Are SSRIs Really More Effective for Anxious Depression?

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Background. Selective Serotonin Reuptake Inhibitors (SSRIs) are well-established first-line agents for Anxiety Disorders. Anxiety is also a frequent manifestation of major depression. Many psychiatrists assume that anxious depression is more responsive to SSRIs than to other antidepressants. The purpose of this literature review was to determine if SSRIs or any other antidepressants are superior.

Methods. A computerized search was conducted of double-blind, English-language studies comparing antidepressants available in the United States. Databases searched included Medline and PsycINFO.

Results. SSRIs were not found to be superior to other antidepressants in the treatment of anxious depression.

Conclusions. The above assumption is not supported. Treatment implications are discussed.

Keywords Depression, Anxiety, Anxious depression, Antidepressants

INTRODUCTION

Numerous authors have attempted to subgroup major depression by symptom type, implying or stating that the subgroups respond differently to medication. Fava et al. (1) compared several subtypes including anxious depression. After adjusting for severity of baseline depression, patients with the anxious subtype were less responsive to fluoxetine on all outcome measures. Fawcett and Barkin (2) describe the high prevalence of anxiety in major depression and the negative effect anxiety has on treatment outcome. However the term anxious depression is variably defined. Originally meant to describe symptoms of anxiety occurring in the course of major depression, some authors also include comorbid anxiety disorders. Lydiard and Brawman-Mintzer (3) discuss treatment of such patients. Selective serotonin reuptake inhibitors (SSRIs) are well-established first-line agents for anxiety disorders (Panic Disorder,Obsessive-Compulsive Disorder, Social Anxiety Disorder, Generalized Anxiety Disorder, Post-Traumatic Stress Disorder). Though the course and treatments of secondary anxiety may differ from those of the primary anxiety disorders, many psychiatrists assume that all forms of anxious depression are more responsive to SSRIs than to other antidepressants. The purpose of this study is to review the literature on whether patients suffering from depression with secondary anxiety are more responsive to any particular antidepressants than to others.

METHODS

The objective was to study medication response for inpatients or outpatients suffering from major depression with secondary anxious features. SSRIs reviewed included fluoxetine, sertraline, paroxetine, and citalopram. While SSRIs vary in terms of serotonin specificity, this study does not discriminate by this factor. Studies were required to be double-blind and to have measures of anxiety. To limit confusion by including too many groups of patients (who may respond differentially to medication), the present review excluded studies of depressed patients meeting criteria for a comorbid anxiety disorder to the extent possible. In other words, the main illness had to be depression. Certain studies are not reviewed individually because they are included in meta-analyses. A large number of studies was excluded.

A computer search of the English-language literature using keywords depression, anxiety, and anxious depression was conducted. Databases searched included Medline and PsycINFO. Double-blind, comparative trials of antidepressants available in the United States were qualitatively reviewed.

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Measurement of anxiety was done with the Hamilton Rating Scale for Anxiety (HAM-A; (4)), the Covi Anxiety Rating Scale (5), or the anxiety/somatization factor (items 10, 11, 12, 13, 15 and 17) on the Hamilton Rating Scale for Depression (HAM-D; (6)). Depression was measured with the HAM-D or with the Montgomery-Asberg Depression Rating Scale (7).

RESULTS

Twenty-eight studies were selected. A large number of studies which did not include measures of anxiety were rejected, as were open studies. Three of these pooled data from 2 or more studies, some of which had been previously published. Studies included in meta-analyses are not listed individually in the tables below. Patients in all but the earliest study met criteria for major depression as defined in DSM-III, DSM-III-R, or DSM-IV (8–10). Exclusion criteria and severity of anxiety also varied between studies. Comparison studies in the treatment of anxious major depression have included selective serotonin reuptake inhibitors (SSRIs; fluoxetine, sertraline, paroxetine, citalopram, escitalopram), tricyclic antidepressants (TCAs), bupropion, nefazodone, venlafaxine, and mirtazapine. SSRIs have been compared most often to bupropion.

SSRIs vs Bupropion

Feighner et al. (11) treated 123 patients with flexible doses of bupropion or fluoxetine (Table 1). Decreases on the HAM-A (59%) and the HAM-D did not differ.

Several groups have compared sertraline with bupropion. Kavoussi et al. (12) compared the antidepressant and anxiolytic effects of these agents in 248 patients in a double-blind trial. No significant differences were found on either measure.

