Management of Patients With Depression Associated With Anxiety Symptoms

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Current diagnostic classifications separate depression from anxiety, yet these conditions commonly coexist in clinical practice, forming a spectrum of disorders between these extremes. Treatment options for depression with anxiety include tricyclic antidepressants (TCAs) and serotonin selective reuptake inhibitors (SSRIs). As SSRIs are nonsedating, this proves that sedation as produced by TCAs is not required for anxiolytic actions. SSRIs are effective in anxiety disorders and against anxiety symptoms in depressed patients. The adverse event profile of SSRIs compares favorably with that of TCAs, and SSRIs are much safer in overdose. When the diagnosis of depression with anxiety is established, it is important to institute prompt, effective treatment in view of the potential risk of suicide. The SSRIs appear to be the treatment of choice for such patients.

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COEXISTENCE OF ANXIETY AND DEPRESSION

Depression and anxiety are considered to be separate entities according to current diagnostic classifications.[1–3] However, in clinical practice, the two conditions are seen to coexist, and a spectrum of disorders can be described, of which anxiety and depression are the two extremes.[2,4–6] As shown in Figure 1, it is now accepted that intermediate disorders exist between these two conditions: anxiety with depressive symptoms (Ad), depression with anxiety symptoms (Da), and mixed anxiety and depression at the syndromal (DA) or symptomological level (ad). This review will concentrate on the management of depression with anxiety symptoms (Da).

PREVALENCE OF DEPRESSION WITH ANXIETY SYMPTOMS

At least 5% of the U.S. population suffers from mood disorders, the vast majority of which are major depressive episodes or dysthymia. Anxiety disorders are even more common, affecting approximately 9% of the population,[7] and anxiety exists to some extent in nearly all depressed patients.[6,8] Over 95% of patients with depression have at least one symptom of anxiety,[8] and 20% to 65% of patients with anxiety also become depressed.[9] In a survey conducted among 200 patients with diagnosed major depression, 72% were found to have at least moderate worry, 62% experienced psychic anxiety, 42% experienced somatic anxiety, and 29% had a history of panic attacks.[10] These results were confirmed by a study that showed the most common anxiety states accompanying depression to be panic disorder, generalized anxiety disorder, and social phobia.[11] The clinical implications of this and subsequent studies were that the presence or absence of certain anxiety symptoms at specified levels of severity may act as predictors of treatment response.

The economic implications are also far reaching. Patients with depression and anxiety require more medication and psychotherapy and place a heavier burden on medical resources. Comorbidity of depression and anxiety has been associated with a 30% to 60% increase in health service use for mental health problems and increased clinical morbidity and suicide rates.[12] Furthermore, comorbidity was associated with an increased need for disability and welfare benefits. Patients with primary depression and a high anxiety rating (at least 16 on the Schedule for Affective Disorders and Schizophrenia scale) are significantly more likely to receive psychotherapy and antidepressants.[13] The optimum treatment plan for patients with depression and anxiety symptoms may depend on the type of depression and/or anxiety present.[14] Anxiety symptoms should therefore be taken into account when assessing which antidepressant therapy is most appropriate for an individual patient.

DIAGNOSTIC ISSUES

Depression is diagnosed when five of the following core symptoms (depressed mood, loss of interest, fatigue or loss

