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Venlafaxine versus other anti-depressive agents for depression

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

1. To determine the efficacy of venlafaxine in comparison with other anti-depressive agents in alleviating the acute symptoms of major depressive disorder.
2. To review acceptability of treatment with venlafaxine in comparison with other anti-depressive agents.
3. To investigate the adverse effects of venlafaxine in comparison with other anti-depressive agents.

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CONTRIBUTIONS OF AUTHORS

All co-authors contributed to the development and drafting of the protocol.

DECLARATIONS OF INTEREST

AC, CB, AS, HM, RC, IO: none declared
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NW has received speaking fees from GlaxoSmithKline, but his speech did not deal with pharmacological agents but with methodology of evidence-based medicine.

This review is one of a number of separate reviews examining head to head comparisons as part of the multiple Meta-Analyses of New Generation Antidepressants (MANGA) Study. These individual reviews will then be combined in a mega-review using multiple treatment model methodology.

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BACKGROUND

Major depression is generally diagnosed when a persistent and unreactive low mood and loss of all interest and pleasure are accompanied by a range of symptoms including appetite loss, insomnia, fatigue, loss of energy, poor concentration, psychomotor symptoms, inappropriate guilt and morbid thoughts of death (APA 1994). It was the third leading cause of burden among all diseases in the year 2002 and it is expected to show a rising trend during the coming 20 years (WHO 2006). This condition is associated with marked personal, social and economic morbidity, loss of functioning and productivity, and creates significant demands on service providers in terms of workload (NICE 2004).

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 2004). Amongst ADs many different agents are available, including tricyclics (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs, such as venlafaxine, duloxetine and milnacipran), and other newer agents (mirtazapine, reboxetine, bupropion).

During the last 20 years, ADs consumption has dramatically risen in western countries, 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 2000), and there is evidence of similar efficacy (Anderson 2000; Geddes 2000; Williams 2000). However, head-to-head comparison provided contrasting findings. Amitriptyline, for example, may have the edge over SSRIs in terms of efficacy (Guaiana 2003), and individual SSRIs and SNRIs may differ in terms of efficacy and tolerability (Puech 1997; Smith 2002; Hansen 2005; Cipriani 2006).

Venlafaxine hydrochloride is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitor of dopamine reuptake. Venlafaxine has no significant affinity for muscarinic, histaminergic, or adrenergic receptors in vitro. In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolites by CYP2D6 and CYP3A4, and that venlafaxine is a relatively weak inhibitor of CYP2D6. Thus, the potential exists for a drug interaction between drugs that inhibit CYP-mediated metabolism and venlafaxine. The efficacy of venlafaxine as a treatment for major depressive disorder has been established in 5 placebo-controlled, short-term trials (www.fda.gov). Four of these were 6-week trials in outpatients meeting DSM-III or DSM-III-R criteria for major depression: two involving dose titration with venlafaxine in a range of 75 to 225 mg/day, the third involving fixed venlafaxine doses of 75, 225, and 375 mg/day, and the fourth involving doses of 25, 75, and 200 mg/day. The fifth was a 4-week study of inpatients meeting DSM-III-R criteria for major depression with melancholia whose venlafaxine doses were titrated in a range of 150 to 375 mg/day. In these 5 studies, venlafaxine was shown to be significantly superior to placebo on the Hamilton Depression Rating Scale and Clinical Global Impression. Data from the 2 fixed-dose outpatient studies were suggestive of a dose-response relationship in the range of 75 to 225 mg/day. There was no suggestion of increased response with doses greater than 225 mg/day; however, venlafaxine treatment has been associated with sustained

increases in blood pressure in some patients. Nineteen percent (537/2897) of venlafaxine patients in phase II and phase III depression studies discontinued treatment due to an adverse event. The more common events (incidence of 1% or greater) leading to discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included nausea, somnolence, insomnia, dizziness and urogenital abnormal ejaculation. The most commonly observed adverse events associated with the use of venlafaxine (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (ie, incidence for venlafaxine at least twice that for placebo) were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, and blurred vision as well as abnormal ejaculation/orgasm and impotence in men. Venlafaxine is among the best sold antidepressants in the world recently. For example, in the EU in 2005, the antidepressant market was worth $4.71 billion and venlafaxine had the greatest market share of 21.0%, followed by sertraline (16.0%).

