09, 2.91]
2 Milancipran vs SSRIs	1	300	Odds Ratio (M-H, Random, 95% Cl)	0.49 [0.14, 1.72]
2.1 Milnacipran vs Fluoxetine	1	300	Odds Ratio (M-H, Random, 95% Cl)	0.49 [0.14, 1.72]

### Analysis 20.1. Comparison 20 Adverse events: Suicide wishes/ gestures/ attempts, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds R			Ratio	tio Weight			Odds Ratio
	n/N	n/N		M-H	I, Rando	m, 95%	CI			M-H, Random, 95% CI
20.1.1 Milnacipran vs Clomipramine	2									
Leinonen 1997	2/52	4/55			-				100%	0.51[0.09,2.91]
	Favo	urs Milnacipran	0.02	0.1	1		10	50	Favours TCAs	



Study or subgroup	Milnacipran	TCAs		мы	Odds Ratio	04 <b>CI</b>		Weight	Odds Ratio
	n/n	n/n	-	M-H	Random, 95	% CI			M-H, Random, 95% CI
Subtotal (95% CI)	52	55						100%	0.51[0.09,2.91]
Total events: 2 (Milnacipran), 4 (TCAs)									
Heterogeneity: Not applicable									
Test for overall effect: Z=0.76(P=0.45)									
Total (95% CI)	52	55						100%	0.51[0.09,2.91]
Total events: 2 (Milnacipran), 4 (TCAs)									
Heterogeneity: Not applicable									
Test for overall effect: Z=0.76(P=0.45)									
	Fav	ours Milnacipran	0.02	0.1	1	10	50	Favours TCAs	

## Analysis 20.2. Comparison 20 Adverse events: Suicide wishes/gestures/attempts, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs			00	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	I			M-H, Random, 95% CI
20.2.1 Milnacipran vs Fluoxetine											
Guelfi 1998a	5/200	5/100	-							100%	0.49[0.14,1.72]
Subtotal (95% CI)	200	100					-			100%	0.49[0.14,1.72]
Total events: 5 (Milnacipran), 5 (SSRIs)											
Heterogeneity: Not applicable											
Test for overall effect: Z=1.12(P=0.26)											
Total (95% CI)	200	100	-				-			100%	0.49[0.14,1.72]
Total events: 5 (Milnacipran), 5 (SSRIs)											
Heterogeneity: Not applicable											
Test for overall effect: Z=1.12(P=0.26)											
	Fav	ours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	

### Comparison 21. Adverse events:Completed suicide

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milancipran vs SSRIs	1	300	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.09, 11.16]
1.1 Milnacipran vs Fluoxetine	1	300	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.09, 11.16]

## Analysis 21.1. Comparison 21 Adverse events: Completed suicide, Outcome 1 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs			00	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	l			M-H, Random, 95% Cl
21.1.1 Milnacipran vs Fluoxetine											
Guelfi 1998a	2/200	1/100	←			-			→	100%	1[0.09,11.16]
Subtotal (95% CI)	200	100								100%	1[0.09,11.16]
	Favo	urs Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	



Study or subgroup	Milnacipran	SSRIs			Od	lds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% C	I			M-H, Random, 95% Cl
Total events: 2 (Milnacipran), 1 (SSRIs)	)										
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
Total (95% CI)	200	100								100%	1[0.09,11.16]
Total events: 2 (Milnacipran), 1 (SSRIs)	1										
Heterogeneity: Not applicable											
Test for overall effect: Not applicable											
	Fav	ours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	

# Comparison 22. Adverse events: Vomitting/ nausea

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	6	756	Odds Ratio (M-H, Random, 95% CI)	2.44 [1.34, 4.42]
1.1 Milancipran vs Imipramine	4	562	Odds Ratio (M-H, Random, 95% CI)	2.31 [1.13, 4.72]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	10.30 [0.54, 196.19]
1.3 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% CI)	2.24 [0.69, 7.19]
2 Milancipran vs SSRIs	6	1102	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.42, 1.27]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	0.51 [0.28, 0.94]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.36, 3.44]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.06, 16.57]
3 Milnacipran vs Heterocyclics	1	179	Odds Ratio (M-H, Random, 95% CI)	5.95 [0.68, 51.99]
3.1 Milancipran vs Mianserin	1	179	Odds Ratio (M-H, Random, 95% CI)	5.95 [0.68, 51.99]