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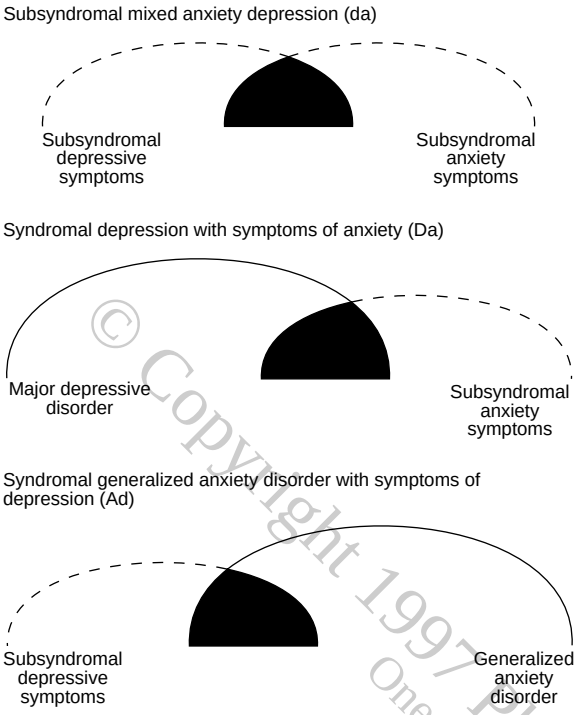
Figure 1. The Concept of Subsyndromal Symptoms in Depression and Anxiety*



*Adapted from reference 2.

of energy, difficulties with concentration, appetite disturbance, agitation or retardation, worthlessness or self blame, and thoughts of suicide) have persisted for 2 weeks and are associated with some occupational and social impairment.[1] The severity of depression is identified according to the number and severity of the depressive symptoms present and includes a measure of anxiety. The severity of an episode of depression is based on severe depressed mood, loss of interest and pleasure, suicidal behavior or thoughts of suicide, and high level of anxiety.

Anxiety disorders are subdivided into panic disorder, agoraphobia, social phobia, simple phobia, obsessive-compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder. The last of these, generalized anxiety disorder, is diagnosed when at least 6 of 18 symptoms indicative of motor tension, autonomic hyperactivity, vigilance, and scanning are present.[1]

The diagnosis of depression with anxiety symptoms is difficult, and as a consequence it is undertreated.[15] In the general population, the prevalence of anxiety and depression is 14% to 18%; only half of the patients (7%–9%), will present to their primary care physician, and the condition will be correctly diagnosed in less than half of these patients (3%–4%); the majority will not receive adequate treatment (0.5%–1%).[15]

There are several barriers to the better recognition and diagnosis of patients with depression and anxiety. The stigma of mental disease often prevents the patient from seeking medical help.[16] A more specific barrier is that many depressive and anxiety disorders remain as poorly understood complexes of symptoms which require better definition and targeted treatment. In addition, diagnosis is further complicated by the frequent coexistence of alcohol or drug abuse with depression and anxiety.[16]

It is important to ensure that depression with anxiety is adequately diagnosed, as patients with depression and symptoms of anxiety are known to have a poorer outcome than those with depression alone.[17–19] In depressed patients, anxiety is a marker of severity,[13] poor outcome,[13,20] response to treatment,[4,13] and suicide risk.[4,18,21,22] Depressed patients who have higher ratings for anxiety are more severely ill, take longer to recover, and show a poor response to antidepressants.[4,13,19,23] Clayton et al. investigated six symptoms of anxiety in 327 patients with primary depression and found that patients with higher ratings for anxiety took significantly longer to recover.[13] In another study, 91 patients with panic attacks and depressive episodes had more severe symptoms of depression and were less likely to recover during the 2-year follow-up period than 417 depressed patients who did not have panic attacks.[4] Suicidal attempts are more frequent in patients with comorbidity of depression and panic disorders,[24] and recent evidence from Fawcett indicates that the presence of severe anxiety is a predictor of suicide in depressed patients.[25]

CURRENT APPROACHES TO MANAGEMENT

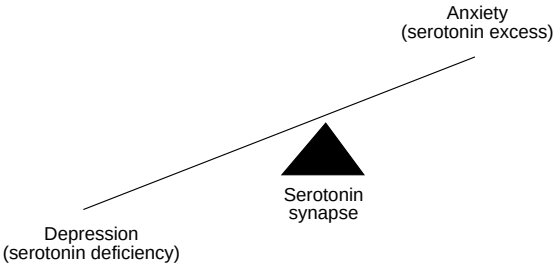
Current treatment options for depression with anxiety include TCAs of the sedating variety and SSRIs.