To shed light on the field of AD trials and treatment of major depressive disorder, a group of researchers agreed to join forces under the rubric of the Meta-Analyses of New Generation Antidepressants Study Group (MANGA Study Group) to systematically review all available evidence for each specific newer antidepressant. We have up to now completed an individual review for fluoxetine (Cipriani 2005), published the protocols for sertraline (Malvini 2006), fluvoxamine (Omori 2006) and mirtazapine (Watanabe 2006), and a number of other reviews are now underway. Thus, the aim of the present review is to assess the evidence for the efficacy and tolerability of venlafaxine in comparison with TCAs, MAOIs, other SSRIs and newer agents in the acute-phase treatment of major depression.

OBJECTIVES

1. To determine the efficacy of venlafaxine in comparison with other anti-depressive agents in alleviating the acute symptoms of major depressive disorder.
2. To review acceptability of treatment with venlafaxine in comparison with other anti-depressive agents.
3. To investigate the adverse effects of venlafaxine in comparison with other anti-depressive agents.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials comparing venlafaxine with all other active anti-depressive agents as monotherapy in the acute phase treatment of depression will be included. Quasi-randomised trials, such as those allocating by using alternate days of the week, will be excluded. For trials which have a crossover design only results from the first randomisation period will be 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 will be included. Most recent studies are likely to have used DSM-IV (APA 1994) or ICD-10 (WHO 1992) criteria. Older 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 will be excluded. On the other hand, studies using Feighner criteria or Research Diagnostic Criteria will be included. Studies in which less than 20% of the participants may be suffering from bipolar depression will be included, but the validity of this decision will be examined in the sensitivity analysis.

A concurrent secondary diagnosis of another psychiatric disorder will not be considered as exclusion criteria. A concurrent primary diagnosis of Axis I or II disorders will be an exclusion criteria. AD trials in depressive patients with a serious concomitant medical illness will be excluded.

Types of interventions—Venlafaxine in comparison with other anti-depressive agents, including conventional tricyclic/heterocyclic ADs, SSRIs (fluoxetine, sertraline, fluvoxamine, citalopram, paroxetine, escitalopram), SNRIs (duloxetine, milnacipran), MAOIs or newer agents (mirtazapine, bupropion, reboxetine) or non-conventional (herbal products - i.e. Hypericum) anti-depressive agents in the treatment of acute depression.

Trials in which venlafaxine is compared to another type of psychopharmacological agent i.e. anxiolytics, anti-convulsants, antipsychotics or mood-stabilizers will be excluded. Trials in which venlafaxine is used as an augmentation strategy will be excluded.

Types of outcome measures—Our primary efficacy outcome measure is:

1. Number of patients who responded to treatment, showing a reduction of at least 50% on the HAM-D (Hamilton 1960) or MADRS (Montgomery 1979), or any other depression scale, or “much or very much improved” (score 1 or 2) on CGI-Improvement. All response rates will be calculated out of the total number of randomised patients. Where more than one criterion is provided, we will prefer the former criterion for judging response. We will use the first criterion whenever possible, even when we need to impute SDs or response rates according to the procedures described below. We will apply the intention-to-treat (ITT) analyses, whereby all the dropouts not included in the analyses will be considered non-responders. We will examine the validity of this decision in the sensitivity analyses by applying worst and best case scenarios (see Methods of the review).

   When studies report response rates at various time points of the trial, we have decided a priori to subdivide the treatment indices as follows:

   a. Early response: between 1 and 4 weeks, the time point closest to 2 weeks will be given preference.

   b. Acute phase treatment response: between 6 and 12 weeks, the time point given in the original study as the study endpoint is given preference.

   c. Follow-up response: between 4 and 6 months, the time point closest to 24 weeks will be given preference.

The acute phase treatment response, i.e. between 6 and 12 weeks, will be our primary outcome of interest.

Our secondary efficacy outcome measures include:

1. Number of patients who will achieve remission. The cut-off point for remission will be set a priori (i) at 7 or less on the 17-item HAM-D and at 8 or less for all the other longer versions of HAM-D, or (ii) at 10 or less on the MADRS (Zimmerman 2004), or (iii) "not ill or borderline mentally ill" (score 1 or 2) on CGI-Severity (Guy 1970). All remission rates will be calculated out of the total number of randomised patients. Where two or more are provided, we prefer the first criteria for judging remission. We will apply the ITT analyses, whereby all the dropouts not included in the analyses will be considered non-remitters. We will examine the validity of this decision in the sensitivity analyses by applying worst and best case scenarios (see Methods of the review).
2. Change scores from baseline to the time point in question (early response, acute phase response, or follow-up response as defined above) on Hamilton Depression Scale (Hamilton 1960), or Montgomery-Asberg Depression Scale (Montgomery 1979), or any other depression scale. We will apply a looser form of ITT analyses, whereby all the patients with at least one post-baseline measurement are represented by their last observations carried forward.
3. Social adjustment, social functioning including the Global Assessment of Function (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.

