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Is severe depression a separate indication?[1]

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Abstract

There is not an accepted definition of severe depression, but using cut-off scores on rating scales severe depression is considered to lie at one extreme of a continuum of severity. The evidence from epidemiological, biological, and clinical efficacy studies does not support severe depression as a separate illness category. A good response to antidepressants is seen in both moderate and severe depression. The available evidence supports the view that in most cases an effective antidepressant in moderate depression is likely to have efficacy in severe depression. Few studies have found differences between antidepressants in their efficacy in treating severe depression. Most evidence of differential efficacy derives from studies of clomipramine, which is perceived as a particularly potent antidepressant by many clinicians. Other tricyclic antidepressants do not appear to have an advantage in severe depression. Separate studies to demonstrate efficacy in severe depression are not necessary for the registration of a new antidepressant. However if efficacy in severe depression is demonstrated in separate studies this information could be included in the summary of product characteristics to provide guidance to clinicians.

Keywords: Depression; Severity; Separate illness

1. Introduction

The efficacy of new putative antidepressants is customarily established in placebo-controlled treatment trials in patients suffering from moderate to severe depression. A question that needs to be addressed is whether antidepressants that are effective in moderate depression are also effective in severe depression. Related questions are whether there are differences in the relative efficacy of different drugs according to severity of depression, and whether there is a separation between moderate and severe depression on terms of choice of drug or dosage.

In September 1996, the European College of Neuropsychopharmacology held a consensus meeting to consider whether severe depression should be viewed as an indication separate from moderate depression or whether they are on a continuum of severity. The meeting considered issues relating to possible differential efficacy. This consensus statement has been produced following the deliberations of the panel.

2. Background

Depression is a disorder that is associated with substantial morbidity and disability. Levels of impairment are acknowledged to be greater than with other chronic disorders such as hypertension and diabetes, and rank close to myocardial infarction (Wells et al., 1989). Dysfunction may be even greater in severe depression and the risk of

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serious consequences increased. There is some evidence of an association between severe depression and increased suicides and also increased physical illness.

Most of the studies in depression have investigated moderate to severe illness, which makes up the bulk of those who suffer from depression. It is not customary to examine severe and moderate depression separately so that the number of studies that have investigated severely ill patients exclusively is limited. Significant differences between antidepressants in the level of efficacy achieved according to the severity of illness would have important implications. Clinicians would need to take the information into account in the selection of the most appropriate treatments for their patients. It would also be reasonable to require the evidence of efficacy from specific studies in different categories of severity in order to avoid the use of a drug by default in certain subtypes of depression without efficacy having been demonstrated.

3. Definitions of severe depression

In the absence of a generally accepted criterion of severe depression a variety of definitions has been used in those efficacy studies that specifically investigated the efficacy of a product in that patient population. These include the presence of melancholia, the inclusion of hospitalised patients, and a cut-off score on a severity rating scale. The varying criteria compromise the task of comparing results from the different studies and some of the definitions are acknowledged to be inadequate.

3.1. Melancholia

Melancholia is normally thought of as a diagnostic subgroup of depression associated with more obviously biological symptoms. The severity of the depression varies depending on the stage of evolution or recovery of the illness. The presence of melancholia is therefore unsatisfactory as an indicator of severe depression because there can be a wide range of severity among patients categorised as having melancholia (Tignol et al., 1992). Severity therefore needs to be defined in addition to the presence of melancholia. Moreover somewhat different approaches are taken to the diagnostic criteria in the US, where melancholia is a category in the DSMIV and severity a dimension of illness, and Europe, where in ICD10 severity overrides the importance of features of melancholia.

3.2. Hospitalization

Though many patients are hospitalised because of the severity of their depression admission to hospital is not in itself a particularly robust definition for severe depression. The likelihood of hospitalisation varies according to local practice and available resources. Areas having a philosophy that supports treatment in the community are, for example, more likely to treat severe depression outside the hospital. Variability in the provision of resources for hospital beds will also determine very largely whether a patient with severe depression is treated as an inpatient or not. Hospitalisation may reflect the social isolation of the individual or the presence of physical or other comorbidity rather than severity. For these and similar reasons hospitalisation cannot be taken on its own to indicate severity of depression.