Tricyclic Antidepressants

TCAs act by inhibiting their uptake of both norepinephrine and serotonin; it is the latter neurotransmitter system that may be crucially involved in depressive and anxiety disorders (see later discussion). The efficacy of TCAs is well established in the treatment of depression, and the effectiveness of monotherapy with TCAs has been demonstrated in treating depressed outpatients with mixed symptoms of anxiety and depression.[26] However, although it may be thought that the sedative effects of TCAs would provide early relief of anxiety symptoms, this has not been demonstrated in controlled trials.[27]

In some studies, TCAs were as effective as benzodiazepines in the treatment of anxiety in patients with mixed symptoms of anxiety and depression.[26,28,29] Nevertheless, it should be borne in mind that the lack of diagnostic rigor in these studies makes it difficult to determine the exact levels of depression and anxiety present. Amitriptyline was as effective as diazepam in the treatment of both anxiety and depression in a placebo-controlled, retrospective study

Figure 2. Anxiety and Depression May Be a Dynamic Serotonergic Continuum



conducted in 240 outpatients stratified into those with primary anxiety and those with primary depression.[30]

Disadvantages associated with the TCAs are daytime sedation, anticholinergic side effects, which can lead to poor compliance, and initial worsening of the patient's condition. Sedating TCAs may therefore not be the treatment of choice for the management of depressed patients with anxiety symptoms.

Serotonin Selective Reuptake Inhibitors

Imbalances in serotonergic neurotransmission may contribute substantially to both depression and anxiety, with an excess of serotonin leading to anxiety and a deficit of serotonin leading to depression (Figure 2). Therefore, by normalizing serotonergic imbalances, it is probable that one drug may be able to treat both conditions.[31] A number of serotonin receptor subtypes have been identified, and their role in different types of anxiety has been established.[32] It is likely that SSRIs that are selective for specific receptor subtypes will be able to target specific types of anxiety disorders and depression.

The SSRIs are at least as effective as TCAs in the treatment of depression.[33–35] This was confirmed by a meta-analysis of controlled studies comparing fluvoxamine, fluoxetine, citalopram, and sertraline with amitriptyline and imipramine.[36] Using fluvoxamine as the example SSRI, this drug was at least as effective as imipramine in the treatment of depression in 15 double-blind comparative studies conducted in over 2000 patients. Similar results were obtained for fluvoxamine compared with desimipramine, clomipramine, maprotiline, mianserin, and dothiepin.

SSRIs are known to be effective in the treatment of some anxiety disorders,[37] and they have good efficacy against anxiety symptoms in depressed patients. Studies have indicated that fluoxetine, fluvoxamine, paroxetine, and citalopram might be useful in depressed patients with significant anxiety symptoms or psychomotor agitation.[38]

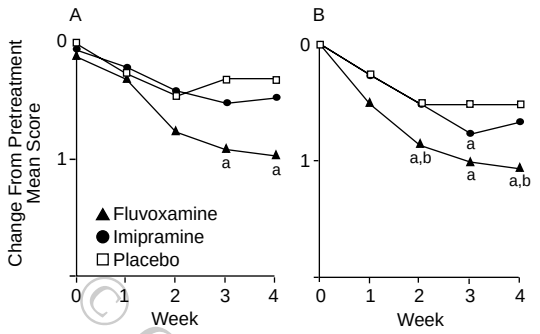
SSRIs and benzodiazepines. SSRIs are at least as effective as benzodiazepines in the treatment of anxiety symptoms in depressed patients. In one double-blind study, fluvoxamine was compared with the benzodiazepine lorazepam in 112 patients with mixed anxiety and depression. Both treatments produced similar, significant improvements in anxiety after 1 week's treatment compared with baseline.[39] Two other double-blind, randomized studies have compared fluvoxamine with diazepam and prazepam and demonstrated equivalent reductions in anxiety.[40,41] In the first of these studies, patients with low mood and anxiety received fluvoxamine (N = 30) or diazepam (N = 30), while in the second study, patients with major depressive syndrome (with somatic complaints) and anxiety received fluvoxamine (N = 44), prazepam (N = 42), or fluvoxamine and prazepam (N = 44). When the results of these three studies were combined in a meta-analysis, it appeared that while there was no difference in the onset of anxiolytic activity between fluvoxamine and the benzodiazepines, fluvoxamine had a somewhat faster onset of action on depressive symptoms at Week 1 (Data on file, Solvay Duphar).[42]

