Safety and Tolerability of the New Antidepressants

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The newer serotonergic antidepressants have become popular particularly because of improved tolerability and safety. The evidence supporting this belief is reviewed. The factors that contribute to the development of somatic symptoms are examined, including the depression itself and the drugs used for treatment. The rates for individual side effects with the serotonin selective reuptake inhibitors, nefazodone, and venlafaxine are presented and compared with the adverse event experience for mirtazapine.
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Because antidepressant drugs are relatively similar in efficacy, tolerability and safety play a prominent role in drug selection. The American Psychiatric Association guidelines[1] for treatment of major depression concluded that, "in nonselected cases of major depression, the data indicate similar rates of response to all antidepressant drugs; therefore, the choice must be predicated on other factors. These include the drug's tendency to evoke a particular constellation of side effects." The success of the new-generation serotonergic drugs is very much related to their improved tolerability. The supporting evidence comes from several sources.

ADVANTAGES OF THE NEW SEROTONERGIC AGENTS

The serotonin selective reuptake inhibitors (SSRIs) are less likely to be discontinued during acute treatment because of adverse reactions than are the tricyclic antidepressants (TCAs). Montgomery et al.[2] performed a meta-analysis of discontinuation rates in 42 studies comparing SSRIs and TCAs. In these studies, with over 2000 patients receiving SSRIs or TCAs, the discontinuation rate was significantly higher for the TCAs: 19% vs. 15 % ($p < .001$). In the placebo-controlled trials, with over 500 patients in each group, the magnitude of the difference was greater: 27% for TCAs vs. 19% for placebo ($p < .01$).

A patient's acceptance of a new drug is determined not only by the more severe adverse effects that result in discontinuation, but also by the subjective symptoms that occur during continued treatment. There are fewer data available evaluating this issue. Often, the data for individual symptoms are presented but without a global estimate of tolerance. One of the few studies examining this issue compared sertraline and amitriptyline.[3] The total "side effect burden" was calculated accounting for both the frequency and severity of side effects that patients experienced while continuing on medications. The side effect burden for amitriptyline was substantially greater than that for sertraline, which was slightly greater than that for placebo.

Another interesting set of data bearing on the question of the global impact of side effects on functioning was reported in a double-blind comparison of nefazodone, imipramine, and placebo.[4] In this study, only 2% of the patients on imipramine were judged by the physician to have no side effects. This is consistent with the clinical experience that patients on TCAs usually have at least mild symptoms, such as dry mouth, tachycardia, light-headedness, or sweating, that remind them that they are taking medication. Alternatively, for nefazodone, about a third of the patients at the lower dose (up to 250 mg/day) and a fifth of the patients at the higher dose (up to 500 mg/day) had no side effects. The percentage of patients who had side effects that interfered with functioning or that outweighed the benefit of treatment was 32% in the patients receiving imipramine but less than 10% for patients on either dose of nefazodone.

From a safety perspective, another major advantage of the newer serotonergic drugs is their safety in overdose.[5] This has important implications not only for the patient's well being, but also for the cost of treatment. An overdose with one of the newer serotonergic agents may not require hospitalization unless the patient remains suicidal.

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Table 1. Side Effects Reported During Clinical Drug Trials for Drug and Placebo*