3.3. Rating scale score definitions

No single, generally accepted, rating scale based definition for severe depression has been established. A variety of cut-offs on severity scales have been used to separate severe from moderate depression. For example, a score of 28 or 30 on the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), a score of 25 or 28 on the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960), and a score of 28 on the 21-item HDRS have all been used to define severity.

The body of evidence is too small to scan for reliably consistent results, however any differences in treatment response between two antidepressants relating to severe depression have generally been reported in patients with a severity of depression registered as a score above these cut-offs. The world-wide database on moclobemide, for example, yielded the result that imipramine was superior to moclobemide only in those confined to the upper third percentile which had a cut off of 28 or greater on the HDRS (Angst and Stabl, 1992). A cut-off of 28 or above on the 17-item HDRS showed a lower level of efficacy for imipramine compared with paroxetine (Montgomery, 1992). The cut-off chosen in particular data sets reflects the severity of the population studied rather than acting as a general criterion for the separation of the severe from the moderately depressed.

There is a need for an accepted definition of severe depression, which, even if arbitrary, would be very useful for research purposes. Definitions using hospitalisation or a diagnostic category such as melancholia are not in practice reliable indicators of severity of depression. The most widely used and accepted definitions are based on severity rating scale scores. Moderate and severe depression turn out to be on a continuum and there is no score on the currently used rating scales that provides an inherent dividing cut-off point. The generally used cut-offs are 25 or 28 on the 17-item HDRS and 28 or 30 on the MADRS but these points are arbitrary rather than a natural separation. These scale score cut-offs would mostly represent severity of depression with a clear cut loss of function but there are insufficient data to identify functional measures. Some diagnostic criteria, e.g. DSM, include a subcategorisation of mild, moderate, severe. Unfortunately, these subcategories are not based on quantifiable criteria and in

practice are relatively insensitive to severity judged on severity scales. Diagnostic criteria should not be confused with severity scales.

4. Severe depression as a separate indication

A requirement for a separate indication for severe depression should be based on data and would be justified if there were a body of evidence supporting the view that severe depression is a separate condition, differing from moderate depression biologically, or pharmacologically. The alternative view is that severe depression lies at one extreme on a continuum of the severity spectrum and is not a separate category.

Relatively few studies have addressed specifically the question of possible differential efficacy though there is a clinical view that some antidepressants are more effective than others in severe depression. Even fewer studies address whether severe depression can be thought of as a separate disorder, as a different condition from moderate depression. A review of the epidemiological data does not provide evidence of a separation of severe and moderate depression on the basis of response to treatment. Likewise, a review of the biological data did not find evidence to support the notion of a biologically based separate category of severe depression.

The balance of the evidence supports the view that severe and moderate depression lie on the same continuum of severity and that severe depression is not a separate condition. The question can be addressed by examining the relative efficacy of treatments for moderate and severe depression and whether different treatments are required for the treatment of severe depression. Differences in response to pharmacological agents between moderate and severe depression might indicate a biologically based separation.

4.1. Treatment response in severe depression

The small number of studies that have investigated possible differences between patients with different levels of severity have found that any differences appear to be dimensional rather than categorical. For example the response to placebo is increased in mild depression, intermediate in moderate depression, and low in severe depression.

The most consistent finding concerning differences in response identified by levels of severity concerns acute mild depression where it is accepted that a significant drug placebo difference is less likely to be detected than in moderate or severe depression. In mild depression there is less space for improvement so that very large numbers of patients would be needed to demonstrate small differences between drug and placebo. Nevertheless, antidepressants have some effect and any underlying biological difference is unlikely to be specifically related to severity.

4.2. Efficacy in moderate and severe depression

A good response to antidepressants is seen in both severe depression and moderate depression. Any differences between antidepressants in their efficacy in severe depression are relative and it would be unsafe to conclude that an antidepressant that is effective in moderate depression would not have some efficacy in severe depression. There is no evidence to suggest that an antidepressant that is effective in severe depression is not also effective in moderate depression.

4.3. Dose and severity

The issue of differential dosage has not been fully resolved in the comparative studies.

