Paroxetine 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 paroxetine in comparison with other anti-depressive agents in alleviating the acute symptoms of major depressive disorder.
2. To review acceptability of treatment with paroxetine in comparison with other anti-depressive agents.
3. To investigate the adverse effects of paroxetine 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, AV, HM, RC: 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.

NOTES

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).

Paroxetine hydrochloride is a component of the class of AD known as SSRIs. In vitro studies suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine and dopamine neuronal reuptake. Paroxetine metabolism is mediated in part by CYP2D6. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions, showing that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine and risperidone. Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment; thus, it has been suggested to reduce the initial dosage in patients with severe renal or hepatic impairment, and also in the elderly.

The efficacy of paroxetine as a treatment for major depressive disorder has been established in 6-week placebo-controlled studies of patients with major depressive disorder (aged 18 to 73). In the clinical trials patients were dosed in a range of 20 to 50 mg/day. In these studies, paroxetine was shown to be more effective than placebo in treating major depressive disorder by the Hamilton Depression Rating Scale (Hamilton 1960) and the Clinical Global Impression-Severity of Illness (Guy 1970). The most commonly observed adverse events associated with the use of paroxetine (incidence of 5% or greater and incidence at least twice that for placebo) were asthenia, sweating, nausea, decreased appetite, somnolence, dizziness,

insomnia, tremor, nervousness, ejaculatory disturbance and other male genital disorders. However, recently some concerns have risen about the tolerability profile of paroxetine. In adults with major depressive disorder (all ages), there was a statistically significant increase in the frequency of suicidal behavior in patients treated with paroxetine compared with placebo (11/3,455 [0.32%] versus 1/1,978 [0.05%]); all of the events were suicide attempts (www.gsk.com). Moreover, in terms of teratogenetic and non-teratogenetic effects, epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects and persistent pulmonary hypertension of the newborn.

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 2007), 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 paroxetine 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 paroxetine in comparison with other anti-depressive agents in alleviating the acute symptoms of major depressive disorder.
2. To review acceptability of treatment with paroxetine in comparison with other anti-depressive agents.
3. To investigate the adverse effects of paroxetine in comparison with other anti-depressive agents.

METHODS

Criteria for considering studies for this review

Types of studies—Randomised controlled trials comparing paroxetine with all other active anti-depressive agents as monotherapy in the acute phase treatment of depression will be included. Quasi-randomized 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—Paroxetine in comparison with other anti-depressive agents, including conventional tricyclic/heterocyclic ADs, SSRIs (fluoxetine, sertraline, fluvoxamine, citalopram, escitalopram), SNRIs (venlafaxine, 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 paroxetine is compared to another type of psychopharmacological agent i.e. anxiolytics, anti-convulsants, antipsychotics or mood-stabilizers will be excluded. Trials in which paroxetine 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.

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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 summarize 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 = Paroxetine

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 = Paroxetine

(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 paroxetine 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 paroxetine 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 paroxetine against any other antidepressant.
- **c.** Patients with major depression, regardless of the diagnostic criteria used.

Studies relating to paroxetine 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 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 with-drawals. Where inadequate details of allocation concealment and other characteristics of trials are provided, the 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, paroxetine 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 reviewer 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 4.2.9 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.** Paroxetine 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 paroxetine, 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%.
- **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 paroxetine as investigational drug vs paroxetine 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 paroxetine. 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 are increasing over 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 metaregression 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 of remission rates and continuous severity measures may be considered additional forms of sensitivity analyses.

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SOURCES OF SUPPORT

Internal sources

- Department of Medicine and Public Health, Section of Psychiatry and Clinical Psychology, University of Verona, Italy.

External sources

- No sources of support supplied

FEEDBACK

June 2007

Summary

Feedback 1. The protocol does not refer to dosage change in the studies that will be included, or how data on the effects of dosage change and its timing will be analysed. A major problem with paroxetine are adverse effects early during treatment and withdrawal symptoms with reduction of dosage, omission of doses, and cessation of treatment. Many RCTs have not examined these aspects, and the review must state how far they have done so.

Feedback 2. Because RCTs are not the main source of information about harmful effects it is important to look at other types of study, including caseseries, in reviewing the evidence. The methods of reviewing adverse effects are discussed in detail in the Handbook for Reviews of Interventions, Appendix 6b (which will be updated and incorporated in theforthcoming 5th edition in the body of the Handbook).

Feedback 3. The evidence that treatment with paroxetine and other SSRIs or withdrawal from it can cause violent behaviour, albeit rarely, should also be considered in the protocol. It has been summarised by Healy, Herxheimer and Menkes. Antidepressants and violence: problems at the interface of medicine and law. PLoS Medicine 2006; 3(9):e372

Reply

Feedback 1—We agree with Dr. Herxheimer that all issues relating to dose change are really important clinical questions. Unfortunately, most RCTs have not reported anything about that. However, in order to be able to show all available information about safety/ tolerability issues, in the protocol we stated that that “in order not to miss any relatively rare or unexpected yet important side effects, in the extraction phase, we will collect all side effects data reported in literature and will discuss ways to summarize them post hoc.”

Feedback 2—RCTs are not the main source of information especially about side effects, because rare adverse events are unlikely to be observed in clinical trials. Furthermore, a through investigation should require the inclusion of observational evidence (cohort studies, case control and even case series). However, the main aim of the present review is to compare head-to-head paroxetine with other active treatments for depression. Thus, we decided to focus only on randomised evidence to reduce the risk of selection bias.

Feedback 3—This is an very interesting paper. We were aware of this issue (and other similar issues) related to tolerability profile of antidepressant drugs (and especially paroxetine). This is the reason why we reported in the protocol that we are going to collect and report in the full text review all available information “about rare or unexpected yet important side effects.”

Contributors

Andrew Herxheimer

Submitter agrees with default conflict of interest statement:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

WHAT’S NEW

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

HISTORY

Protocol first published: Issue 2, 2007

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* *Indicates the major publication for the study*