Side Effect	Fluoxetine[a] 1730/799	Sertraline[a] 861/853	Paroxetine[a] 421/421	Venlafaxine[a] 1033/609	Nefazodone[a] 393/394	Mirtazapine[b] 580/361
Nervous system						
Headache	20.3/15.5	20.3/19.0	17.6/17.3	25/24	36/33	11.0/15.8
Agitation	…	5.6/4.0	2.1/1.9	**2/0**	≤	…
Nervousness	14.9/8.5	3.4/1.9	**5.2/2.6**	**13/6**	…	4.4/4.2
Anxiety	9.4/5.5	**2.6/1.3**	5.0/2.9	**6/3**	≤	…
Tremors	**7.9/2.4**	**10.7/2.7**	**8.3/1.9**	**5/1**	**2/1**	**1.5/0.6**
Insomnia	13.8/7.1	16.4/8.8	**13.3/6.2**	18/10	11/9	3.8/5.8
Drowsiness	11.6/6.3	**13.4/5.9**	**23.3/9.0**	**23/9**	25/14	**53.6/18.0**
Fatigue	**4.2/1.1**	10.6/8.1	**15.0/5.9**	**12/6**	**11/5**	7.5/4.7
Confusion	…	…	**1.2/0.2**	**2/1**	**7/2**	**2.0/0.3**
Dizziness	5.7/3.3	11.7/6.7	**13.3/5.5**	**19/7**	**17/5**	**7.3/3.3**
Blurred vision	2.8/1.8	**4.2/2.1**	**3.6/1.4**	**6/2**	**9/3**	2.4/1.7
Cardiovascular						
Palpitations	1.3/1.4	**3.5/1.6**	**2.9/1.4**	≤	≤	2.0/2.2
Orthostatic hypotension	…	…	**1.2/0.5**	**1/0**	**4/1**	1.1/0.6
Hypertension	…	…	…	**2/0**		
Gastrointestinal						
Nausea	**21.1/10.1**	**26.1/11.8**	**25.7/9.3**	**37/11**	22/12	4.2/5.3
Vomiting	2.4/1.3	**3.8/1.8**	2.4/1.7	**6/2**	≤	…
Dyspepsia	6.4/4.3	**6.0/2.8**	1.9/1.0	5/4	9/7	2.9/2.5
Diarrhea	12.3/7.0	17.7/9.3	11.6/7.6	8/7	8/7	2.4/4.4
Constipation	4.5/3.3	8.4/6.3	13.8/8.6	**15/7**	14/8	12.6/6.6
Anorexia	**8.7/1.5**	2.8/1.6	**6.4/1.9**	**11/2**	≤	…
Increased appetite	…	1.3/0.9	**1.4/0.5**	≤	5/3	**16.8/1.9**
Metabolic						
Edema	…	…	…	…	≤	**1.3/0.3**
Weight gain	…	…	…	…	≤	**11.9/1.7**
Sexual dysfunction						
Abnormal ejaculation/ orgasm (men)	1.9/<1	**15.5/2.2**	**12.9/0**	**12/0**	0.2/0	…
Orgasm disturbance (women)	…	**1.7/0.2**	**1.8/0**	**2/0**	0.1/0	…
Autonomic						
Dry mouth	9.5/6.0	16.3/9.3	18.1/12.1	**22/11**	25/13	24.7/15.0
Sweating	**8.4/3.8**	**8.4/2.9**	**11.2/2.4**	**12/3**	≤	1.1/0.8
Skin						
Rash	2.7/1.8	2.1/1.5	**1.7/0.7**	3/2	**2/1**	…

*N/N = active drug/placebo. **Bold: active ≥ 2 × placebo.**
[a]Physicians' Desk Reference.[11]
[b]From the data for mirtazapine. New Drug Application on file with the Food and Drug Administration.
[c]For all agents, rates ≥ 1% reported; for venlafaxine and nefazodone, rates ≥ 1% *and* greater than placebo reported. Ellipses indicate no information provided; this indicates that either the rate was ≤ 1% or it was not coded or studied.

A TCA overdose frequently requires a 48-hour admission with cardiac monitoring. This important difference helps to explain the increased hospitalization costs for the TCAs, which contribute to the greater overall cost of TCA treatment.[6]

The SSRI agents have minimal effects on the cardiogram, although studies of these effects have usually been limited to normal subjects. Studies of the effects of SSRIs in patients with cardiac disease have been limited to fluoxetine[7] and paroxetine.[8] These agents appear to be safe in such patients.

FACTORS CONTRIBUTING TO SOMATIC SYMPTOMS

Somatic Symptoms and Depression

The evaluation of somatic symptoms in depressed patients is complicated. Somatic symptoms may be caused by the depression or by the medications used for treatment. Depressed patients report many somatic symptoms. In one of the earliest quantitative reports, Cassidy and colleagues[9] examined somatic symptoms reported by 100 patients with severe depressive illness. Some of the most common symptoms, such as loss of appetite, loss of energy, or insomnia, later became symptom criteria for major depression. But other somatic symptoms that commonly occurred in these depressed patients, such as constipation (60%), dyspnea (77%), nausea (48%), and palpitations (57%), are frequently regarded as side effects of medication.