## Analysis 22.1. Comparison 22 Adverse events: Vomitting/ nausea, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
22.1.1 Milancipran vs Imipramine					
Lopez-Ibor 2004	7/51	3/49	+	17.74%	2.44[0.59,10.03]
Tignol 1998	8/112	5/109	<b>=</b>	26.83%	1.6[0.51,5.05]
Van Amerongen 2002	7/53	3/56	+ +	17.87%	2.69[0.66,11]
Yamashita 1995	5/66	1/66	+	7.5%	5.33[0.61,46.91]
Subtotal (95% CI)	282	280	•	69.95%	2.31[1.13,4.72]
Total events: 27 (Milnacipran), 12 (TCA	s)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.02, df=3	8(P=0.8); I <sup>2</sup> =0%				
Test for overall effect: Z=2.31(P=0.02)					
22.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	4/52	0/55		4.09%	10.3[0.54,196.19]
Subtotal (95% CI)	52	55		4.09%	10.3[0.54,196.19]
Total events: 4 (Milnacipran), 0 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.55(P=0.12)					
22.1.3 Milnacipran vs Amitriptyline					
Annseau 1989c	10/44	5/43	<b>_</b>	25.97%	2.24[0.69.7.19]
Subtotal (95% CI)	44	43		25.97%	2.24[0.69.7.19]
Total events: 10 (Milnacipran), 5 (TCAs	)				- / -
Heterogeneity: Not applicable	,				
Test for overall effect: Z=1.35(P=0.18)					
Total (95% CI)	378	378	•	100%	2.44[1.34,4.42]
Total events: 41 (Milnacipran), 17 (TCA	s)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =2, df=5(P=	=0.85); I <sup>2</sup> =0%				
Test for overall effect: Z=2.93(P=0)					
Test for subgroup differences: Chi <sup>2</sup> =0.9	96, df=1 (P=0.62), l <sup>2</sup> =0				
	Favo	ours Milnacipran	0.02 0.1 1 10 50	Favours TCAs	

## Analysis 22.2. Comparison 22 Adverse events: Vomitting/ nausea, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs			Ode	ds Rat	io			Weight	Odds Ratio
	n/N	n/N		I	/I-H, Ran	ndom,	95% CI				M-H, Random, 95% CI
22.2.1 Milnacipran vs Fluvoxamine											
Annseau 1991c	32/86	22/41			•	+				25.71%	0.51[0.24,1.09]
Clerc 2001	7/57	12/56			+	+-				18.44%	0.51[0.19,1.42]
Subtotal (95% CI)	143	97		-		-				44.15%	0.51[0.28,0.94]
Total events: 39 (Milnacipran), 34 (SS	RIs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1(F	P=1); I <sup>2</sup> =0%										
Test for overall effect: Z=2.17(P=0.03)											
22.2.2 Milnacipran vs Fluoxetine											
Annseau 1994	19/97	16/93								26.3%	1.17[0.56,2.45]
Guelfi 1998a	12/200	11/100			•	+				22.56%	0.52[0.22,1.22]
Lee 2002b	7/39	0/31							→	3.36%	14.54[0.8,265.38]
Subtotal (95% CI)	336	224								52.21%	1.12[0.36,3.44]
	Favo	ours Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs	

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Study or subgroup	Milhacipran	SSRIS			Ud	as kat	10			weight	Odds Ratio	
	n/N	n/N			M-H, Ra	ndom,	95% CI				M-H, Random, 95% Cl	
Total events: 38 (Milnacipran), 27 (SS	RIs)											
Heterogeneity: Tau <sup>2</sup> =0.58; Chi <sup>2</sup> =5.91,	df=2(P=0.05); I <sup>2</sup> =66.18%	)										
Test for overall effect: Z=0.19(P=0.85)	1											
22.2.3 Milnacipran vs Paroxetine												
Sechter 2000	1/149	1/153	←			+				3.64%	1.03[0.06,16.57]	]
Subtotal (95% CI)	149	153								3.64%	1.03[0.06,16.57]	l
Total events: 1 (Milnacipran), 1 (SSRI	s)											
Heterogeneity: Not applicable												
Test for overall effect: Z=0.02(P=0.99)	1											
												_
Total (95% CI)	628	474								100%	0.73[0.42,1.27]	1
Total events: 78 (Milnacipran), 62 (SS	RIs)											
Heterogeneity: Tau <sup>2</sup> =0.16; Chi <sup>2</sup> =7.87,	df=5(P=0.16); I <sup>2</sup> =36.45%	)										
Test for overall effect: Z=1.11(P=0.27)	1											
Test for subgroup differences: Chi <sup>2</sup> =1	.55, df=1 (P=0.46), l <sup>2</sup> =0%	)										
	Favou	rs Milnacipran	0.1	0.2	0.5	1	2	5	10	Favours SSRIs		