Traditional practice has been to raise the dose of conventional antidepressants in the case of non-response, particularly in severely depressed patients. A minimum effective dose has been established for very few antidepressants and there is a widely held clinical opinion that this dose may be higher in severe depression. If the need for higher doses to achieve response in severe depression was found to be consistent this might be taken as an indication of a separation from moderate depression, at least as a functional group. Data from a few studies suggest that a better response to some antidepressants may be seen in some patients with severe depression if a higher dose is used (Dunbar et al., 1991; Montgomery et al., 1992; Rudolph et al., 1997) but, in general, scientific data on a possible dose response relationship related to severity are lacking. Simply raising the dose of a treatment for severe depression would not normally be considered an indication of a separate disorder.

The issue of a possible differential response to dose in severe depression has a bearing on the design of studies to investigate differences between different antidepressants. The optimum dose of both the target antidepressant and the comparator is needed, if equivalent efficacy is to be shown. Dose–response relationships in relation to severity have not been investigated for the majority of antidepressants and a linear relationship cannot be assumed. For some antidepressants, for example nortriptyline, a curvilinear relationship has been reported (Braithwaite et al., 1978; Kragh-Sorensen et al., 1976).

4.4. Psychotic depression

The only evidence for a possible biologically based separate category of severe depression relates to psychotic depression, where this term is used for the presence of delusions. There is some evidence that antidepressants are effective in this group but the view of many clinicians is

that the level of efficacy is at best modest and that adjunctive treatment with antipsychotics is helpful. Most of the studies in severe depression exclude delusional depression. Psychotic depression can, of course, have different levels of severity and it represents a diagnostic subcategory rather than an absolute measure of severity.

5. Differences between antidepressants in severe depression

Establishing whether there are differences in the efficacy of antidepressants in severe depression is hampered by the lack of adequate specific comparator studies. Meta-analysis of published studies risks bias due to the inevitable exclusion of unpublished data, many of which may have provided negative results on particular antidepressants.

The lack of a universally accepted methodology for establishing differential efficacy in severe depression compromises the assessment of the results of the very small number of studies that have reported an advantage for one antidepressant over another in severe depression. The evidence has to be weighed with considerable caution since the studies are few in number, often small with less than adequate methodology, did not always include patients who were severely depressed, and were not all placebo controlled.

Any assessment should also take into account the far greater body of studies where no difference in efficacy was found between antidepressants.

5.1. Efficacy of reference antidepressants in severe depression

The relative efficacy of a new antidepressant has traditionally been assessed in comparison with a reference tricyclic antidepressant (TCA). However, the large studies that are now customarily conducted with new putative antidepressants, and the metanalyses of the clinical trial databases are providing evidence that casts doubt on the efficacy of some tricyclic antidepressants in severe depression.

Specific head to head comparisons of different TCAs to investigate potential differential efficacy in subgroups are lacking but there is evidence from the clinical trial database with serotonin reuptake inhibitors (SSRI) that imipramine, although effective in moderate depression was not significantly different from placebo in severe depression whereas the SSRI was effective across the range (Ottevanger, 1991; Montgomery, 1992). The suggestion that imipramine performs less well in severe depression in these studies is consistent with earlier reports (Wittenborn et al., 1973; Bielski and Friedel, 1976).

In view of the doubts about the efficacy in severe depression of some TCAs it is important that efficacy across the range of depression should not be extrapolated from the most successful drug, for example clomipramine, and attributed to the TCAs as a class. The selection of a reference drug for comparisons with a new antidepressant should take this into account. Moreover, although the TCAs are used across the range of severity many of them have not been investigated in severe depression and their status as an adequate reference is not established.

The evidence from direct comparisons that particular antidepressants may be better than others in severe depression relates mainly to clomipramine. An advantage for this TCA has been reported compared with newer antidepressants including various of the SSRIs and the reversible monoamine oxidase inhibitor moclobemide (Andersen et al., 1986; Danish University Antidepressant Group, 1990, 1993).

Metanalyses of the published studies are to some extent limited by the difficulty of comparing studies that used different methodologies. Nevertheless, it appears that a somewhat greater effect size may be achieved with clomipramine than with some other antidepressants in severe depression (Anderson and Tomenson, 1994). These findings are in accord with the general clinical perception of clomipramine as a particularly potent antidepressant.