We examined this issue in a study of 43 depressed inpatients using a 23-item Somatic Symptom Checklist before and after treatment with desipramine.[10] Many somatic symptoms usually considered to be "side effects," such as dry mouth, light-headedness, sweating, tremors, and constipation, were frequently present in depressed patients before treatment. Headache is another interesting example.

Headache was present in 40% of the depressed patients prior to treatment. In the clinical trials for the new serotonin (5-HT) agents, frequently headache was reported as a side effect, with rates ranging from 17.6% to 36% (see Table 1), but the rates reported for placebo were similarly high (15.5% to 33%). It appears that headache is more often a symptom of depression than a side effect of medication.

Because depression influences patients' reporting of symptoms, the number and severity of somatic symptoms will vary with the severity of depression during treatment. We examined this relationship in the previous study of depressed inpatients during treatment with desipramine.[10] Nine individual symptoms, often considered side effects, significantly *improved during treatment*. The 14 remaining items, which did not significantly improve, were examined in relation to severity of depression during treatment. This 14-item total varied significantly with the severity of depression, as assessed with the Hamilton Rating Scale for Depression (HAM-D) after 3 weeks of treatment ($r = .60$, $p < .001$). More severely depressed inpatients reported more symptoms. The concentration of desipramine was not significantly correlated with the severity of the 14-item total ($r = –.26$, p = n.s.). In fact the correlation was slightly negative, apparently reflecting that patients with higher antidepressant blood levels tended to have greater improvement and to report fewer "side effects." We concluded that the best treatment for many of these somatic symptoms was an increased dose of desipramine.

In a second study,[12] we treated depressed inpatients with desipramine adjusted to attain a target plasma concentration. In this sample, the relationship of somatic symptoms to severity of depression was examined. An 11-item somatic symptom total was calculated from the Somatic Symptom Checklist[10] using the items Asberg et al. described in a study of nortriptyline side effects.[13] (Drowsiness was substituted for decreased energy, which was not assessed on the checklist). We then determined the correlation of the 11-item total with depression severity on the HAM-D at each week of the 4-week study in 34 patients for whom both ratings were available. Correlations of the 11-item total and HAM-D scores at each week ranged from .46 to .64, all significant at $p < .01$. In this study, as in the preceding, severity of depression was a major determinant of the somatic symptoms reported.

Our findings were determined in studies of inpatients with severe depression. In these patients, depression plays a major role in the somatic symptoms that patients experience. In mild depression, however, the pharmacologic effects of the drug may be a relatively more important determinant of somatic symptoms reported during treatment. Further, a side effect of moderate severity may be perceived by a patient with mild depression as more severe relative to their illness and is more likely to influence decisions about whether to continue treatment.

Individual Sensitivity

A second general factor influencing the development of somatic symptoms is individual sensitivity. For almost every side effect, an important predictor of that side effect is the individual's prior history of vulnerability. For example, the best predictor of orthostatic hypotension during TCA treatment is the patient's orthostatic drop in blood pressure prior to treatment.[14] Cardiac arrhythmia at therapeutic TCA levels is most common in patients with preexisting conduction delay.[15] Patients who are prone to seizures during antidepressant therapy are the patients with a lower seizure threshold or a history of seizures.[16] This general principle holds true for almost all symptoms.

Drug Effects

Although the expression of side effects is the result of the multiple factors described above, the pharmacologic properties of the drug amplify certain symptoms and, therefore, different overall rates of adverse experiences are reported for different antidepressant drugs. In vitro receptor affinity studies are useful for defining this pharmacologic profile. A listing of receptor affinities for several new antidepressants is presented in another article in this Supplement.[30]

MECHANISMS OF ACTION AND IMPLICATIONS FOR SIDE EFFECTS

How "Selective" Are the SSRIs?

The SSRIs are referred to as "selective" because they act primarily on the serotonin system rather than on noradrenergic, dopaminergic, cholinergic, or histaminic neurons. Yet, our knowledge of the serotonin system has grown substantially. Seven classes of serotonin receptors have now been identified and several of these classes have subreceptors.[17] These receptors mediate a variety of functions including appetite, sleep, and sexual function and appear to be associated with a variety of symptoms including pain, nausea, depression, and anxiety. When serotonin uptake is blocked, more serotonin is available at the synaptic cleft to act on all of the presynaptic and postsynaptic serotonin receptors. As a result, the side effects seen with the serotonin uptake blockers are in large part the result of the diffuse effects of serotonin acting at a variety of postsynaptic sites. For example, nausea may result from stimulation of the 5-HT_3 receptor. It seems likely that new drug development will attempt to design drugs that target specific serotonin receptors.