# Analysis 22.3. Comparison 22 Adverse events: Vomitting/ nausea, Outcome 3 Milnacipran vs Heterocyclics.

Study or subgroup	Milnacipran	Heterocyclics			Od	lds Rat	io			Weight	Odds Ratio
	n/N	n/N		I	M-H, Ra	ndom,	95% CI				M-H, Random, 95% CI
22.3.1 Milancipran vs Mianserin											
Endo 1995	5/84	1/95			-	_				100%	5.95[0.68,51.99]
Subtotal (95% CI)	84	95			-					100%	5.95[0.68,51.99]
Total events: 5 (Milnacipran), 1 (Hetero	cyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.61(P=0.11)											
Total (95% CI)	84	95			-					100%	5.95[0.68,51.99]
Total events: 5 (Milnacipran), 1 (Hetero	cyclics)										
Heterogeneity: Not applicable											
Test for overall effect: Z=1.61(P=0.11)											
	Fa	vours Heterocyclic	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

### Comparison 23. Adverse events: Diarrhoea

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	5	656	Odds Ratio (M-H, Random, 95% CI)	1.24 [0.29, 5.29]
1.1 Milancipran vs Imipramine	3	462	Odds Ratio (M-H, Random, 95% CI)	0.47 [0.12, 1.75]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	5.50 [0.26, 117.22]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1.3 Milnacipran vs Amitripty- line	1	87	Odds Ratio (M-H, Random, 95% CI)	7.34 [0.37, 146.43]
2 Milancipran vs SSRIs	6	1102	Odds Ratio (M-H, Random, 95% CI)	0.69 [0.37, 1.27]
2.1 Milnacipran vs Fluvoxam- ine	2	240	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.29, 2.00]
2.2 Milnacipran vs Fluoxetine	3	560	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.31, 1.58]
2.3 Milnacipran vs Paroxetine	1	302	Odds Ratio (M-H, Random, 95% Cl)	0.20 [0.01, 4.26]

# Analysis 23.1. Comparison 23 Adverse events: Diarrhoea, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
23.1.1 Milancipran vs Imipramine					
Tignol 1998	2/112	6/109		35.54%	0.31[0.06,1.58]
Van Amerongen 2002	0/53	1/56 —		15.35%	0.35[0.01,8.68]
Yamashita 1995	1/66	0/66		15.38%	3.05[0.12,76.13]
Subtotal (95% CI)	231	231		66.27%	0.47[0.12,1.75]
Total events: 3 (Milnacipran), 7 (TCAs)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.58, df=2	(P=0.45); I <sup>2</sup> =0%				
Test for overall effect: Z=1.13(P=0.26)					
23.1.2 Milnacipran vs Clomipramine					
Leinonen 1997	2/52	0/55		16.59%	5.5[0.26,117.22]
Subtotal (95% CI)	52	55		16.59%	5.5[0.26,117.22]
Total events: 2 (Milnacipran), 0 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.09(P=0.28)					
23.1.3 Milnacipran vs Amitriptyline					
Annseau 1989c	3/44	0/43		17.14%	7.34[0.37,146.43]
Subtotal (95% CI)	44	43		17.14%	7.34[0.37,146.43]
Total events: 3 (Milnacipran), 0 (TCAs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.3(P=0.19)					
Total (95% CI)	327	329		100%	1.24[0.29,5.29]
Total events: 8 (Milnacipran), 7 (TCAs)					
Heterogeneity: Tau <sup>2</sup> =0.85; Chi <sup>2</sup> =5.81, d	f=4(P=0.21); I <sup>2</sup> =31.14	%			
Test for overall effect: Z=0.3(P=0.77)					
Test for subgroup differences: Chi <sup>2</sup> =4.1	.7, df=1 (P=0.12), l <sup>2</sup> =5	52.03%			
	Favo	ours Milnacipran	0.02 0.1 1 10 50	Favours TCAs	