Coleman et al. (13) treated 364 patients with recurrent major depression with bupropion, sertraline or placebo. It is not clear whether anxiety preceded or followed the onset of depression. In terms of depression, only bupropion was superior to placebo. Neither active treatment was superior to placebo on the HAM-A at any point in the study.

Croft et al. (14) compared bupropion SR (sustained-release), sertraline and placebo in a flexible-dose study involving 360 patients. HAM-D and HAM-A measurements decreased equally compared with placebo in both active treatment groups.

Trivedi et al. (15) found improvement in HAM-D and HAM-A scales in two pooled studies involving 692 patients. No differences were found on either scale between the medications, nor in time until a 50% decrease in HAM-A scores occurred. In a separate report but using the same groups of patients, these authors (Rush et al. (16)) also studied the effect of pretreatment levels of anxiety on medication response. Severity of baseline anxiety did not affect response to either medication, nor was there a difference between medications.

The same authors found the same results in another study (17) measuring antidepressant and anxiolytic efficacy, and the effect of baseline anxiety on each measure. Sertraline and bupropion SR showed the same efficacy on both measures, and the same time to anxiolysis. Baseline anxiety did not predict antidepressant efficacy.

Weihs et al. (18) treated anxious major depression in 100 elderly patients with paroxetine or bupropion SR. The groups responded equally well to either agent on HAM-A and HAM-D measures.

Nieuwstraten and Dolovich (19) performed a meta-analysis of 1332 patients treated in 5 of the above studies. Qualitatively, bupropion and sertraline were equal in terms of depression. Quantitatively, there was no difference in the decrease on the HAM-A with paroxetine, sertraline or fluoxetine.

Mirtazapine vs. SSRIs or Amitriptyline

Leinonen et al. (20) compared mirtazapine to citalopram in a double-blind study (Table 2). Both were equally effective for depression and anxiety, but mirtazapine was faster than citalopram.

Benkert (21) found identical results in comparing mirtazapine to paroxetine.

Schatzberg et al. (22) compared mirtazapine and paroxetine in elderly depressed outpatients. Mirtazapine was superior in terms of percentage of patients responding by day 14, percentage achieving remission by day 42, and extent of reduction in the anxiety/somatization factor. Mirtazapine was also better tolerated.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Bupropion vs. SSRIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Authors, length</td>
<td>SSRI, dose</td>
</tr>
<tr>
<td>Feighner et al., 1991(11) 6 weeks</td>
<td>fluoxetine 38 mg</td>
</tr>
<tr>
<td>Kavoussi et al., 1997 (12) 16 weeks</td>
<td>sertraline 50–200 mg</td>
</tr>
<tr>
<td>Coleman et al., 1999 (13) 8 weeks</td>
<td>sertraline 106 mg</td>
</tr>
<tr>
<td>Croft et al., 1999 (14) 8 weeks</td>
<td>sertraline 50–200 mg</td>
</tr>
<tr>
<td>Trivedi et al., 2001 (15) 8 weeks</td>
<td>sertraline 50–200 mg</td>
</tr>
<tr>
<td>Rush et al., 2001 (17) 8 weeks</td>
<td>sertraline 50–200 mg</td>
</tr>
<tr>
<td>Weihs et al., 2000 (18) 44 weeks</td>
<td>paroxetine 10–40 mg</td>
</tr>
</tbody>
</table>
Wheatley et al. (23) compared fluoxetine and mirtazapine in 66 moderately to severely depressed patients. Significantly greater decreases in the HAM-D were observed in the patients receiving mirtazapine at weeks 3 and 4, with a trend at week 6 favoring mirtazapine. There was also a trend favoring mirtazapine in reduction of the anxiety/somatization factor.

Fawcett et al. (2) performed a meta-analysis of 5 published and 3 unpublished double-blind trials comparing mirtazapine with amitriptyline. Doses of the two medications ranged from 5 to 35 mg for mirtazapine, and from 40 to 280 mg for amitriptyline. Both produced the same reduction of the HAM-D anxiety/somatization factor. Both medications reduced anxiety beginning at week 1. How the authors of the meta-analysis obtained the anxiety data is not always identified, as some of the original studies did not include anxiety data (Smith (24) and Halikas (25) did not, while Bremner (26) did). It is also not clear if anxiety preceded or followed the onset of depression.