SSRIs and TCAs. The SSRIs are clinically equipotent with the TCAs in the treatment of major depression[36] and are as effective as the TCAs in the treatment of anxiety disorders.[37] They may offer greater benefit than the TCAs in treating depressed patients with concomitant anxiety.

The superior efficacy of SSRIs compared with TCAs can be seen with fluvoxamine, which significantly improved the psychic anxiety item of the Hamilton Rating Scale for Depression (HAM-D) score compared with imipramine in a placebo-controlled multicenter study involving 338 depressed patients; furthermore, fluvoxamine had a significantly greater effect than placebo at Weeks 3 and 4 on both the somatic and psychic anxiety items ($p < .05$), while the only significant difference between placebo and imipramine was seen at Week 3 in the psychic anxiety item (Figure 3).[42]

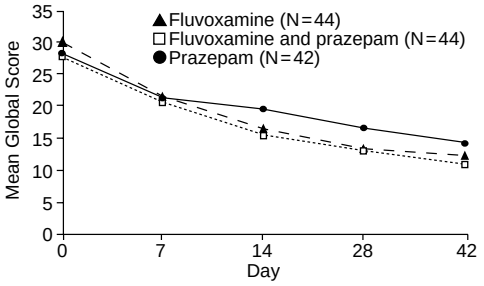
There is evidence that other SSRIs are superior to TCAs in treating depression with anxiety. Paroxetine was significantly superior to imipramine on two anxiety scales following 6 weeks' treatment in a double-blind, randomized study conducted in 120 patients with depression.[43] Paroxetine was found to be significantly superior to imipramine and placebo on the Covi Anxiety Scale and for somatic anxiety on the HAM-D scale ($p < .05$). These findings were confirmed by a comparative analysis of 2963 patients with depression and anxiety or agitation receiving paroxetine, 1151 patients receiving standard antidepressants, and 554 patients receiving placebo.[44] Both paroxetine and the comparator antidepressants were significantly better than placebo in reducing psychic anxiety and somatic anxiety. Fluoxetine was found to be comparable to imipramine and superior to placebo in reducing the symptoms of anxiety in 688 patients with major depression.[45] These results were independent of the patient's baseline psychomotor activity. Similarly, sertraline has been shown to improve anxiety symptoms in depression, with fewer side effects than clomipramine.[46]

Figure 3. Mean Individual Item Hamilton Rating Scale for Depression Scores for (A) Somatic Anxiety (B) Psychic Anxiety*



*Adapted from reference 42.
[a]p ≤ .05 vs placebo.
[b]p ≤ .05 vs imipramine.

Figure 4. Mean Global Hamilton Anxiety Scale Scores*



*Adapted from reference 41.

SSRIs are better tolerated than the TCAs, and it is known that the unwanted effects of TCAs can compromise compliance. When the number of withdrawals from treatment were compared in a meta-analysis of 67 trials, there were significantly fewer withdrawals due to side effects in the SSRI group than in the TCA group ($p < .01$).[47]

Antidepressants in Combination With Benzodiazepines

Benzodiazepines are rapid acting, widely used agents.[48] However, although they have been given as monotherapy in patients with depression and anxiety symptoms, with the exception of alprazolam,[49] they have no beneficial effect on endogenous depression.[26]

It has been suggested that there may be a complementary effect between antidepressants and benzodiazepines when coprescribed.[2] An approach involving a combination of an antidepressant (TCA) and an anxiolytic (benzodiazepine) is used in some areas, such as Southern Europe and Canada, to treat depression and anxiety,[50] but there is little published evidence to support this regimen. Some evidence of a complementary effect has also been reported with SSRIs and benzodiazepines; for example, the study by Chabannes et al. demonstrated a superior improvement in anxiety score with fluvoxamine plus prazepam compared with fluvoxamine or prazepam alone (Figure 4).[41] However, as with the TCA and benzodiazepine combination, there are few data currently available.