Mirtazapine is a new antidepressant with a unique mechanism of action that affects both noradrenergic and serotonergic systems. It displays α_2, 5-HT_2, and 5-HT_3 antagonism. Because mirtazapine blocks α_2 autoreceptors on noradrenergic neurons and blocks α_2 heteroreceptors on 5-HT neurons, mirtazapine increases the release of norepinephrine and serotonin. Because it blocks the 5-HT_2 and

5-HT_3 receptors, the effect on the serotonin system is more specific. These neuropharmacologic effects predict certain side effects. Because the 5-HT_3 receptors are blocked, nausea might be expected to be less of a problem. Because the 5-HT_2 receptors are blocked, nervousness during initiation of drug treatment may be reduced. Mirtazapine also has antihistaminic effects and modest α_1 effects. The antihistaminic effects might contribute to sedation, increased appetite, and weight gain. The sedation, however, might be countered by arousal associated with the α_2 antagonism. Because mirtazapine has both α_1 and α_2 effects, there may be some balancing of these effects on blood pressure.

SIDE EFFECTS OF THE SEROTONERGIC ANTIDEPRESSANTS

Discontinuation Rates

The best estimate of discontinuation rates because of adverse effects for the SSRIs comes from a meta-analysis reported by Montgomery and colleagues.[2] They found that the adverse event discontinuation rate for the SSRIs in comparison studies with TCAs was about 15%. In the placebo-controlled studies it was 19% for the SSRIs and 5% for placebo.

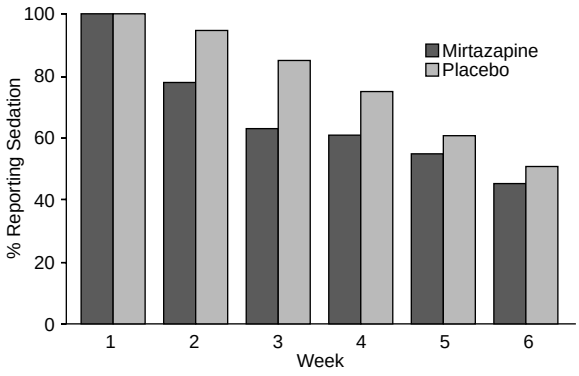
For the other new antidepressants, there are few data that allow direct comparisons among the new drugs. The U.S. clinical trial data for each drug provide the largest samples and relatively comparable reporting procedures from which to estimate discontinuation rates. For nefazodone the discontinuation rate for side effects was 16% in all U.S. clinical trial patients.[11] The rate for nefazodone was 12% in placebo-controlled studies and 7% for placebo.[18] For venlafaxine, the discontinuation rate for all U.S. clinical trial patients was 19%.[11] For mirtazapine, the discontinuation rate because of adverse effects in controlled trials was 17% and 7% for placebo. (Data are from the mirtazapine New Drug Application on file with the FDA.) The discontinuation rate was 28.4% for all U.S. clinical trial patients. The most common reasons for discontinuation of mirtazapine were somnolence (10.4%), weight gain (8%), and increased appetite (4%).

Side Effects During Continued Treatment

Because a patient's report of somatic symptoms is influenced by depression, placebo rates are very important. Most studies do not report rates of symptoms prior to treatment, but the placebo rate is another method of controlling for symptoms that are not related to the drug itself.

Ideally, drugs would be compared at comparably effective doses because side effects increase with dose.[2,19] These comparisons have seldom been made. The clinical trial data include patients from fixed-dose studies along with those from flexible-dosing studies. For some drugs, the early clinical trials were conducted at doses that were later determined to be higher than necessary. For example, in the initial trials with fluoxetine, drug dose was increased up to 80 mg/day, and many patients received 60 to 80 mg/day. Yet later fixed-dose studies for fluoxetine found 5 mg/day to be the minimal effective dose and 20 mg/day appeared to be in the middle of the dose range.[20,21]

Figure 1. Percentage of Patients Reporting Somnolence During Weekly Visits*



*The sample includes 116 patients treated with mirtazapine and 21 patients receiving placebo who reported somnolence at the first visit and completed 6 weeks of treatment (data on file, Organon).