Acceptability will be evaluated using the following outcome measures:

1. Number of patients who dropped out during the trial as a proportion of the total number of randomised patients - Total drop out rate.
2. Number of patients who dropped out due to inefficacy during the trial as a proportion of the total number of randomised patients
    - Drop out rates due to inefficacy.
3. Number of patients who dropped out due to side effects during the trial as a proportion of the total number of randomised patients
    - Drop out rates due to side effects.

Tolerability will be evaluated using the following outcome measures:

1. Total number of patients experiencing at least some side effects.
2. Total number of patients experiencing the following specific side effects will be sought for:
    a. Sleepiness/drowsiness.

b. Insomnia.

c. Dry mouth.

d. Constipation.

e. Urination problem.

f. Hypotention.

g. Agitation/anxiety.

h. Suicide wishes/gestures/attempts.

i. Completed suicide.

j. Vomiting/nausea.

k. Diarrhoea.

In order not to miss any relatively rare or unexpected yet important side effects, in the data extraction phase, we will collect all side effects data reported in the literature and will discuss ways to summarise them post hoc.

Search methods for identification of studies

(1) Electronic Databases—CCDANCTR-Studies will be searched using the following search strategy:

Diagnosis = Depress* or Dysthymi* or “Adjustment Disorder*” or “Mood Disorder*” or “Affective Disorder” or “Affective Symptoms”

and

Intervention = Venlafaxine

CCDANCTR-References will be 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 = Venlafaxine

(2) Handsearches—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) will be hand-searched for published, unpublished and ongoing controlled trials. Appropriate journals and conference proceedings relating to venlafaxine

treatment for depression have already been hand-searched and incorporated into the CCDANCTR databases.

(3) Personal communication—Pharmaceutical companies and experts in this field will be asked if they know of any study which meets the inclusion criteria of this review.

(4) Reference checking—Reference lists of the included studies, previous systematic reviews and major textbooks of affective disorder written in English will be checked for published reports and citations of unpublished research. The references of all included studies will be checked via Science Citation Index for articles which have cited the included study.

Data collection and analysis

(1) Selection of trials—Studies relating to venlafaxine generated by the electronic search of the CCDANCTR-Studies will be scanned by HMG. Those studies which meet the following rough inclusion criteria will constitute the preliminary list and their full texts will be retrieved. The rough inclusion criteria are:

- **a.** Randomised trial
- **b.** Comparing venlafaxine against any other antidepressant
- **c.** Patients with major depression, regardless of the diagnostic criteria used.

Studies relating to venlafaxine generated by the search strategies of the CCDANCTR-References and the other complementary searches will be checked by HMG and another independent review author to see if they meet the rough inclusion criteria, firstly based on the title and abstracts. All the studies rated as possible candidates by either of the two review authors will be added to the preliminary list and their full texts will be retrieved. All the full text articles in this preliminary list will then be assessed by two independent review authors to see if they meet the strict inclusion criteria. If the raters disagree the final rating will be made by consensus with the involvement (if necessary) of another member of the review group. Non-congruence in selection of trials will be reported as percentage disagreement. Considerable care will be taken to exclude duplicate publications.

(2) Quality assessment—Two independent review authors will independently assess trial quality in accordance with the Cochrane Handbook (Higgins 2005). This pays particular attention to the adequacy of the random allocation concealment and double blinding (6.11 of the Handbook). Studies will be given a quality rating of A (adequate), B (unclear), and C (inadequate) according to these two items. The studies which score A or B on these criteria will constitute the final list of included studies. In addition, a general appraisal of study quality will be made by assessing key methodological issues such as completeness of follow-up and reporting of study withdrawals. Where inadequate details of allocation concealment and other characteristics of trials are provided, the trial authors will be contacted in order to obtain further information.

If the raters disagree the final rating will be made by consensus with the involvement (if necessary) of another member of the review group. Non-congruence in quality assessment will be reported as percentage disagreement.

The ratings will also be compared with those in the completed reviews of individual antidepressants in the Cochrane Library. If there are any discrepancies, they will be fed back to the authors of the completed reviews.