However, it is important to bear in mind that there is a potential for drug-drug interactions when antidepressants are given in combination with a benzodiazepine.[51] For example, cytochrome P_{450} 3A4 metabolizes a number of benzodiazepines, such as midazolam and diazepam, but is also inhibited by the SSRI fluoxetine. Similarly, pharmacokinetic interactions and increased impairment of psychomotor performance have been reported during combined treatment with benzodiazepines and tricyclic antidepressants.[52,53]

SAFETY AND TOLERABILITY CONCERNS

A good safety and tolerability profile is important in depressed patients with anxiety symptoms as they often have significant somatization. Safety in overdose is also important as there is a higher risk of early suicide in depressed patients with increased psychic anxiety than in those with depression alone.[23,54]

Current opinion suggests that the SSRIs may be the treatment of choice for depressed patients with anxiety symptoms. However, some SSRIs (fluoxetine, zimeldine) are associated with transient increases in nervousness, agitation, or anxiety early in treatment.[14,55–59] Therefore, some SSRIs may be too stimulating for effective treatment of depression with anxiety symptoms. Fluvoxamine is associated with a lower incidence of nervousness, anxiety, and agitation compared with other SSRIs,[60] and its safety has been established in worldwide studies conducted in more than 34,000 patients; in this analysis, the only adverse event occurring with a frequency greater than 10% was nausea, and additionally, the drug was associated with a very low suicidality rate.[61]

Overall, the SSRIs have a favorable tolerability profile compared with TCAs.[61] SSRIs are first choice antidepressants because they lack the cholinergic and sedative effects associated with TCAs, have a lower cardiotoxicity threshold, are not epileptogenic, and are less likely to cause weight gain.[62,63] TCAs are associated with orthostatic hypotension, cardiotoxicity, toxic psychosis, convulsions, and hypnosedation.[64]

Another difference in side effects between the SSRIs and the TCAs is in the impairment of cognitive skills and psychomotor ability.[65] The high incidence of these side effects with TCAs has profound implications for patients' safety during day-to-day activities such as driving and operating machinery. The risk of road traffic accidents is increased more than twofold in patients receiving TCAs.[66] In contrast, the SSRIs are relatively free of these side effects.[65] In a recent survey of 11 studies, TCAs significantly impaired two measures of behavioral toxicity, the critical flicker fusion threshold and choice reaction time. Fluvox-

amine had no effect on these parameters, whereas some other SSRIs (paroxetine, sertraline) showed evidence of CNS stimulation.[65]

CONCLUSIONS

In depressed patients, the presence of anxiety is a marker of disease severity, poor outcome, poor response to treatment, and increased suicide risk. It is therefore important to select the most effective treatment regimen for patients with depression associated with anxiety symptoms.

Current strategies for the management of depression with anxiety symptoms include the use of TCAs and SSRIs, alone or possibly in association with a benzodiazepine. While the TCAs are effective, there are drawbacks associated with their use including poor safety in overdose, which is a particular concern for some patients with depression and anxiety who may be at increased risk of suicide.

Conventional benzodiazepines are rapid-acting anxiolytics that generally have no effect on the underlying depression when used as monotherapy. Therefore, they are usually used in combination with an antidepressant for the management of patients with depression and symptoms of anxiety. However, it is important to bear in mind the potential for drug-drug interactions when using this combination.

