Which antidepressants have demonstrated superior efficacy? A review of the evidence

Stuart A. Montgomery[a], David S. Baldwin[b], Pierre Blier[f], Naomi A. Fineberg[c], Siegfried Kasper[h], Malcolm Lader[d], Raymond W. Lam[g], Jean-Pierre Lépine[i], Hans-Jürgen Möller[k], David J. Nutt[e], Frederic Rouillon[j], Alan F. Schatzberg[l] and Michael E. Thase[m]

A review of published evidence of superior efficacy of a particular antidepressant in major depressive disorder may assist clinicians in making considered treatment choices. To identify such candidates, an international group of experts met to assess published evidence (identified through searches in *Medline* and *Embase* databases and discussions with experts in the field) from randomized, controlled trials and meta-analyses comparing two antidepressants under conditions of fair comparison. Criteria were defined to judge the strength of evidence. Two pivotal studies in moderate-to-severe major depressive disorder that demonstrate superiority on the primary efficacy measure, or alternatively one pivotal study supported by consistent results from meta-analyses, was considered to constitute evidence for definite superiority. Three antidepressants met these criteria: clomipramine, venlafaxine, and escitalopram. Three antidepressants were found to have probable superiority: milnacipran, duloxetine, and mirtazapine. Only escitalopram was found to have definite superiority in the treatment of severe depression; probable superiority was identified for venlafaxine and possible superiority for milnacipran and clomipramine. This review of published data found evidence that only a very few antidepressants are shown to be more effective than others. *Int Clin Psychopharmacol* 22:323–329 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]Imperial College School of Medicine, University of London, [b]Clinical Neuroscience Division, University of Southampton, [c]Department of Psychiatry, School of Clinical Medicine, University of Cambridge, Cambridge, [d]Institute of Psychiatry, Kings College, London, [e]Psychopharmacology Unit, University of Bristol, UK, [f]Institute of Mental Health Research, University of Ottawa, Ontario, [g]University of BC, Vancouver, Canada, [h]Department of General Psychiatry, University of Vienna, Austria, [i]Hôpital Fernand Vidal, [j]St Anne Hospital, Paris, France, [k]Psychiatric Hospital, Ludwig-Maximilians-University, Munich, Germany, [l]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Paulo Alto, California and [m]University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA

Correspondence to Stuart A Montgomery, PO Box 8751, London W13 8WH, UK
E-mail: Stuart@samontgomery.co.uk

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Introduction

A group of experts met to discuss the data providing evidence for the potential superior efficacy of one antidepressant compared with others.

A preliminary review of the literature was conducted to identify possible candidate antidepressants with some evidence of superiority in clinical studies. The decision was taken to rely on evidence from published randomized controlled trials (RCT) in major depressive disorder (MDD) or the equivalent in which two antidepressants were compared with each other. Studies were accepted, whether or not placebo controlled, providing that recognized effective doses (as reflected in the data sheets of each antidepressant) were used for both the candidate and comparator antidepressants. Unpublished data, when available, were taken into account but were accorded a lower level of evidence. The search for relevant studies was based on a search of *Medline* and *Embase* databases, a manual search of bibliographies of published papers and a discussion with experts in the field.

Particular attention was paid to adherence to the conditions of fair comparison, which were regarded as important. An example of exclusion by this criterion is the study that reported that sertraline was superior to desipramine in obsessive compulsive disorder concurrent with MDD (Hoehn-Saric *et al.*, 2000). This study did not meet the criterion of fair comparison as only selective serotonin reuptake inhibitors (SSRIs) have been shown to be effective in obsessive compulsive disorder and the result could not therefore be accepted as showing superiority for sertraline in MDD.

Several factors were taken into account. These included:

(a) The validity of the outcome variable, such as a change in the rating scale score,

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(b) The usefulness of clinical measures, such as those of response and remission,
(c) Methods of statistical analysis,
(d) Speed of onset of action, and accordingly, time course of response,
(e) Usefulness of combining data as compared with meta-analyses,
(f) Types and subgroups of patients, particularly severely depressed patients.