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Analysis 23.2.	Comparison 23 Adverse events: Diarrhoea, Outcome 2 Milancipran vs SSRIs.
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Study or subgroup	Milnacipran	SSRIs	Odds R	atio	Weight	Odds Ratio
	n/N	n/N	M-H, Randor	m, 95% Cl		M-H, Random, 95% Cl
23.2.1 Milnacipran vs Fluvoxamine						
Annseau 1991c	10/86	7/41			33.91%	0.64[0.22,1.82]
Clerc 2001	2/57	1/56			6.3%	2[0.18,22.7]
Subtotal (95% CI)	143	97			40.21%	0.76[0.29,2]
Total events: 12 (Milnacipran), 8 (SSRI	5)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.72, df=1	(P=0.4); I <sup>2</sup> =0%					
Test for overall effect: Z=0.55(P=0.58)						
23.2.2 Milnacipran vs Fluoxetine						
Annseau 1994	4/97	3/93		•	15.99%	1.29[0.28,5.93]
Guelfi 1998a	9/200	7/100			35.85%	0.63[0.23,1.73]
Lee 2002b	0/39	2/31	<b>4</b> +		3.94%	0.15[0.01,3.23]
Subtotal (95% CI)	336	224		-	55.78%	0.7[0.31,1.58]
Total events: 13 (Milnacipran), 12 (SSR	ls)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =1.64, df=2	2(P=0.44); I <sup>2</sup> =0%					
Test for overall effect: Z=0.87(P=0.38)						
23.2.3 Milnacipran vs Paroxetine						
Sechter 2000	0/149	2/153	<b>↓</b>		4.01%	0.2[0.01,4.26]
Subtotal (95% CI)	149	153			4.01%	0.2[0.01,4.26]
Total events: 0 (Milnacipran), 2 (SSRIs)						
Heterogeneity: Not applicable						
Test for overall effect: Z=1.03(P=0.3)						
Total (95% CI)	628	474		-	100%	0.69[0.37,1.27]
Total events: 25 (Milnacipran), 22 (SSR	ls)					
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =3.03, df=5	6(P=0.7); I <sup>2</sup> =0%					
Test for overall effect: Z=1.2(P=0.23)						
Test for subgroup differences: Chi <sup>2</sup> =0.6	67, df=1 (P=0.72), I <sup>2</sup> =0	9%				
	Favo	ours Milnacipran	0.1 0.2 0.5 1	2 5 10	Favours SSRIs	

# Comparison 24. Subgroup analysis: Response at early phase (1-4 weeks)-High dose milnacipran

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 vs TCAs	2	194	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.42, 1.12]
1.1 vs Clomipramine	1	107	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.23, 1.21]
1.2 vs Amitryptyline	1	87	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.44, 1.45]



# Analysis 24.1. Comparison 24 Subgroup analysis: Response at early phase (1-4 weeks)-High dose milnacipran, Outcome 1 vs TCAs.

Study or subgroup	Milnacipran	TCAs	Risk Ratio	Weight	<b>Risk Ratio</b>
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
24.1.1 vs Clomipramine					
Leinonen 1997	7/52	14/55		34.57%	0.53[0.23,1.21]
Subtotal (95% CI)	52	55		34.57%	0.53[0.23,1.21]
Total events: 7 (Milnacipran), 14 (TCAs)	1				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.51(P=0.13)					
24.1.2 vs Amitryptyline					
Annseau 1989c	13/44	16/43	<b></b>	65.43%	0.79[0.44,1.45]
Subtotal (95% CI)	44	43		65.43%	0.79[0.44,1.45]
Total events: 13 (Milnacipran), 16 (TCAs	s)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
Total (95% CI)	96	98		100%	0.69[0.42,1.12]
Total events: 20 (Milnacipran), 30 (TCAs	s)				
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.62, df=1	(P=0.43); I <sup>2</sup> =0%				
Test for overall effect: Z=1.5(P=0.13)					
Test for subgroup differences: Chi <sup>2</sup> =0.6	1, df=1 (P=0.43), I <sup>2</sup> =0	0%			
		Favours TCAs 0.1	0.2 0.5 1 2 5	<sup>10</sup> Favours Milnacipran	1

## Comparison 25. Subgroup analysis: Response at acute phase (6-12 weeks)-Flexible dosing

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	2	328	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.32, 1.63]
1.1 Milnacipran vs Imipramine	1	221	Odds Ratio (M-H, Random, 95% CI)	1.05 [0.61, 1.79]
1.2 Milancipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% Cl)	0.45 [0.21, 0.98]

# Analysis 25.1. Comparison 25 Subgroup analysis: Response at acute phase (6-12 weeks)-Flexible dosing, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs			Od	lds Rat	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% Cl
25.1.1 Milnacipran vs Imipramine											
Tignol 1998	67/112	64/109			_	-				55.76%	1.05[0.61,1.79]
Subtotal (95% CI)	112	109			-	$\blacklozenge$	►			55.76%	1.05[0.61,1.79]
Total events: 67 (Milnacipran), 64 (T	CAs)										
Heterogeneity: Not applicable											
Test for overall effect: Z=0.17(P=0.8	7)										
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