The role of SSRIs in the management of patients with depression and anxiety is appealing because of the involvement of the serotonergic system in the development of depression and anxiety. The safety and tolerability of the SSRIs compare very favorably with that of the TCAs; in particular, the SSRIs are safe in overdose. An analysis of one of the largest SSRI safety data bases (over 34,000 patients) has demonstrated the safety and tolerability of fluvoxamine.[67]

Efficacy and safety considerations indicate that, in the future, the SSRIs will play an increasing role in the management of depression with concomitant anxiety symptoms.

Drug names: alprazolam (Xanax), amitriptyline (Elavil and others), clomipramine (Anafranil), desipramine (Norpramin and others), diazepam (Valium and others), fluoxetine (Prozac), fluvoxamine (Luvox), imipramine (Tofranil and others), lorazepam (Ativan and others), maprotiline (Ludiomil), mianserin (Tolvin, Bolvidon), midazolam (Versed), paroxetine (Paxil), prazepam (Centrax), sertraline (Zoloft), zimeldine (Zelmid).

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987:124–125
2. Stahl SM. Mixed anxiety and depression: clinical implications. J Clin Psychiatry 1993;54(suppl 1):33–38
3. ICD-10. Classification of Mental and Behavioral Disorders: Clinical Descriptions and Diagnostic Guidelines. Geneva, Switzerland: World Health Organization; 1992
4. Coryell W, Endicott J, Andreasen N, et al. Depression and panic attacks: the significance of overlap as reflected in follow-up and family study data. Am J Psychiatry 1988;145:293–300
5. Wittchen H-U, Essau CA. Comorbidity and mixed anxiety-depressive disorders: is there epidemiologic evidence? J Clin Psychiatry 1993;54(suppl 1):9–15
6. Angst J, Dobler-Mikola A. A continuum from depression to anxiety disorders? Eur Arch Psychiatry Clin Neurosci 1985;235:179–186
7. Regier DA, Boyd JH, Burke JD, et al. One-month prevalence of mental disorders in the US: based on five Epidemiologic Catchment Area sites. Arch Gen Psychiatry 1988;45:977–986
8. Hamilton M. Distinguishing between anxiety and depressive disorders. In: Last CA, Hersen M, eds. Handbook of Anxiety Disorders. New York, NY: Pergamon Press; 1988:143–155
9. Roth M, Gurney C, Garside RF, et al. Studies in the classification of affective disorders: the relationship between anxiety states and depressive illness. Br J Psychiatry 1972;121:147–161
10. Fawcett J, Kravitz HM. Anxiety syndromes and their relationship to depressive illness. J Clin Psychiatry 1983;44:8–11
11. Lydiard RB. Coexisting depression and anxiety: special diagnostic and treatment issues. J Clin Psychiatry 1991;52(suppl 6):48–54
12. Judd L. Comorbidity and health costs. International Med News 1994; 92(2):4–5
13. Clayton PJ, Grove WM, Coryell W, et al. Follow-up and family study of anxious depression. Am J Psychol 1991;148:1512–1517