Criteria used to judge the strength of evidence

The evidence of superiority for an antidepressant was categorized:

Class A evidence

The most convincing level of evidence was accorded to data from an RCT that on the primary efficacy analysis under conditions of fair comparison showed a significant advantage in moderate or severe MDD of one antidepressant over another at approved doses. A single positive study demonstrating a significant advantage of one antidepressant over another in a head-to-head comparison was taken to indicate probable superiority. Two positive RCTs showing significant superiority in efficacy on the primary efficacy measure were taken to show clear-cut or definite superiority. The evidence is more persuasive if the data come from RCTs of a reasonable size compatible with those needed to find a difference from placebo, as very small studies are prone to problems with replication. Class A evidence that finds a treatment difference in individual studies of the same order as the drug placebo difference used to establish efficacy in licensing is by definition clinically relevant.

Class B evidence

The demonstration of the superiority of one antidepressant over other antidepressants on the primary efficacy measure in a meta-analysis of head-to-head comparisons in RCTs in moderate-to-severe MDD at approved doses and under conditions of fair comparison was categorized as Class B evidence. Meta-analyses of studies are almost always, by definition, carried out *post hoc* so that the evidence could be regarded as hypothesis generating rather than confirmatory.

Meta-analyses are subject to potential imbalances in populations studied, differing severities, and differing methodology employed in each study. Moreover, there is the risk that a significant difference reported in a large meta-analysis might reflect a small or very small difference between the treatments, which may not be clinically relevant. For these reasons, the evidence from meta-analyses is regarded as less strong than evidence from well-designed, individual controlled studies. The analysis of subgroup efficacy, for example responders or remitters, reported in some meta-analyses, although interesting, is less convincing than the conventional change from baseline on the pivotal efficacy measure.

It is possible that positive results from meta-analyses might be affected by including only the results from positive studies. Contradictory results from more comprehensive meta-analyses including more studies would weaken the claim for superiority. Consistent evidence of superiority from more than one meta-analysis, although the same datasets are usually included, was taken to provide evidence of probable superior efficacy.

Evidence of superiority from one Class A study showing superiority allied with consistent evidence of superiority from meta-analysis was taken as definite evidence of superior efficacy.

Class C evidence

Evidence from uncontrolled studies or from RCTs that did not meet all the criteria for Class A evidence was designated Class C evidence. Class C evidence is regarded only as hypothesis generating, providing evidence at most of possible superiority. Open studies and case reports were discounted.

The experts considered the available evidence indicating that an antidepressant might possess superior efficacy and identified whether the evidence met criteria for possible, probable or definite superior efficacy. This review of antidepressants with superior efficacy may assist clinicians in making considered treatment choices.

Superior antidepressant candidates

The candidate antidepressants identified on the basis of published claims that they might have advantage over other antidepressants in terms of efficacy were clomipramine, duloxetine, escitalopram, milnacipran, mirtazapine, and venlafaxine.

Clomipramine

In two randomized controlled studies, the Danish University Antidepressant Group DUAG (1986, 1990) reported a significant advantage for clomipramine (150 mg) over the SSRIs citalopram (40 mg) and paroxetine (30 mg). Clomipramine was also superior to the reversible monoamine oxidase inhibitor (RIMA) moclobemide but the dose of moclobemide might have been too low for the study to meet conditions of fair comparison (DUAG, 1993). Clomipramine treatment was associated with a significantly greater reduction in Hamilton Depression Rating Scale (HAMD) score than either of the SSRIs. These two studies provide reasonable class A evidence that clomipramine has definite superior efficacy as an antidepressant.

The studies, however, have design flaws, which to some degree compromise this evidence. The diagnostic criteria varied between studies so that it is difficult to generalize to other populations. It has been argued that the HAMD measure may have favoured the much more sedative clomipramine and possibly compromised the blindness. When clusters of HAMD items were analysed separately in the studies, significant difference was clearly most evident for sleep disturbance, which accounted for nearly half of the total difference (DUAG, 1986). It can be argued that improvement in sleep is an important part of the clinical response to an antidepressant. Inpatient status may also convey an indirect advantage for the less well tolerated tricyclic antidepressants (TCAs), as nursing support facilitates both adherence and management of some side effects (i.e. constipation or orthostatic hypotension). Nevertheless, despite these issues, the presence of at least two positive studies constitutes Class A evidence of the superiority of clomipramine in treating depression.