**SSRIs vs TCAs**

Dunbar et al. (27) compared paroxetine, imipramine and placebo in 717 patients (Table 3). Active medications were equally effective for depression on the HAM-D. Anxiolytic effects were faster for paroxetine on both the HAM-A and the Covi scale.

Marchesi et al. (28) performed a double-blind comparison of fluoxetine with amitriptyline. Both were effective for anxiety.

**SSRIs vs SSRIs**

Fava et al. (30) compared sertraline, paroxetine and fluoxetine in anxious major depression (Table 4). No significant differences were found.

Stahl (31) found citalopram 60 mg superior to sertraline 150 mg in terms of the anxious component of major depression.

**Bupropion vs TCAs**

Branconnier et al. (32) found bupropion to be equal to imipramine for the depressive and anxious components of major depression, with the greatest anxiolytic effect seen in the high-dose bupropion group on one measure (Table 5). Another measure found equal antianxiety effects.

### Table 2 Mirtazapine vs. SSRIs or Amitriptyline

<table>
<thead>
<tr>
<th>Author, length</th>
<th>Comparator</th>
<th>Mirtazapine dose, total patients, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheatley et al., 1998 (23) 6 weeks</td>
<td>fluoxetine 20–60 mg</td>
<td>15–60 mg, n=133, Mirtazapine superior for depression and nonsignificantly superior for anxiety</td>
</tr>
<tr>
<td>Leinonen et al., 1999 (20) 8 weeks</td>
<td>citalopram 20–60 mg</td>
<td>15–60 mg, n=270 mirtazapine faster on MADRS, HAM-A</td>
</tr>
<tr>
<td>Benkert et al., 2000 (21) 6 weeks</td>
<td>paroxetine 33.9 mg</td>
<td>32.7 mg, n=275 mirtazapine faster on HAM-A and -D</td>
</tr>
<tr>
<td>Schatzberg et al., 2002 (22) 8 weeks</td>
<td>paroxetine up to 40 mg</td>
<td>30–45 mg, n=246 Faster depression response, higher remission and greater anxiolysis with mirtazapine</td>
</tr>
<tr>
<td>Fawcett et al., 1998 (2) (8 studies)</td>
<td>amitriptyline 40-280 mg</td>
<td>5–35 mg, n=385, same decrease on HAM-D anxiety/somatization factor</td>
</tr>
</tbody>
</table>

The same results were found by Versiani et al. (29) using the same comparators.

### Table 3 TCAs vs SSRIs

<table>
<thead>
<tr>
<th>Authors</th>
<th>SSRI</th>
<th>TCA dose, total patients, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dunbar et al., 1991 (27) 6 weeks</td>
<td>paroxetine 10–50 mg</td>
<td>imipramine 65–275 mg, n=717 both effective on HAM-D, paroxetine faster on Covi, HAM-A</td>
</tr>
<tr>
<td>Marchesi et al., 1998 (28) 10 weeks</td>
<td>fluoxetine 20 mg</td>
<td>amitriptyline 115 mg, n=142 no difference on HAM-D anxiety symptoms</td>
</tr>
<tr>
<td>Versiani et al., 1999 (29) 8 weeks</td>
<td>fluoxetine 20 mg</td>
<td>amitriptyline 138 mg, n=157 no difference on HAM-A or -D</td>
</tr>
</tbody>
</table>

### Table 4 SSRIs vs. SSRIs

<table>
<thead>
<tr>
<th>Authors</th>
<th>SSRIs, doses</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fava et al., 2000 (30) 16 weeks</td>
<td>paroxetine, sertraline, fluoxetine 20–60 mg, 50–200 mg, 20–60 mg</td>
<td>n=208, no difference on HAM-D anxiety</td>
</tr>
<tr>
<td>Stahl, 2000 (31) 24 weeks</td>
<td>sertraline, citalopram, placebo 150 mg, 60 mg</td>
<td>N=323. Citalopram faster for depression, better for anxiety</td>
</tr>
</tbody>
</table>