14. Liebowitz MR. Depression with anxiety and atypical depression. J Clin Psychiatry 1993;54(suppl 2):10–14
15. Goldberg D, Huxley P. Common Mental Disorders. London, England: Routledge; 1992
16. Kamerow DB. Anxiety and depression in the medical setting: an overview. Med Clin North Am 1988;72(4):745–751
17. Clayton PJ. Comorbidity factor: establishing the primary diagnosis in patients with mixed symptoms of anxiety and depression. J Clin Psychiatry 1990;51(suppl 11):35–39
18. Fawcett J, Scheftner WA, Fogg L, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry 1990;147:1189–1194
19. Murphy J, Oliver DC, Sobol AM, et al. Diagnosis and outcome: depression and anxiety in a general population. Psychol Med 1986;16:117–126
20. Noyes RJ, Clancy J, Hoenk PR, et al. The prognosis of anxiety neurosis. Arch Gen Psychiatry 1980;37:173–178
21. Johnson J, Weissman MM, Kierman GL. Panic disorder, comorbidity and suicide attempts. Arch Gen Psychiatry 1990;47:805–808
22. Young LT, Cooke RG, Robb JC, et al. Anxious and non-anxious bipolar disorder. J Affect Disord 1993;29:49–52
23. Fawcett J. Targeting treatment in patients with mixed symptoms of anxiety and depression. J Clin Psychiatry 1990;51(suppl 11):40–43
24. Regier DA, Narrow WE, Rae DS, et al. Epidemiological Catchment Area prospective one-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993;50:85–94
25. Fawcett J. The detection and consequences of anxiety in clinical depression. J Clin Psychiatry 1997;58(suppl 8):35–40
26. Rickels K, Schweizer E. The treatment of generalized anxiety disorder in patients with depressive symptomatology. J Clin Psychiatry 1993;54(suppl 1):20–23
27. Kasper S. Pharmacological treatment of mixed anxiety and depression [abstract]. Proceedings of the VII Congress of the European College of Neuropsychopharmacology; Oct 16–21, 1994; Jerusalem, Israel
28. Hoehn-Saric R, McLeod DR, Zimmerli WD. Differential effects of alprazolam and imipramine in generalized anxiety disorder: somatic versus psychic symptoms. J Clin Psychiatry 1988;49:293–301
29. Rickels K, Downing R, Schweizer E. Antidepressants for the treatment of generalized anxiety: a placebo-controlled comparison of imipramine, trazodone, and diazepam. Arch Gen Psychiatry 1993;50:884–895
30. Johnstone EC, Owens DGC, Frith CD, et al. Neurotic illness and its response to anxiolytic and antidepressant treatment. Psychol Med 1980;10: 321–328
31. Eison MS. Serotonin: a common neurobiologic substrate in anxiety and depression. J Clin Psychopharmacol 1990;10:26S–30S
32. Baldwin D, Rudge S. The role of serotonin in depression and anxiety. Int Clin Psychopharmacol 1995;9(suppl 4):41–45
33. Anderson IM, Tomenson BM. The efficacy of selective serotonin re-uptake inhibitors in depression: a meta analysis of studies against tricyclic antide-