Clomipramine has definite evidence of superiority as an antidepressant

The extrapolation of the results from studies with clomipramine to the efficacy of other TCAs as suggested by Anderson and Tomenson (1994) does not appear to be justified. Meta-analyses of data for imipramine or amitriptyline have not produced evidence of superiority, at least at the doses used in RCTs, which tended to be low. A subsequent report by Anderson (1998), which limited the meta-analysis to inpatient studies, did report a significant difference favouring TCAs over SSRIs, with a secondary analysis indicating that the entire advantage was accounted for by the studies utilizing the tertiary amine TCAs (i.e. amitriptyline, clomipramine, and imipramine). As the secondary amine TCAs and maprotiline are generally considered to be predominantly noradrenaline reuptake inhibitors, these findings are often viewed as supporting the notion that antidepressants with 'dual effects' might convey stronger antidepressant effects. Moreover, there is a suggestion from a meta-analysis of imipramine data, taken from some of the placebo-controlled studies submitted to the licensing authorities in which imipramine was used as a comparator, that higher doses of imipramine may be more effective (Storosum *et al.*, 2001).

Venlafaxine

Two RCTs provide Class A evidence of definite superiority. Venlafaxine in a daily dosage of 200 mg was found to be significantly more effective on the primary outcome measure (HAMD) than fluoxetine 40 mg in hospitalized MDD patients with severe depression, as reflected by a HAMD score of 29 or more at baseline (Clerc *et al.*, 1994). The advantage on the primary measure was supported by advantages for venlafaxine over fluoxetine seen on the secondary measures. De Nayer *et al.* (2002) reported a significantly greater response on venlafaxine 75–150 mg compared with fluoxetine 20–40 mg over a 12-week period in 120 depressed outpatients with high levels of concomitant anxiety on both the HAMD and Montgomery–Asberg Depression Rating Scale (MADRS). The failure to use any recognized diagnostic criteria or to exclude concomitant generalized anxiety disorder or panic disorder is a potential bias as venlafaxine, but not fluoxetine, is licensed for the treatment of generalized anxiety disorder and panic disorder. This raises questions as to whether the study meets criteria for a fair comparison. As anxiety is recognized to be part of depression, the study, however, provides some evidence of the superiority of venlafaxine in the treatment of depression. A study in resistant depression showed venlafaxine to be superior to paroxetine but as resistance was mostly to SSRIs and not to SNRIs, the study does not meet the criterion of a fair comparison (Poirier and Boyer, 1999). Resistant depression is in any case not quite the same as nonresistant depression. In a further study, venlafaxine was reported to be superior to fluoxetine (Dierick *et al.*, 2006) but in this study, the dose in nonresponders was only allowed to be raised with venlafaxine which compromises the conditions of fair comparison.

The results of numerous meta-analyses of the efficacy data for venlafaxine compared with fluoxetine (Cipriani *et al.*, 2005), a mixture of several SSRIs (Stahl *et al.*, 2002), and to all antidepressants used in comparator studies, support the conclusion that venlafaxine is a superior antidepressant. These large meta-analyses have mainly focused on the secondary measure of remission (Thase *et al.*, 2001; Smith *et al.*, 2002; Thase, 2004) but also provide evidence of superiority over comparators on the primary measure of change from baseline on the HAMD, at least in some of the analyses.

The conclusion that venlafaxine has definite superior efficacy as an antidepressant is supported by Class A evidence from the study of Clerc *et al.* (1994) using a dose of 200 mg/day and the study of De Nayer *et al.* (2002) at the lower dose of 75–15 mg and by consistent Class B evidence from several meta-analyses. This conclusion holds largely for the higher doses of venlafaxine used in the studies and not for the lower daily dosages of 75–150 mg (Thase *et al.*, 2001).

Milnacipran

The superiority of milnacipran 100 mg/day was reported in a study that compared milnacipran with the SSRI fluvoxamine 200 mg/day (Clerc *et al.*, 2001). Milnacipran was significantly more effective measured in the change from baseline on the pivotal MADRS at the 6-week end point. The superiority of milnacipran 100 mg/day compared with fluoxetine 20 mg/day was not shown at the

12-week end point in a study by Guelfi *et al.* (1998); only a post-hoc analysis showed a significant advantage at 4 weeks on the MADRS. As the superiority was not sustained at end point, the evidence from this study is discounted. Class A evidence from a single study (Clerc *et al.*, 2001) supports the probable superiority of milnacipran.

