Annals of Clinical Psychiatry, 17[1]:23–29, 2005

ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230590905317

Are SSRIs Really More Effective for Anxious Depression?

MICHAEL J. PANZER, M.D.
Fox Valley Psychiatric Associates, Appleton, WI, USA

Background. *Selective Serototonin 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.

Address correspondence to Michael J. Panzer, Fox Valley Psychiatric Associates, 1531 S. Madison, Suite 550 Appleton, WI 54915. E-mail: EPanzer@new.rr.com

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 differently 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.

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 1 Bupropion vs. SSRIs

Authors, length	SSRI, dose	Bupropion dose, total patients, comments
Feighner et al., 1991(11) 6 weeks	fluoxetine 38 mg	382 mg, n=123 same decrease in HAM-A and -D
Kavoussi et al., 1997 (12) 16 weeks	sertraline 50–200 mg	100–300 mg, n=248 same decrease in HAM-A and -D
Coleman et al., 1999 (13) 8 weeks	sertraline 106 mg	290 mg, n=364 bupropion superior on HAM-D;neither superior to placebo on HAM-A
Croft et al., 1999 (14) 8 weeks	sertraline 50–200 mg	150–400 mg, n=360 same decrease in HAM-A and -D
Trivedi et al., 2001 (15) 8 weeks	sertraline 50–200 mg	150–400 mg, n=692 same decrease in HAM-A and -D
Rush et al., 2001 (17) 8 weeks	sertraline 50–200 mg	100–300 mg, n=248 same decrease in HAM-A and -D
Weihs et al., 2000 (18) 44 weeks	paroxetine 10–40 mg	100–300 mg, n=100 same decrease in HAM-A and -D

Table 2 Mirtazapine vs. SSRIs or Amitriptyline

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

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/somatixation 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 and depression.

Table 3 TCAs vs SSRIs

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

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

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 4 SSRIs vs. SSRIs

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

Table 5 Bupropion vs. TCAs

Author	TCA, dose	Bupropion dose, patients, comments
Branconnier et al., 1983 (32) 5 weeks	imipramine 150 mg	150 or 450 mg, n=63 bupropion as good or betteron anxiety measures
Feighner et al., 1986 (33) 13 weeks	doxepin 150–200 mg	300–400 mg, n=147 bupropion superior on HAM-A
Mendels et al., 1983 (34) 4 weeks	amitriptyline 120 mg	380 mg, n=101same decrease on HAM-A

Table 6 Nefazodone vs. TCAs or SSRIs

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

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 a 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.

Venlafazine 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 7 Venlafaxine vs. Trazodone or SSRIs

Author	Comparator	Venlafaxine dose, comments
Cunningham et al., 1984 (39) 6 weeks	trazodone, placebo 300 mg	160 mg, n=225, all groups equal on HAM-D anxiety/ somatization factor
Silverstone et al., 1999 (40) 12 weeks	fluoxetine 39.9 mg, placebo	140.8 mg, n=359,
Ballus et al., 2000 (41) 24 weeks	paroxetine 20-40 mg no placebo	75–150 mg, n=84
Davidson et al., 2002 (42) 6 weeks		

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 venlafaxone 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 bupropion SR, nor did anxiety differentiate between responders to sertraline and responders to bupropion 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

The author wishes to thank Deo S. Bukenya, Pharm.D. for his assistance and support in the preparation of this review. The cheerful help of Karen Knorr of the Medical Library at St. Elizabeth Hospital in Appleton, Wisconsin is also greatly appreciated. This study was supported by a grant from Glaxo-Smith-Kline (manufacturer of Wellbutrin SR). Tracy Donald was very helpful in starting the paper.

REFERENCES

1. Fava M, Uebelacker L, Alpert J, Nierenberg A, Pava J, Rosenbaum J: Major depressive subtypes and treatment response. *Biol Psych* 1997; 42(7):568–576.
2. Fawcett J, Barkin R: A meta-analysis of eight randomized, double-blind, controlled clinical trials of mirtazapine for the treatment of patients with major depression and symptoms of anxiety. *J Clin Psych* 1998; 59(3):123–127.
3. Lydiard R, Brawman-Mintzer O: Anxious depression. *J Clin Psych* 1998; 59(Suppl 18):10–17.
4. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 134:382–389.
5. Covi L, Rickels K, Lipman O: Effects of psychotropic agents on primary depression. *Psychopharm Bull* 1981; 17:100–101.
6. Hamilton M: A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960; 23:56–62.
7. Montgomery S, Asberg M: A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979; 134:382–38.
8. *Diagnostic and statistical manual for mental disorders*; DSM-III. Washington, DC: American Psychiatric Association; 1980.
9. *Diagnostic and statistical manual for mental disorders: DSM-III-R*, 3rd ed. Revised. Washington, DC: American Psychiatric Association; 1989.
10. *Diagnostic and statistical manual for mental disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.