pressants. J Clin Psychopharmacol 1994;8:238–249
34. Feighner JP, Boyer WF. Paroxetine in the treatment of major depression. Acta Psychiatr Scand 1989;80:125–129
35. Feighner JP, Boyer WF, Meredith CH, et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine in major depression. Int Clin Psychopharmacol 1989;4:239–244
36. Kasper S, Fuger J, Moller HJ. Comparative efficacy of antidepressant. Drugs 1992;43(suppl 2):11–23
37. Den Boer JA, Westenberg HGM, Kamerbeek WDJ, et al. Effect of serotonin uptake inhibitors in anxiety disorders: a double blind comparison of clomipramine and fluvoxamine. Int Clin Psychopharmacol 1987;2:21–32
38. Kasper S. Neurobiology and new psychopharmacological strategies for treatment of anxiety disorders. In: Racagni, Brunelli, eds. Current Therapeutical Approaches on Panic and Other Anxiety Disorders. Basel, Switzerland: Karger; 1995
39. Laws D, Ashford JJ, Anstee JA. A multicentre double-blind comparative trial of fluvoxamine versus lorazepam in mixed anxiety and depression treated in general practice. Acta Psychiatr Scand 1990;81:185–189
40. Chabannes J-P, Séchier P, Baro P. Traitement des états anxiodépressifs. Étude comparative en double insu de la fluvoxamine versus diazépam. Nervure 1989;7(suppl):1–4
41. Chabannes JP, Douge R, Baro P, et al. Fluvoxamine and anxiety: efficacy of fluvoxamine on anxiety in two double blind comparative studies among anxio-depressed patients. Presented at the VIII World Congress of Psychiatry; October 1989; Athens, Greece
42. Kasper S, Möller H-J, Montgomery SA, et al. Antidepressant efficacy in relation to item analysis and severity of depression: a placebo-controlled trial of fluvoxamine versus imipramine. Int Clin Psychopharmacol 1995;9 (suppl 4):3–12
43. Feighner JP, Boyer WF. Paroxetine in the treatment of depression: a comparison with imipramine and placebo. J Clin Psychiatry 1992;53(suppl 2):44–47
44. Dunner DL, Dunbar GC. Managing the patient with depression and anxiety. European Psychiatry 1993;8(suppl 1):9–12
45. Beasley CM, Sayler ME, Bosomworth JC, et al. High-dose fluoxetine: efficacy and activating-sedating effects in agitated and retarded depression. J Clin Psychopharmacol 1991;11:166–174
46. Nutt D. The anxiety factor in depression. J Clin Psychopharmacol 1995;9 (suppl):185–189
47. Montgomery SA, Kasper S. Comparison of compliance between serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. Int Clin Psychopharmacol 1995;9(suppl 4):33–40
48. Sussman N, Chou JCY. Current issues in benzodiazepine use for anxiety disorders. Psychiatr Ann 1988;18:139–145
49. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. Br J Psychiatry 1992;160:191–202
50. Nutt DJ, Bell CJ, Potokar JP. Drug treatment of chronic anxiety. In: Ancill RJ, Lader MH, eds. Pharmacologic Management of Chronic Psychiatric Disorders. London: Balliere Tindall;1995
51. Cook MD, Conner J. Retrospective review of hypnotic use in combination with fluoxetine or sertraline. Clinical Drug Investigation 1995;9:212–216
52. Patat A, Klein MJ, Hucher M, et al. Acute effects of amitriptyline on human performance and interactions with diazepam. Eur J Clin Pharmacol 1988; 35:585–592
53. Grasela TH Jr, Ereshefsky L, Wells BG, et al. An evaluation of population pharmacokinetics in therapeutic trials, part II: detection of a drug-drug interaction. Clin Pharmacol Ther 1987;42:433–441
54. De Jonghe F, Swinkels JA. The safety of antidepressants. Drugs 1992;43 (suppl 2):40–47
55. Gorman JM, Liebowitz MR, Fyer AJ, et al. An open trial of fluoxetine in the treatment of panic attacks. J Clin Psychopharmacol 1987;7:329–332
56. Benfield P, Heel RC, Lewis SP. Fluoxetine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. Drugs 1986;32:481–508
57. Huitfeldt B, Montgomery SA. Comparison between zimelidine and amitriptyline of efficacy and adverse symptoms. Acta Psychiatr Scand 1983;69 (suppl 308):55–69
58. Sommi RW, Crismon ML, Bowden CL. Fluoxetine: a serotonin-specific, second-generation antidepressant. Pharmacotherapy 1987;7:1–15
59. Stokes PE. Fluoxetine: a five-year review. Clin Ther 1993;15:216–243
60. Wagner W, Zaborny BA, Gray TE. Fluvoxamine: a review of its safety profile in world-wide studies. Int Clin Psychopharmacol 1994;9:223–227
61. Fox T. Drug treatment of anxiety and depression. Practitioner 1990;233: 681–683
62. Leonard BE. Pharmacological differences of serotonin reuptake inhibitors and possible clinical relevance. Drugs 1992;43:3–9
63. Rudorfer MV, Manji HK, Potter WZ. Comparative tolerability profiles of the newer versus older antidepressants. Drug Saf 1994;10:18–46
64. Swinkels JA, de Jonghe F. Safety of antidepressants. Int Clin Psychopharmacol 1995;9(suppl 4):19–25
65. Hindmarch I. The behavioral toxicity of the selective serotonin reuptake inhibitors. Int Clin Psychopharmacol 1995;9(suppl 4):13–17
66. Ray WA, Fought RL, Decker MD. Psychoactive drugs and the risk of injurious motor vehicle crashes in elderly drivers. Am J Epidemiol 1992; 136:873–883
67. Wagner W, Zaborhni BA, Grey G, et al. Fluvoxamine: a review of its safety profile in worldwide studies. Int Clin Psychopharmacol 1994;9:223–227