The meta-analysis carried out by Lopez-Ibor *et al.* (1996) reported significantly higher responder rates on milnacipran 100 mg day (64%) than with the SSRIs fluoxetine and fluvoxamine (50%). This advantage was apparently driven substantially by the positive results in patients with more severe depression. The 6-week data was used as the end point in this analysis rather than the 12-week end point in which superiority was not observed in the study of Guelfi *et al.* (1998) and the strength of the evidence is therefore less secure. A recent meta-analysis (Papakostas and Fava, 2007), which included all published studies including a large study mainly in patients with mild-to-moderate depression (Sechter *et al.*, 2004), did not find evidence of superiority for milnacipran. The results from the meta-analyses are therefore inconsistent and evidence of superiority is based on the single positive study of Clerc *et al.* (2001).

The data indicate the probable superiority of milnacipran but there are insufficient data to support a conclusion of definite superiority.

Duloxetine

Duloxetine in a dose of 80 mg/day was reported to be superior to paroxetine 20 mg at the 8-week end point measured on the change from baseline in the primary measure, the HAMD. In this study, paroxetine was not significantly different from placebo (Goldstein *et al.*, 2004). The effect was identified using the mixed model repeated measures analytical approach, but not using the standard last observation carried forward analysis.

A meta-analysis, as yet unpublished, is claimed to report a significant 5% advantage for duloxetine compared with its comparators when mild depression is excluded (Thase, personal communication). Insufficient numbers of patients with severe depression were included in these studies to assess relative efficacy of duloxetine in severe depression (EMEA EPAR on duloxetine, 2005).

Duloxetine (80 mg) is considered to have probable superiority based on Class A evidence from one study, but the data are not sufficiently clear-cut to indicate definite superiority. The evidence of superiority applies only to doses of 80 mg/day and not to the commonly used dose of 60 mg/day.

Mirtazapine

Mirtazapine in a dose of 24–72 mg was shown to have a significantly better response compared with trazodone 150–450 mg on the primary efficacy measure, the HAMD, in hospitalized patients with moderate or severe depression with an entry score of 18 or more on the HAMD (Van Moffaert *et al.*, 1995).

This finding was not replicated in subsequent studies (Benkert *et al.*, 2006) or in meta-analysis (Montgomery *et al.*, 2002; Blier, 2003), which showed a consistent early response rather than a clear superiority for mirtazapine at end point. This early response was observed even when the sleep items of the HAMD were excluded which shows that this early response is not exclusively dependent on the sedative effect of mirtazapine.

Mirtazapine is considered from the evidence of a single study to have probable superiority as an antidepressant.

Escitalopram

Two separate studies have shown the superiority of 20 mg escitalopram compared with 40 mg citalopram (Moore *et al.*, 2005) and 40 mg paroxetine (Boulenger *et al.*, 2006) in conditions of fair comparison in 8-week randomized controlled comparator studies in patients with severe MDD. The significant superiority was observed on the pivotal primary measure MADRS and on secondary measures. This constitutes Class A evidence of definite superiority.

Meta-analyses of the comparator studies have been able to show a significant advantage for escitalopram compared with citalopram (Gorman *et al.*, 2002; Auquier *et al.*, 2003; Lepola *et al.*, 2004), and all comparator antidepressants tested (Kennedy *et al.*, 2006). The individual studies and the meta-analysis of all studies show the superiority of escitalopram. Superiority is seen most clearly in the severely depressed population (Lam and Andersen, 2006).

The superiority of escitalopram in treating depression is clear cut and definite and is based on Class A evidence from two studies and supported as well by consistent results from meta-analyses.

Superiority in severe depression

The hospitalized patients included in the DUAG studies, on which the conclusion of superior efficacy of clomipramine in MDD is based, were in retrospect not particularly severely ill, with minimum entry scores on the HAMD 17 of 18, which is barely in the moderate range and the mean total HAMD scores on entry appear to be too low to justify the claim for efficacy in severe depression. No pooled analysis of these studies is available to give a subanalysis of the data in moderate and severe patient subgroups. The lack of an adequate prospective definition of severity on a severity scale weakens the evidence

of the superiority of clomipramine in severe depression to the level in which it can only be considered possible.