11. Feighner J, Gardner E, Johnston J, Batey S, Khayrallah M, Ascher J, Lineberry C: Double-blind comparison of bupropion and fluoxetine in depressed outpatients. *J Clin Psych* 1991; 52: 329–335.
12. Kavoussi R, Segraves R, Hughes A, Ascher J, Johnston J: Double-blind comparison of bupropion sustained release and sertraline in depressed outpatients. *J Clin Psych* 1997; 58: 532–537.
13. Coleman C, Cunningham L, Foster V, Batey S, Donahue R, Houser T, Ascher J: Sexual dysfunction associated with the treatment of depression: A placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Annals of Clin Psych* 1999; 11(4):205–215.
14. Croft H, Settle E, Houser T, Batey S, Donahue R, Ascher J: A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther* 1999; 12:643–658.
15. Trivedi M, Rush A, Carmody T, Donahue R, Bolden-Watson C, Houser T, Metz A: Do bupropion SR and sertraline differ in their effects on anxiety in depressed patients? *J Clin Psych* 2001; 62:776–781.
16. Rush A, Batey S, Donahue R, Ascher J, Carmody T, Metz A: Does pretreatment anxiety predict response to either bupropion SR or sertraline? *J Aff Dis* 2001; 64:81–87.
17. Rush A, Trivedi M, Carmody T, Donahue R, Houser T, Bolden-Watson C, Batey S, Ascher J, Metz A: Response in relation to baseline anxiety levels in major depressive disorder treated with bupropion sustained release or sertraline. *Neuropsychopharm* 2001; 25:131–138.
18. Weihs K, Settle E, Batey S, Houser T, Donahue R, Ascher J: Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psych* 2000; 61:196–202.
19. Nieuwstraten C, Dolovich L: Bupropion versus selective serotonin-reuptake inhibitors for treatment of depression. *Ann Pharmacother* 2001; 35(12):1608–1613.
20. Leinonen E, Skarstein J, Behnke K, Agren H, Helsdingen J, and the Nordic Antidepressant Study Group: Efficacy and tolerability of mirtazapine versus citalopram: a double-blind, randomized study in patients with major depressive disorder. *Int Clin Psychopharmacol* 1999; 14:329–337.
21. Benkert O, Szegedi A, Kohnen R: Mirtazapine compared with paroxetine in major depression. *J Clin Psych* 2000; 61: 656–663.
22. Schatzberg A, Kremer C, Rodrigues H, Murphy G, and The Mirtazapine vs. Paroxetine Study Group: Double-blind, randomized comparison of mirtazapine and paroxetine in elderly depressed patients. *Am J Geriatr Psychiatry* 2002; 10(5):541–555.
23. Wheatley D, Moffaert M, Timmerman L: Mirtazapine: Efficacy and tolerability in comparison with fluoxetine in patients with moderate to severe major depressive disorder. *J Clin Psych* 1998; 59:306–312.
24. Smith W, Glaudin V, Panagides J, Gilvary E: Mirtazapine vs. amitriptyline vs. placebo in the treatment of major depressive disorder. *Psychopharm* Bull 1990; 26(2):191–196.
25. Halikas J: Org 3770 (mirtazapine) versus trazodone: A placebo-controlled trial in depressed elderly patients. *Human Psychopharm* 1995; 10:S125–S133.
26. Bremner J: A double-blind comparison of Org 3770, amitriptyline, and placebo in major depression. *J Clin Psych* 1995; 56: 519–525.
27. Dunbar G, Cohn J, Fabre L, Feighner J, Fieve R, Mendels J, Shrivastava R: A comparison of paroxetine, imipramine and placebo in depressed out-patients. *Br J Psych* 1991; 159:394–398.
28. Marchesi C, Ceccerininelli A, Rossi A, Maggini C: Is anxious-agitated major depression responsive to fluoxetine? A double – blind comparison with amitriptyline. *Pharmacopsych* 1998; 31(6): 216–221.