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Study or subgroup	Milnacipran	TCAs			00	dds Ra	tio			Weight	Odds Ratio
	n/N	n/N			M-H, Ra	ndom	, 95% CI			8	M-H, Random, 95% Cl
25.1.2 Milancipran vs Clomipramin	9										
Leinonen 1997	22/52	34/55			-	_				44.24%	0.45[0.21,0.98]
Subtotal (95% CI)	52	55								44.24%	0.45[0.21,0.98]
Total events: 22 (Milnacipran), 34 (TC	As)										
Heterogeneity: Not applicable											
Test for overall effect: Z=2.01(P=0.04)											
Total (95% CI)	164	164			$\checkmark$		-			100%	0.72[0.32,1.63]
Total events: 89 (Milnacipran), 98 (TC	As)										
Heterogeneity: Tau <sup>2</sup> =0.24; Chi <sup>2</sup> =3.04,	df=1(P=0.08); I <sup>2</sup> =67.129	%									
Test for overall effect: Z=0.78(P=0.43)											
Test for subgroup differences: Chi <sup>2</sup> =3	.04, df=1 (P=0.08), I <sup>2</sup> =67	7.12%									
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

### Comparison 26. Subgroup analysis: Response at early phase (1-4 weeks)-Flexible dosing

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	3	460	Odds Ratio (M-H, Random, 95% Cl)	1.03 [0.55, 1.92]
1.1 Milancipran vs Imipramine	2	353	Odds Ratio (M-H, Random, 95% CI)	1.35 [0.82, 2.21]
1.2 Milnacipran vs Clomipramine	1	107	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.17, 1.24]

# Analysis 26.1. Comparison 26 Subgroup analysis: Response at early phase (1-4 weeks)-Flexible dosing, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs		Odds Ra	atio		Weight	Odds Ratio
	n/N	n/N	М	-H, Randon	n, 95% Cl			M-H, Random, 95% Cl
26.1.1 Milancipran vs Imipramine								
Tignol 1998	23/112	16/109			-		37.34%	1.5[0.75,3.03]
Yamashita 1995	28/66	25/66					37.55%	1.21[0.6,2.43]
Subtotal (95% CI)	178	175					74.9%	1.35[0.82,2.21]
Total events: 51 (Milnacipran), 41 (TCA	s)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.19, df=1	(P=0.67); I <sup>2</sup> =0%							
Test for overall effect: Z=1.18(P=0.24)								
26.1.2 Milnacipran vs Clomipramine								
Leinonen 1997	7/52	14/55		•	-		25.1%	0.46[0.17,1.24]
Subtotal (95% CI)	52	55					25.1%	0.46[0.17,1.24]
Total events: 7 (Milnacipran), 14 (TCAs)								
Heterogeneity: Not applicable								
Test for overall effect: Z=1.54(P=0.12)								
Total (95% CI)	230	230					100%	1.03[0.55,1.92]
		Favours TCAs	0.2	0.5 1	2	5	Favours Milnacipran	



Study or subgroup	Milnacipran	TCAs		00	lds Rat	io		Weight	Odds Ratio
	n/N	n/N		M-H, Ra	ndom,	95% CI			M-H, Random, 95% Cl
Total events: 58 (Milnacipran), 5	5 (TCAs)								
Heterogeneity: Tau <sup>2</sup> =0.14; Chi <sup>2</sup> =									
Test for overall effect: Z=0.08(P=	0.94)								
Test for subgroup differences: Cl	ni²=3.62, df=1 (P=0.06), I²=	72.37%							
		Favours TCAs	0.2	0.5	1	2	5	Favours Milnacipran	

### Comparison 27. Subgroup analysis: Response at acute phase [6-12 weeks]-Outpatient

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs SSRIs	4	615	Risk Ratio (M-H, Random, 95% Cl)	0.99 [0.72, 1.36]
1.1 Milnacipran vs Fluoxetine	2	260	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.53, 1.50]
1.2 Milnacipran vs Paroxetine	1	302	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.17]
1.3 Milnacipran vs Sertraline	1	53	Risk Ratio (M-H, Random, 95% CI)	2.89 [0.88, 9.50]