In Table 1, selected symptom rates for active drug and placebo are presented. The data presented do not reflect direct comparisons but rather are the rates reported for each drug independently in the U.S. clinical trials. For each agent, rates ≥ 1% are reported. For venlafaxine and nefazodone, rates ≥ 1% and greater than placebo are reported. For these latter agents, some symptoms for which rates were less than or equal to placebo were explicitly documented and are noted in Table 1. Some items are not mentioned at all for some agents, indicating either that the rate was less than 1% or that it was not coded. From these rates, one can calculate a risk ratio, i.e., the difference between drug and placebo, as a means of controlling for non-drug-related factors. Ratios of rates for active drug to placebo ≥ 2 are in bold print.

Nervousness, anxiety, and agitation have attracted attention because they appear to be increased with the SSRIs. Unfortunately comparisons of these symptoms are complicated by lack of uniform definitions. As a group, the SSRIs are associated with rates of nervousness, anxiety, and insomnia that are 1.8 to 2.2 times greater than that for placebo (see Table 1). These symptoms do not appear to be increased for nefazodone or mirtazapine. Anxiety, reported as a side effect, is actually significantly lower with nefazodone than placebo.[18] For mirtazapine, reports of nervousness were comparable for drug and placebo, and insomnia appeared to be reduced with the active drug.

The incidence of tremor is increased with all of these antidepressants, but the rates for the SSRIs and venlafaxine (3.3 to 5.0 times higher than placebo) are higher

than those for nefazodone and mirtazapine (2.0 and 2.5 times higher than placebo, respectively). Drowsiness is reported with all of the SSRIs (11.6% to 25%), but is substantially increased for mirtazapine (53.6%) (see Table 1). Drowsiness with mirtazapine occurs early with initiation of treatment even though the starting dose is low. The incidence of sedation decreases with time as accommodation occurs (Figure 1). It appears that individual sensitivity and tolerance are more important than dose-related changes.

A few other side effects warrant comment. Modest orthostatic hypotension appears to occur with nefazodone, and occasional supine hypertension is associated with venlafaxine. Mirtazapine did not appear to affect blood pressure or the ECG in clinical trial patients without heart disease.[22] Mirtazapine has been studied intensively in 10 depressed patients without heart disease and compared to patients treated with imipramine and normal controls.[23] Mirtazapine had no significant effect on total peripheral resistance, stroke volume, blood pressure, or blood pressure variability, either at rest supine or with orthostatic challenge and did not induce postural hypotension. Mirtazapine did increase heart rate 15% and decreased heart rate variability, but these changes were less than those observed with imipramine. Nausea and vomiting are increased with the conventional SSRIs, venlafaxine, and nefazodone. These side effects are not increased with mirtazapine, apparently as a result of its 5-HT_3 antagonism. For the SSRIs and venlafaxine, anorexia occurs at rates 1.7 to 5.8 times that for placebo (see Table 1). For nefazodone, anorexia is not increased but increased appetite can occur. For mirtazapine, appetite and weight gain are more common. In the clinical trials, 7.5% of the mirtazapine-treated patients experienced weight gain $\geq 7\%$ of body weight.[22]

An area of substantial interest has been sexual dysfunction. The SSRIs and venlafaxine are associated with increased sexual dysfunction. The rates for sexual dysfunction in men during 6- to 8-week clinical trials for sertraline, paroxetine, and venlafaxine were 12% to 15.5% (see Table 1). These rates may underestimate the incidence of sexual dysfunction encountered during continued treatment. The rate initially reported for fluoxetine (Table 1) occurred before the effect of the SSRIs on sexual functioning was appreciated and appears to be an underestimate.[24] Rates of sexual dysfunction are substantially lower for nefazodone. Effects of mirtazapine on sexual function are less clear. Decreased libido does not appear to be associated with mirtazapine,[25] but information about the effects of this drug on ejaculation and orgasm are not available.