### Table 5 Bupropion vs. TCAs

<table>
<thead>
<tr>
<th>Author</th>
<th>TCA, dose</th>
<th>Bupropion dose, patients, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Branconnier et al., 1983 (32) 5 weeks</td>
<td>imipramine 150 mg</td>
<td>150 or 450 mg, n=63 bupropion as good or better on HAM-A anxiety measures</td>
</tr>
<tr>
<td>Feighner et al., 1986 (33) 13 weeks</td>
<td>doxepin 150–200 mg</td>
<td>300–400 mg, n=147 bupropion superior on HAM-A</td>
</tr>
<tr>
<td>Mendels et al., 1983 (34) 4 weeks</td>
<td>amitriptyline 120 mg</td>
<td>380 mg, n=101 same decrease on HAM-A</td>
</tr>
</tbody>
</table>
Feighner et al. (33) found bupropion at least as effective as doxepin, considered a sedating antidepressant, for depression and associated anxiety.

Mendels et al. (34) compared bupropion to amitriptyline, and bupropion again was as effective as the TCA.

**Nefazodone vs. TCAs or SSRIs**

Rickels et al. (35) compared nefazodone and imipramine in 126 patients treated in a family practice setting (Table 6). Both agents were superior to placebo on the HAM-D. Nefazodone was at least as effective for anxiety as measured by several scales. Results were greater for primary care patients than for another group treated by psychiatrists with either medication.

Fontaine et al. (36) also compared nefazodone with imipramine or placebo in major depression. Again, both agents were effective on the HAM-D as well as the HAM-A, though only nefazodone showed effectiveness on self-report.

Fawcett et al. (37) performed a meta-analysis of 6 uncited studies comparing nefazodone and amitriptyline. (It is not clear if the above two trials were included in the Fawcett meta-analysis.) Nefazodone was as effective for depression, and faster for anxiety, than amitriptyline. In this study it is difficult to know if patients had primary or secondary anxiety.

Baldwin et al. (38) in an 8-week, multicenter study compared nefazodone and paroxetine in 206 moderately to severely depressed outpatients. Patients received an average of 32.7 mg of paroxetine or 472 mg of nefazodone. There were no significant differences in improvement on the HAM-D, HAM-A, or MADRS. The medications were tolerated equally well.

**Venlafaxine vs. Trazodone or SSRIs**

Cunningham (39) conducted a year-long, continuation-phase study finding no difference between venlafaxine, trazodone and placebo on the anxiety/somatization factor (Table 7). However both active treatments were superior to placebo on various other measures of depression.

Silverstone and Ravindran (40) treated 359 outpatients with major depression with fluoxetine, venlafaxine or placebo for 12 weeks. The HAM-D remission rate for venlafaxine was superior to placebo at more time points than with fluoxetine. At week 12 the HAM-A remission rate was higher for venlafaxine than fluoxetine.

<table>
<thead>
<tr>
<th>Author</th>
<th>TCA, dose</th>
<th>Nefazodone, patients, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rickels et al., 1994 (35) weeks</td>
<td>imipramine 100–300 mg</td>
<td>200-600 mg, n=126 equal on HAM-D and anxiety/somatization; nefazodone superior on HAM-A</td>
</tr>
<tr>
<td>Fontaine et al., 1994 (36) 6 weeks</td>
<td>imipramine 214 mg</td>
<td>460 mg, n=180 equal on HAM-D, HAM-A; nefazodone superior on self-report</td>
</tr>
<tr>
<td>Fawcett et al., 1995 (37) (6 studies)</td>
<td>imipramine 178 mg</td>
<td>391 mg, n=817. Nefazodone equal for depression, faster on HAM-A</td>
</tr>
<tr>
<td>Baldwin et al., 1996 (38) 8 weeks</td>
<td>paroxetine 32.7 mg</td>
<td>472 mg nefazodone. Same decreases in HAM-D, HAM-A and HAM-A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Comparator</th>
<th>Venlafaxine dose, comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham et al., 1984 (39) 6 weeks</td>
<td>trazodone, placebo 300 mg</td>
<td>160 mg, n=225, all groups equal on HAM-D anxiety/somatization factor</td>
</tr>
<tr>
<td>Silverstone et al., 1999 (40) 12 weeks</td>
<td>fluoxetine 39.9 mg, placebo</td>
<td>140.8 mg, n=359,</td>
</tr>
<tr>
<td>Ballus et al., 2000 (41) 24 weeks</td>
<td>paroxetine 20-40 mg no placebo</td>
<td>75–150 mg, n=84</td>
</tr>
</tbody>
</table>

Ballus et al. (41) compared venlafaxine and paroxetine in 41 outpatients with dysthymia or major depression in a 24-week study. Patients were more likely to show response to venlafaxine at week 6, and remission at week 8, than to paroxetine. There was no difference in reduction on the HAM-A.