Some caution is needed, however, before drawing firm conclusions. Although it seems clear that clomipramine is effective in severe depression, the apparent advantage relative to newer drugs may be explained by the use of less than optimal doses of the more recent drugs. Examples are moclobemide and citalopram which were investigated initially in doses which the results from later studies suggest might have been too low (Angst and Stabl, 1992; Nutt and Montgomery, 1996).

The perception that SSRIs are not effective in severe depression is not based on empirical data. In the metanalyses of large databases they have been shown to be as effective as TCAs in severe depression and in some cases to be significantly more effective (Ottevanger, 1991; Montgomery, 1992; Pande and Sayler, 1993). The available evidence supports the efficacy of SSRIs in both moderate and severe depression.

Other reported differences between antidepressants in the treatment of severe depression include an advantage for milnacipran and for venlafaxine compared with fluoxetine in treating hospital based depressed patients. Both these antidepressants have a reuptake blocking action on both serotonin and noradenaline (Clerc et al., 1996; Lopez-Ibor et al., 1996). An advantage compared with fluoxetine is seen with mirtazapine, which also has effects on both transmitters although by a different mechanism (Wheatley et al., 1998).

There is agreement that the evidence for efficacy in severe depression is better established for some drugs than others. More research is needed to determine the consistency of any observed differences. A small number of studies in severe depression report differences in efficacy between different antidepressants but an important body of

negative results shows no difference between compounds. In general the level of efficacy in severe depression of the different antidepressants appears to be similar.

6. Are separate studies in severe depression needed for the registration of new antidepressants?

The question whether drug licensing authorities should require specific studies in severe depression relates to their function in protecting public health against the use of treatments without demonstration of efficacy.

The evidence suggests that severe depression is at one end of a spectrum and is not a separate disease entity. There is no evidence that antidepressants that are clearly effective in moderate depression are not to some extent effective in severe depression. The consensus view is that evidence is lacking to support a requirement of separate studies in severe depression for an antidepressant to be licensed. A licence for the treatment of depression is preferred for practical reasons rather than a licence for different grades of severity in a disorder where severity appears to be a continuous variable and where the divisions between different grades of severity are not simple and obvious.

Specific studies in severe depression can however provide information, which, though not essential for registration of the drug, can be very useful for the clinician. For example, if a significant advantage for one drug over another is demonstrated in a study that has used good methodology in a defined population of severe depression, information on this clinical advantage should be included in the summary of product characteristics. The purpose is to help inform clinicians, and not to fulfil a basic registration requirement.

There is insufficient evidence to support the need for specific dosage studies in severe depression and they are not required for registration. If, however, studies are carried out which show that different dosage regimes carry an advantage in severe depression this would be useful information for the education of clinicians in the best use of a drug and could be included in the dosage information.

7. Conclusions

Severe depression is considered to lie at one extreme of a continuum of severity. There is no evidence to suggest that severe depression should be considered a separate illness category. Only psychotic depression appears to merit a separate category and this is based on the appearance of delusional symptoms not on the associated severity of illness. Any reported differences in response related to severity level appear to be dimensional rather than categorical.

A good response to antidepressants is seen in both severe depression and moderate depression. It is considered that an effective antidepressant in moderate depression will also have some efficacy in severe depression.

The evidence to support differences in efficacy in severe depression between antidepressants is not substantial. The majority of studies that have compared active antidepressants have found similar levels of efficacy regardless of severity level.

Evidence of differential efficacy in severe depression is based mainly on a very small number of studies that reported an advantage for clomipramine and venlafaxine, both antidepressants are perceived by clinicians to be particularly potent. Results from the most successful TCA should not be extrapolated to the TCAs as a class without further testing. Concern that the newer antidepressants, such as the SSRIs, are less effective than the older TCAs in severe depression is not justified by the results from comparator studies. In some studies particular TCAs have been shown to be less effective than the SSRIs.

Separate studies to demonstrate efficacy at different levels of efficacy are not necessary for the registration of an antidepressant. Specific studies in severe depression may however provide useful information on how to obtain the optimum benefit from a drug. They are therefore a welcome additional, though not essential, source of data. If efficacy is shown separately in well-defined severely depressed patients, this could be labelled in the summary of product characteristics but is not a separate indication.

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