# Analysis 27.1. Comparison 27 Subgroup analysis: Response at acute phase [6-12 weeks]-Outpatient, Outcome 1 Milnacipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Risk Ratio	Weight	<b>Risk Ratio</b>
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
27.1.1 Milnacipran vs Fluoxetine					
Annseau 1994	32/97	43/93		31.37%	0.71[0.5,1.02]
Lee 2002b	17/39	11/31		18.72%	1.23[0.68,2.22]
Subtotal (95% CI)	136	124		50.09%	0.89[0.53,1.5]
Total events: 49 (Milnacipran), 54 (SSR	ls)				
Heterogeneity: Tau <sup>2</sup> =0.08; Chi <sup>2</sup> =2.36, d	f=1(P=0.12); I <sup>2</sup> =57.56	%			
Test for overall effect: Z=0.45(P=0.65)					
27.1.2 Milnacipran vs Paroxetine					
Sechter 2000	86/149	91/153	+	43.49%	0.97[0.8,1.17]
Subtotal (95% CI)	149	153	<b>+</b>	43.49%	0.97[0.8,1.17]
Total events: 86 (Milnacipran), 91 (SSR	ls)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
27.1.3 Milnacipran vs Sertraline					
Yang 2003	9/27	3/26	+	- 6.42%	2.89[0.88,9.5]
Subtotal (95% CI)	27	26		6.42%	2.89[0.88,9.5]
Total events: 9 (Milnacipran), 3 (SSRIs)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.75(P=0.08)					
Total (95% CI)	312	303	• • • • •	100%	0.99[0.72,1.36]
		Favours SSRIs 0	0.1 0.2 0.5 1 2 5	<sup>10</sup> Favours Milnaciprar	1



Study or subgroup	Milnacipran	SSRIs			Ris	sk Rat	io			Weight	Risk Ratio
	n/N	n/N			M-H, Rai	ndom	, 95% CI				M-H, Random, 95% CI
Total events: 144 (Milnacipran), 1	48 (SSRIs)										
Heterogeneity: Tau <sup>2</sup> =0.05; Chi <sup>2</sup> =6	.58, df=3(P=0.09); l <sup>2</sup> =54.4	1%									
Test for overall effect: Z=0.07(P=0	.94)										
Test for subgroup differences: Ch	i²=3.32, df=1 (P=0.19), I²=	39.68%									
		Favours SSRIs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

### Comparison 28. Subgroup analysis: Response at early phase [1-4 weeks]-Outpatient

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milancipran vs SSRIs	2	372	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.73, 1.52]
1.1 Milnacipran vs Fluoxetine	1	70	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.41, 2.73]
1.2 Milnacipran vs Paroxetine	1	302	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.71, 1.56]

# Analysis 28.1. Comparison 28 Subgroup analysis: Response at early phase [1-4 weeks]-Outpatient, Outcome 1 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs		Risk Rati	0		Weight	Risk Ratio
	n/N	n/N		M-H, Random,	95% CI			M-H, Random, 95% Cl
28.1.1 Milnacipran vs Fluoxetine								
Lee 2002b	8/39	6/31					14.64%	1.06[0.41,2.73]
Subtotal (95% CI)	39	31					14.64%	1.06[0.41,2.73]
Total events: 8 (Milnacipran), 6 (SSRIs)								
Heterogeneity: Not applicable								
Test for overall effect: Z=0.12(P=0.9)								
28.1.2 Milnacipran vs Paroxetine								
Sechter 2000	38/149	37/153					85.36%	1.05[0.71,1.56]
Subtotal (95% CI)	149	153		-			85.36%	1.05[0.71,1.56]
Total events: 38 (Milnacipran), 37 (SSRI	s)							
Heterogeneity: Not applicable								
Test for overall effect: Z=0.27(P=0.79)								
Total (95% CI)	188	184		-			100%	1.06[0.73,1.52]
Total events: 46 (Milnacipran), 43 (SSRI	s)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0, df=1(P=	0.99); I <sup>2</sup> =0%							
Test for overall effect: Z=0.29(P=0.77)								
Test for subgroup differences: Chi <sup>2</sup> =0, c	lf=1 (P=0.99), I <sup>2</sup> =0%							
		Favours SSRIs	0.1 0.2	0.5 1	2 5	10	Favours Milnacipran	

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	3	342	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.01]
1.1 Milancipran vs Imipramine	1	109	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.24]
1.2 Milnacipran vs Amitripty- line	2	233	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.51, 1.04]
2 Milancipran vs SSRIs	3	468	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.86, 1.69]
2.1 Milnacipran vs Fluvoxam- ine	1	127	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.83, 2.79]
2.2 Milnacipran vs Fluoxetine	1	300	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.96, 1.87]
2.3 Milnacipran vs Paroxetine	1	41	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.47, 1.40]