Overdose

As a group, the SSRIs, venlafaxine, and nefazodone appear to be safe in overdose, a major advantage over the TCAs. To date, mirtazapine also appears to be safe in overdose, but the data are limited. During clinical trials with mirtazapine, eight patients overdosed. Four patients ingested mirtazapine alone in doses from 100 to 315 mg. Two additional patients took mirtazapine with a benzodiazepine. One of these cases involved the largest overdose of mirtazapine recorded: 975 mg of mirtazapine and 30 mg of clonazepam. In one case, mirtazapine was ingested with "pain killers." There were no fatalities among these seven cases, and no ECG changes were observed. One fatality occurred in a patient who ingested 30 to 45 mg of mirtazapine with an overdose of amitriptyline and chlorprothixene. At autopsy, elevated concentrations of amitriptyline in the blood implicated that drug as the cause of death (data on file, Food and Drug Administration).

Rarely Occurring Serious Adverse Events

The new serotonergic drugs as a group have been reasonably free of life-threatening adverse events. The serotonin syndrome is one potentially fatal disorder linked to serotonergic agents. It is characterized by myoclonus, hyperreflexia, sweating, shivering, incoordination, and changes in mental status such as agitation, confusion, and hypomania.[26] It has usually been associated with combinations of serotonergic agents given together, particularly the monoamine oxidase inhibitors and SSRIs or MAOIs and meperidine. For this reason, these combinations are contraindicated. It is not clear whether antidepressants such as nefazodone or mirtazapine, which block specific postsynaptic 5-HT receptors, are less likely to contribute to the development of this syndrome.

Leukopenia is infrequently or rarely associated with the SSRIs or venlafaxine, and agranulocytosis has not been reported to date. In the premarketing clinical trials of mirtazapine, agranulocytosis occurred in two patients.[22] One of the two patients had Sjogren's syndrome, and it is possible this person was unusually vulnerable to this problem. Neutropenia occurred rarely in patients treated with mirtazapine in the clinical trials, and in the majority of cases, it occurred as a single episode that resolved spontaneously without interruption of therapy. In 13 patients who had neutropenia prior to treatment, none went on to develop moderate-to-severe neutropenia during treatment with mirtazapine. In the mirtazapine clinical trials, one case of agranulocytosis was associated with imipramine, the comparator drug, and two cases with mirtazapine. The two patients who developed agranulocytosis and the one patient who developed severe neutropenia recovered after mirtazapine was discontinued. The rapid recovery after discontinuation of the drug suggested an autoimmune effect on late progenitor cells rather than bone marrow suppression.

The three cases of severe neutropenia in the clinical trials, including the two with associated signs and symptoms, result in a crude incidence of 1.1 per 1000 patients exposed to mirtazapine.[22] Because the clinical trial database is relatively small for estimating a rarely occurring event (about 3000 patients), the confidence interval is

quite wide: 3.1 cases per 1000 to 2.2 cases per 10,000. Agranulocytosis occurs as a rare event with many psychotropic and other drugs.[27–29] At this juncture, it is not possible to tell if the rate with mirtazapine is greater than that for other antidepressants. Data from the Netherlands provide additional evidence that agranulocytosis is a rare event. Agranulocytosis has not been reported in approximately 9000 patients treated with mirtazapine.[25]

SUMMARY

In summary, the new-generation antidepressants appear to be better tolerated in terms of both severe events that interrupt treatment and subjective side effects experienced during continued treatment. As a group, they appear to be safe in overdose and have not been associated with the electrocardiographic changes typical of the TCAs. Among the newer agents, the SSRIs and venlafaxine are more frequently associated with anxiety, nervousness, insomnia, tremor, nausea, and sexual dysfunction. Nefazodone and mirtazapine are less likely to be associated with anxiety and nervousness, perhaps in part because of their 5-HT_2 antagonism. Nefazodone and mirtazapine are also less likely to be associated with insomnia, possibly because of their 5-HT_2 antagonism, and because they are somewhat sedating. Mirtazapine is not likely to produce nausea because of its 5-HT_3 antagonism. Mirtazapine is associated with appetite and weight gain apparently related to its antihistaminic effects. Agranulocytosis is extremely rare, and a causal relationship with mirtazapine has not been established.

Drug names: amitriptyline (Elavil and others), clonazepam (Klonopin), desipramine (Norpramin and others), fluoxetine (Prozac), imipramine (Tofranil and others), meperidine (Demerol and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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