The superior efficacy of venlafaxine in severe depression is based on the single positive comparator study in hospitalized severe MDD (Clerc *et al.*, 1994) and on a meta-analysis of data from comparator studies with a higher level of severity. The entry scores are variable defined as more than 20 on the HAMD or more than 25 on the MADRS (Stahl *et al.*, 2002). Class A evidence of definite superior efficacy in patients with severe depression is therefore available from a single study and is supported by some positive results from a meta-analysis Class B data from meta-analysis of studies with more severe patients with a mean MADRS of 30–31. No subanalysis of the results in the severe patients has, however, been published (Stahl *et al.*, 2002). On these data, it is concluded that venlafaxine has probable superior efficacy compared with fluoxetine and other conventional SSRIs in the treatment of severe depression. Clinical opinion holds firmly to the conclusion that venlafaxine has superior efficacy compared with conventional SSRIs in severe depression but this is not yet properly documented in the published data.

The evidence that milnacipran may be superior in treating severe depression depends on the subanalysis of patients with severe depression in the meta-analysis of the studies of Guelfi *et al.* (1998) in endogenous depression and Clerc *et al.* (2001) in moderate and severe depression, published by Lopez-Ibor *et al.* (1996). No prospective study, however, exists in severe depression. Milnacipran 100 mg/day has possible superior efficacy in severe depression.

The single study demonstrating the superiority of mirtazapine was conducted in hospitalized patients with a minimum score of 18 on the HAMD 17 (Van Moffaert *et al.*, 1995). The high mean baseline scores (HAMD 28–29) indicate that a large proportion of patients were probably suffering from severe depression. Unfortunately, there was no report of the differential efficacy in moderate or severe subgroups and there was no prospective definition of severe on a severity scale so that the evidence from this single study is weakened to a level where superiority can only be considered possible. On the basis of these data, mirtazapine is considered to have possible superiority.

Evidence of superior efficacy in severe depression is found with escitalopram, which has positive results from two individual studies that included only patients with prospectively defined severe depression (defined as a baseline score of at least 30 on the MADRS). Escitalopram was superior to citalopram (Moore *et al.*, 2005) and paroxetine (Boulenger *et al.*, 2006) on both primary and secondary measures. In a subanalysis of patients with severe depression in a single study, escitalopram was significantly better than venlafaxine (Montgomery & Andersen, 2006). In other subanalyses of data from patients with severe depression in the meta-analysis of comparator studies, the superiority of escitalopram was also observed compared with citalopram (Lepola *et al.*, 2004; Llorca *et al.*, 2005; Lam and Andersen, 2006) to SSRIs and to all comparator antidepressants combined (Kennedy *et al.*, 2006). Class A evidence from two studies allows the conclusion of definite superior efficacy but only for the 20-mg dose of escitalopram. The evidence is supported by superiority shown in several meta-analysis in severe depression.

Conclusion on superiority in severe depression

The available evidence supports the definite superior efficacy in severe depression compared with comparator antidepressants of escitalopram (two prospective studies supported by meta-analyses), and probable superiority of venlafaxine (one prospective study supported partially by one meta-analysis) and possible superiority of milnacipran (one study). Evidence of superiority of clomipramine is based on two studies in hospitalized patients, in which the severity was defined as moderate-to-severe rather than severe alone without a published subanalysis, and is therefore questionable but accepted as evidence of possible superiority in the treatment of severe depression.

Only escitalopram show definite superiority in the treatment of severe depression. Venlafaxine has probable superiority and milnacipran and clomipramine possible superiority in the treatment of severe depression.

Overall conclusion

The criterion for definite superiority of an antidepressant is based on results from two pivotal studies in moderate-to-severe MDD, carried out under conditions of fair comparison at approved doses of the antidepressants, which demonstrate superiority on the primary efficacy measure, or alternatively one pivotal study supported by consistent results from meta-analyses. The criterion for probable efficacy is based on consistent positive results from meta-analyses of studies in patients suffering from moderate or severe MDD. A review of the published data finds evidence that some antidepressants are more effective than others on the basis of these criteria. It should be noted that conclusions for superiority are generally dose-specific and may not hold true throughout the approved dose range for the particular antidepressant.

Using these criteria, only three antidepressants are considered to have definite superior efficacy — clomipramine, venlafaxine, and escitalopram. Three antidepressants have probable superiority — milnacipran,

duloxetine, and mirtazapine. Only escitalopram is considered to have evidence of definite superiority in the treatment of severe depression with venlafaxine having probable superiority.

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