Davidson et al. (42) pooled data from 5 studies including 1454 patients taking venlafaxine or fluoxetine. Three of the studies were placebo-controlled. In patients with moderate anxiety, a significantly higher remission rate than with placebo was achieved at week 4 with venlafaxine but only at week 6 with fluoxetine. In those with severe anxiety, the remission rate for fluoxetine was not superior to placebo while that for venlafaxine was, starting at week 6.

**DISCUSSION**

Numerous authors have attempted to identify depressive subtypes on the basis of differential treatment responses. In 1966 Overall (43) identified a symptom cluster in anxious depression that was relatively unresponsive to tricyclics and MAOIs. VanValkenburg et al. (44) reviewed the early literature describing a poorer prognosis for anxious depression. The same group compared patients with depression, anxiety, anxiety secondary to depression or depression due to anxiety. Their careful description of the primary or secondary nature of symptoms is unique in the literature on anxious depression. They found that patients with both depression and panic attacks, whichever occurred first, had worse outcomes. Subsequent epidemiological studies have shown primary anxiety to be more common than anxious depression.
Separate from prognostic implications of depressive subgroups is the question of whether some subgroups are more responsive to certain medications than to others. Many psychiatrists consider SSRIs to be more effective than other antidepressants in anxious depression. This assumption is taken as a given by many in the field, even though the studies do not support this belief. Although several recent studies are better designed, the literature as a whole has important methodological limitations. Studies employ different versions of DSM, define or measure anxiety differently, and have different exclusion criteria. In addition, almost no studies clearly indicate the relationship between symptoms of depression and those of anxiety. While SSRIs are superior to other antidepressants in anxiety disorders, published trials do not make clear which anxious depressive patients had pre-existing anxiety, versus anxiety following onset of depression. In the latter case, any antidepressant alleviating depression may help anxiety as well. In clinical practice, psychiatrists and other physicians are unlikely to make this distinction, and avoid non-SSRI antidepressants under the (invalid) assumption that SSRIs are superior for this large but ill-defined group.

Rush et al. 2001 (16) assessed whether the severity of baseline anxiety was related to antidepressant response. Anxiety severity was not related to response to sertraline or to bupropan SR, nor did anxiety differentiate between responders to sertraline and responders to bupropan SR.

In addition to clinical trials, it would be useful if more were learned about the biological correlates of anxious depression. Meller et al. (45) discuss that neuroendocrine perturbations are more severe in anxious depression, but point out the ambiguity of the term anxious depression in the literature. Rao et al. (46) have studied thyroid measures in depression, anxiety disorders, and anxious depression.

This review is limited by its retrospective, qualitative nature, and prospective studies are needed comparing the various groups of antidepressants.

Methodological issues aside, SSRIs have not been shown to be more effective in the treatment of anxious depression, and no medication or medication group has been convincingly shown to be superior. To the contrary, there is limited evidence that mirtazapine, bupropion, and nefazodone may be superior to SSRIs. In the treatment of anxious depression, clinicians are unnecessarily ruling out other treatments under an incorrect assumption. It may be that in one or more groups of patients labeled “anxious depressives,” certain medications are more effective. Lydiard and Brawman-Mintzer (3) provide a thoughtful discussion of some of the combinations of anxiety symptoms (or disorders) and depression, and the limited guidance from the literature on treatment. Given a lack of study of patients with anxiety clearly following onset of depression, and a similar lack in mixed anxiety-depressive disorder, it is important that future treatment studies in the heterogeneous group of anxious depressives be designed more rigorously.

A potential bias in this study is that funding was provided by the manufacturer of bupropion. However, the decision to write this article came out of a clinical impression formed over several years of clinical experience and observation on the article’s hypothesis. The author’s own clinical impression that SSRIs are not more effective in anxious impression was formed long before funding of this paper was ever considered.

CONCLUSIONS

SSRIs have not been shown to be more effective in the treatment of anxious depression. The author’s experience is also that no antidepressant is superior. When treating anxious depression, clinicians are unnecessarily ruling out other treatments under an incorrect assumption.

ACKNOWLEDGMENTS

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