29. Versiani M, Ontiveros A, Mazzotti G, Ospina J, Davila J, Mata S, Pacheco A, Plewes J, Tamura R, Palacios M: Fluoxetine versus amitriptyline in the treatment of major depression with associated anxiety (anxious depression): a double-blind comparison. *Int Clin Psychopharm* 1999; 14(6):321–327.
30. Fava M, Rosenbaum R, Hoog S, Tepner R, Kopp J, Nilsson M: Fluoxetine versus sertraline and paroxetine in major depression: tolerability and efficacy in anxious depression. *J Affect Dis* 2000; 59:119–126.
31. Stahl S: Placebo-controlled comparison of the selective serotonin reuptake inhibitors citalopram and sertraline. *Biol Psych* 2000; 48:894–901.
32. Branconnier, Cole J, Ghazvinian S, Spera K, Oxenkrug G, Bass J: Clinical pharmacology of bupropion and imipramine in elderly depressives. *J Clin Psych* 1983; 44(5):130–133.
33. Feighner J, Hendrickson G, Miller L, Stern W: Double-blind comparison of doxepin versus bupropion in outpatients with a major depressive disorder. *J Clin Psychopharm* 1986; 6(1): 27–32.
34. Mendels J, Amin A, Chouinard G, Cooper A, Miles J, Remick R, Saxena B, Secunda S, Singh A: A comparative study of bupropion and amitriptyline in depressed outpatients. *J Clin Psychopharm* 1983; 44:118–120.
35. Rickels K, Schweizer E, Clary C: Nefazodone and imipramine in major depression: a placebo-controlled trial. *Br J Psych* 1994; 164:802–805.
36. Fontaine R, Ontiveros A, Elie R, Kensler T, Roberts D, Kaplita S, Ecker J, Faludi G: A double-blind comparison of nefazodone, imipramine and placebo in major depression. *J Clin Psych* 1994; 55:234–241.
37. Fawcett J, Marcus R, Anton S, O'Brien K, Schwiderski U: Response of anxiety and agitation symptoms during nefazodone treatment of major depression. *J Clin Psych* 1995; 56(suppl 6): 37–42.
38. Baldwin D, Hawley C, Abed R, Maragakis B, Cox J, Buckingham S, Pover G, Ascher A: A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. *J Clin Psych* 1996; 57(suppl 2): 46–52.
39. Cunningham L, Borison R, Carman J, Chouinard G, Crowder J, Diamond B, Fischer D, Hearst E: A comparison of venlafaxine, trazodone, and placebo in major depression. *J Clin Psychopharm* 1994; 14(2):99–106.
40. Silverstone P, Ravindran A: Once-daily venlafaxine extended release (XR) compared with fluoxetine in outpatients with depression and anxiety. *J Clin Psych* 1999; 60:22–28.
41. Ballus C, Quiros G, Flores T, Torre J, Palao D, Rojo L, Guteirrez M, Casais L, Riesgo Y:The efficacy and tolerability of venlafaxine and paroxetine in outpatients with depressive disorder or dysthymia. *Int Clin Psychopharm* 2000; 15(1): 43–48.
42. Davidson J, Meoni P, Haudiquet V, Cantillon M, Hackett D: Achieving remission with Venlafaxine and fluoxetine in major

depression: its relationship to anxiety symptoms. *Depression and Anxiety* 2002; 16:4–13.
43. Overall J, Hollister L, Johnson M, Pennington V: Nosology of depression and differential response to drugs. *J Am Med Assoc* 1966; 195:162–164.
44. VanValkenburg C, Akiskal H, Puzantian V, Rosenthal T: Anxious depressions: Clinical, family history, and naturalistic outcome: Comparisons with panic and major depressive disorders. *J Aff Dis* 1984; 6(1):67–82.
45. Meller M, Kathol R, Samuelson S, Gehris T: CRH challenge test in anxious depression. *Biol Psych* 1995; 37(6):376–382.
46. Rao M, Vartzopoulos D, Fels K: Thyroid function in anxious and depressed patients.*Pharmacopsychiatry* 1989; 22(2): 66–70.