(3) Data extraction—One review author will first extract 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, venlafaxine as investigational drug or as comparator drug, sponsorship) and outcome measures of interest from the included studies. The results will be compared with those in the completed reviews of individual antidepressants in the Cochrane Library. If there are any discrepancies, a second review author will intervene and the agreed-upon results will be used in the review as well as fed back to the authors of the completed reviews.

If the trial is a three (or more)-armed trial involving a placebo arm, the data will be extracted from the placebo arm as well.

(4) Data analysis—Data will be entered into RevMan 4.2.10 software by two review authors (double data entry). Responders and remitters to treatment will be calculated on the ITT basis: drop-outs will always be included in this analysis. Where participants have withdrawn from the trial before the endpoint, it will be assumed they would have experienced the negative outcome by the end of the trial (e.g. failure to respond to treatment). When there are missing data and the method of “last observation carried forward” (LOCF) has been used to do an ITT analysis, then the LOCF data will be used, with due consideration of the potential bias and uncertainty introduced.

For dichotomous, or event-like data, odds ratios (OR) will be calculated with 95% confidence intervals. The primary analysis will use a random effects model OR, which had the highest generalisability in our empirical examination of summary effect measures for meta-analyses (Furukawa 2002a). The robustness of this summary measure will be routinely examined by checking the fixed effect model OR and the random effects model RR. Material differences between the models will be reported.

Continuous data will be analysed using weighted mean differences (with 95% confidence intervals) or standardised mean differences (where different measurement scales are used) using the random effects model. Fixed effect analyses will be 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 will be reported.

Skewed data and non-quantitative data will be presented descriptively. An outcome whose minimum score is zero can be considered skewed when the mean is smaller than twice the SD.

Heterogeneity between studies will be investigated by the I-squared statistic (Higgins 2003) (I-squared equal to or more than 50% will be considered indicative of heterogeneity) and by visual inspection of the forest plots.

(5) Missing data—When dichotomous or continuous outcomes are not reported, authors will be asked to supply the data. When only the SE or t-statistics or p values are reported, SDs are 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/ remission rates will be calculated according to the validated imputation methods (Furukawa 2005; Furukawa 2006). We will examine the validity of this imputations in the sensitivity analyses.

(6) Pre-planned subgroup analyses—Subgroup analyses should be performed and interpreted with caution because multiple analyses will lead to false positive conclusions (Oxman 1992). However, we will perform the following subgroup analyses, where possible, for the following a priori reasons:

- **a.** Venlafaxine dosing (fixed low dosage, fixed standard dosage, fixed high dosage; flexible low dosage, flexible standard dosage, flexible high dosage), because there is evidence to suspect that low dosage antidepressant may 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 may affect estimates of treatment effectiveness (Khan 2003). In the case of venlafaxine, based on the Defined Daily Dosage by World Health Organisation (WHO), low dosage refers to <100, standard dosage to >100 but <200, and high dosage to >200 mg/day.
- **b.** Comparator dosing (low effective range, medium to high effective range), as it is easy to imagine that there are greater chances of completing the study on the experimental drug than on the comparator drug that is increased to the maximum dosage.
- **c.** Depression severity (Severe major depression, moderate/mild major depression).
- **d.** Treatment settings (psychiatric inpatients, psychiatric outpatients, primary care).
- **e.** Elderly patients (>65 years of age), separately from other adult patients.

(7) Funnel plot analysis and sensitivity analyses—Funnel plot analysis will be performed to check for existence of small study effects including publication bias.

The following sensitivity analyses are planned a priori. By limiting the studies to be included to those with higher quality, we will examine if the results change, and check for the robustness of the observed findings.

- **a.** Excluding trials with unclear concealment of random allocation and/or unclear double blinding.
- **b.** Excluding trials whose drop out rate is greater than 20%.

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c. 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 negative outcome).

d. 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).

e. Examination of "wish bias" by comparing venlafaxine as investigational drug vs venlafaxine as comparator, as there is evidence to suspect that a new antidepressant might perform worse when used as a comparator than when used as an experimental agent (Barbui 2004).

f. Excluding studies funded by the pharmaceutical company marketing venlafaxine. This sensitivity analysis is 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 have been increasing over the past 20 years (Buchkowsky 2004).

If subgroups within any of the subgroup or sensitivity analyses turn out to be significantly different from one another, we will run meta-regression for exploratory analyses of additive or multiplicative influences of the variables in question. Our routine application of random effects and fixed effect models as well as our secondary outcomes.

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WHAT'S NEW

Date	Event	Description
2 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 2, 2007

Date	Event	Description
21 December 2006	New citation required and conclusions have changed	Substantive amendment

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* *Indicates the major publication for the study*

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