## Comparison 29. Subgroup analysis: Response at early phase [1-4 weeks]-Inpatient

# Analysis 29.1. Comparison 29 Subgroup analysis: Response at early phase [1-4 weeks]-Inpatient, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs		Risk Rati	io		Weight	Risk Ratio
	n/N	n/N		M-H, Random,	95% CI			M-H, Random, 95% CI
29.1.1 Milancipran vs Imipramine								
Van Amerongen 2002	24/53	30/56					46.41%	0.85[0.58,1.24]
Subtotal (95% CI)	53	56					46.41%	0.85[0.58,1.24]
Total events: 24 (Milnacipran), 30 (To	CAs)							
Heterogeneity: Not applicable								
Test for overall effect: Z=0.86(P=0.39	)							
29.1.2 Milnacipran vs Amitriptylin	e							
Annseau 1989a	29/97	21/49					34.57%	0.7[0.45,1.09]
Annseau 1989c	13/44	16/43			-		19.01%	0.79[0.44,1.45]
Subtotal (95% CI)	141	92					53.59%	0.73[0.51,1.04]
Total events: 42 (Milnacipran), 37 (To	CAs)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.12, df	=1(P=0.73); I <sup>2</sup> =0%							
Test for overall effect: Z=1.73(P=0.08	3)							
Total (95% CI)	194	148		•			100%	0.78[0.6,1.01]
Total events: 66 (Milnacipran), 67 (To	CAs)							
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.42, df	=2(P=0.81); I <sup>2</sup> =0%							
Test for overall effect: Z=1.85(P=0.06	i)							
Test for subgroup differences: Chi <sup>2</sup> =0	0.3, df=1 (P=0.58), I <sup>2</sup> =0%	Ď						
		Favours TCAs	0.2	0.5 1	2	5	Favours Milnacipran	

# Analysis 29.2. Comparison 29 Subgroup analysis: Response at early phase [1-4 weeks]-Inpatient, Outcome 2 Milancipran vs SSRIs.

Study or subgroup	Milnacipran	SSRIs	Risk Ratio	Weight	<b>Risk Ratio</b>
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
29.2.1 Milnacipran vs Fluvoxamine					
Annseau 1991c	32/86	10/41	+	23.78%	1.53[0.83,2.79]
Subtotal (95% CI)	86	41		23.78%	1.53[0.83,2.79]
Total events: 32 (Milnacipran), 10 (SSR	ls)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.37(P=0.17)					
29.2.2 Milnacipran vs Fluoxetine					
Guelfi 1998a	83/200	31/100		49.06%	1.34[0.96,1.87]
Subtotal (95% CI)	200	100	◆	49.06%	1.34[0.96,1.87]
Total events: 83 (Milnacipran), 31 (SSR	ls)				
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
29.2.3 Milnacipran vs Paroxetine					
Shinkai 2004	10/20	13/21		27.16%	0.81[0.47,1.4]
Subtotal (95% CI)	20	21		27.16%	0.81[0.47,1.4]
Total events: 10 (Milnacipran), 13 (SSR	ls)				
Heterogeneity: Not applicable					
Test for overall effect: Z=0.76(P=0.45)					
Total (95% CI)	306	162	•	100%	1.2[0.86,1.69]
Total events: 125 (Milnacipran), 54 (SS	RIs)				
Heterogeneity: Tau <sup>2</sup> =0.03; Chi <sup>2</sup> =3.05, d	f=2(P=0.22); I <sup>2</sup> =34.48	3%			
Test for overall effect: Z=1.06(P=0.29)					
Test for subgroup differences: Chi <sup>2</sup> =2.9	96, df=1 (P=0.23), l <sup>2</sup> =3	32.48%			
		Favours SSRIs 0.1	0.2 0.5 1 2 5 1	<sup>10</sup> Favours Milnaciprar	1

# Comparison 30. Subgroup analysis: Response at acute phase [6-12 weeks]-Inpatient

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Milnacipran vs TCAs	2	209	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.81, 1.31]
1.1 Milnacipran vs Imipramine	2	209	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.81, 1.31]

# Analysis 30.1. Comparison 30 Subgroup analysis: Response at acute phase [6-12 weeks]-Inpatient, Outcome 1 Milnacipran vs TCAs.

Study or subgroup	Milnacipran	TCAs			Ri	isk Ra	tio			Weight	<b>Risk Ratio</b>
	n/N	n/N			M-H, Ra	ndom	, 95% CI				M-H, Random, 95% Cl
30.1.1 Milnacipran vs Imipramine											
Lopez-Ibor 2004	20/51	20/49			_	-	_			25.39%	0.96[0.59,1.55]
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	



Study or subgroup	Milnacipran	TCAs			Ri	sk Rat	io			Weight	<b>Risk Ratio</b>
	n/N	n/N			M-H, Ra	ndom,	95% CI				M-H, Random, 95% CI
Van Amerongen 2002	35/53	35/56				+				74.61%	1.06[0.8,1.4]
Subtotal (95% CI)	104	105				+				100%	1.03[0.81,1.31]
Total events: 55 (Milnacipran), 55 (	TCAs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.12, c	lf=1(P=0.73); I <sup>2</sup> =0%										
Test for overall effect: Z=0.25(P=0.8	;)										
Total (95% CI)	104	105				•				100%	1.03[0.81,1.31]
Total events: 55 (Milnacipran), 55 (1	TCAs)										
Heterogeneity: Tau <sup>2</sup> =0; Chi <sup>2</sup> =0.12, c	lf=1(P=0.73); I <sup>2</sup> =0%										
Test for overall effect: Z=0.25(P=0.8	3)										
		Favours TCAs	0.1	0.2	0.5	1	2	5	10	Favours Milnacipran	

## ADDITIONAL TABLES

### Table 1. Comparative efficacy and acceptability of milnacipran for acute major depression

	MTM (Cipriani 2009a)	Current review	
	OR (95%CI)	OR (95%CI)	Relative ratio of OR- s <sup>a</sup>
Efficacy (response rate)			
Fluvoxamine	1.03 (0.73-1.47)	1.76 (0.81-3.83)	0.59
Fluoxetine	1.01 (0.76-1.35)	0.93 (0.55-1.58)	1.09
Paroxetine	1.00 (0.74-1.33)	0.93 (0.59-1.47)	1.08
Sertraline	0.81 (0.60-1.11)	3.83 (0.90-16.26)	0.21
Acceptability (total dropout rate)			
Fluvoxamine	0.85 (0.57-1.32)	0.82 (0.36-1.86) <sup>b</sup>	1.03
Fluoxetine	1.03 (0.76-1.45)	1.02 (0.71-1.46)	1.01
Paroxetine	0.94 (0.68-1.31)	0.88 (0.50-1.54)	1.07
Sertraline	1.17 (0.84-1.72)	1.70 (0.57-5.05) <sup>b</sup>	0.69

For efficacy, OR higher than 1 favour milnacipran. For acceptability, OR lower than 1 favour milnacipran .

<sup>a</sup>ORs of the current review as reference.

<sup>b</sup>Two trials comparing milnacipran with fluvoxamine (Annseau 1991c) and with sertraline (Shinkai 2004) were excluded because these 4-week trials were not included in MTM.

Abbreviations: MTM=multiple-treatments meta-analysis, OR=odds ratio, CI=confidence interval

#### HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2009

Date	Event	Description
20 April 2009	Amended	Changed title from 'Milnacipran versus types of pharmacother- apy for depression' to 'Milnacipran versus other antidepressive agents for depression'
8 October 2008	Amended	Converted to new review format.
20 September 2008	Amended	Substantive amendment

### CONTRIBUTIONS OF AUTHORS

AN, NW, TAF, AC, CB, RC and HMG conceived and designed the review. AN, NW and HMG identified and acquired reports of trials, and contacted authors of trials and pharmaceutical industries for additional information. AN and NW extracted data. AN, NW and TAF analysed and interpreted the data. AC, CB and HMG contributed to the interpretation of the data. AN wrote the first draft of the manuscript. All authors contributed to make critical revision of the manuscript for important intellectual content and have approved the final version of the manuscript.

#### DECLARATIONS OF INTEREST

#### AN, NW, AC, CB, HMG, RC: none declared

TAF has received several research grants and fees for speaking from some pharmaceutical companies, which market antidepressants (paroxetine, fluvoxamine, milnacipran, trazodone, mianserin), antipsychotics (risperidone, olanzapine, quetiapine, paliperidone, asenapine), nootropics (donepezil) and anxiolytics (loflazepate, tandospirone).

#### DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

#### INDEX TERMS

#### Medical Subject Headings (MeSH)

Antidepressive Agents [adverse effects] [\*therapeutic use]; Cyclopropanes [adverse effects] [\*therapeutic use]; Depressive Disorder, Major [\*drug therapy]; Milnacipran; Randomized Controlled Trials as Topic; Selective Serotonin Reuptake Inhibitors [adverse effects] [\*therapeutic use]

#### **MeSH check words**

Humans