

# Managing Treatment-Resistant Major Depression

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A sizable proportion of patients suffering from nonpsychotic unipolar depression experience only partial or no clinical response to antidepressant treatment. Switching, augmenting, and combining various pharmaceutical agents can be effective strategies for patients with treatment-resistant depression. The empirical evidence supporting these approaches is inconsistent, however, and there is a paucity of controlled studies to support their efficacy. Additionally, it has been difficult to demonstrate the advantages of these strategies over increasing the dose or duration of the initial drug treatment. This article will review available evidence and clinical considerations regarding switching, augmenting, and combining various agents in the treatment of patients suffering from nonpsychotic unipolar depression who have failed adequate courses of antidepressant treatment. More research is needed that controls for continued time on the initial agent, that compares different strategies, and that determines which patients are the best candidates for which treatment.

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**P**harmacologic treatments for depression are currently safer, more convenient, and more tolerable for the average patient than they have been at any other time in history; yet, in controlled studies, remission rates are typically less than 50%.<sup>1,2</sup> This means that many patients are left with considerable symptomatology.

*Treatment-resistant* and *treatment-refractory* are terms that have been defined in different ways but are frequently used interchangeably to identify patients with depression that does not initially respond well to treatment. These and Rush<sup>3</sup> have aided researchers in the often ambiguous process of classifying groups of patients with treatment-resistant depressions by suggesting specific criteria that define the extent of prior treatment. In practice, however, the clinician is more likely to encounter a spectrum of cases. This article will review some of the studies of new approaches for treatment of nonpsychotic unipolar depression that has failed to respond to adequate prior treatment.

## STRATEGIES FOR MANAGING TREATMENT-RESISTANT DEPRESSION

Generally, patients with nonpsychotic unipolar depression start treatment with antidepressant monotherapy, but when their symptoms fail to respond to an adequate course

of treatment, switching, augmenting, and combining various pharmaceutical agents can be effective management strategies. Switching has some advantages compared with combining or augmenting, but the reverse is also true (Table 1). Switching simply refers to changing from one antidepressant drug to another. Relative to augmenting or combining, switching is simpler and thus may facilitate compliance. It may be less expensive. Switching also reduces the potential for drug interactions that occur when multiple agents are used.

Augmentation strategies involve adding a second pharmacologic agent that is not generally used as an antidepressant but may enhance the effect of an antidepressant. Combination therapy refers to adding another antidepressant, typically from a different class, to enhance effects. In some cases, augmentation or combination strategies may produce a more rapid response than switching, not only because of neuropharmacologic potentiation, but also because the time lost discontinuing one drug and starting another is avoided. The addition of a second agent also helps to maintain any improvement that occurred with the first drug. This appears to explain why augmentation or combination strategies are especially popular in partial responders.

The term *bridging* refers to the addition of a second agent to enhance response with the intent that if the patient does well, the first drug is withdrawn, and the patient continues on the second. Of course, the option of returning to monotherapy always exists when combination strategies are employed.

### General Principles

Psychiatry is moving to an emphasis on evidence-based treatments; yet, the interpretation of studies that provide that evidence is limited due to problems with methodology.

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**Table 1. Comparison Between Switching and Augmentation or Combination Treatment Options**

Treatment Option	Advantages
Switching	Improved compliance Reduced medication costs Fewer drug interactions
Augmentation or combination	Rapid response No titration necessary Initial improvements maintained

The definition of treatment-refractory varies across studies and sometimes is not adequately characterized. Use of the patients' history of prior response to drug treatment is likely to be less accurate than prospective evaluation of treatment outcome.

Although the importance of an adequate duration of initial treatment is generally acknowledged, it may be underestimated. This is particularly significant when evaluating augmentation or combination strategies. If a change is made too early in the course of a drug trial, then it will be more difficult to determine the advantage of the additional agent versus more time on the initial treatment. A recent study conducted by Licht and Qvitzau<sup>4</sup> provides a good example. In this study, 295 patients were identified as nonresponders from a group of 1629 patients with major depression who had received 6 weeks of treatment with up to 100 mg/day of sertraline. These 295 nonresponders were then randomly assigned to double-blind treatment for another 5 weeks with 100 mg/day of sertraline and placebo, 200 mg/day of sertraline and placebo, or 100 mg/day of sertraline and 30 mg/day of mianserin. Interestingly, the patients who stayed on 100 mg/day of sertraline and placebo had a similar response rate (70%) to the patients who received the combination of mianserin and sertraline (67%) and had a better rate of response than those who received 200 mg/day of sertraline (70% vs. 56%,  $p < .05$ ). Their study illustrated that longer duration of treatment on the initial dose was just as effective as a combination strategy, and, in fact, the effectiveness of the combination could be explained by the longer duration, rather than the addition of mianserin. The study emphasizes the importance of controlling for the effects of duration.

### SWITCHING ANTIDEPRESSANTS

Most patients are now started on a selective serotonin reuptake inhibitor (SSRI); therefore, those studies that have examined the usefulness of switching from one SSRI to another or switching from an SSRI to another class of antidepressants will be reviewed here (Table 2).

#### SSRI to SSRI

Four studies<sup>5-8</sup> that examined switching from one SSRI to another suggest that patients who either fail to respond

or are intolerant of the initial SSRI treatment may positively respond to another SSRI.

In a 6-week clinical trial conducted by Thase et al.,<sup>5</sup> 106 outpatients with major depressive disorder and a history of intolerance or nonresponse to treatment with sertraline were switched to a mean dose of 37.2 mg/day of fluoxetine. Of the 106 patients, 67 (63%) experienced 50% or greater improvement on a 28-item Hamilton Rating Scale for Depression (HAM-D). In another study<sup>6</sup> of somewhat similar design, patients who were unable to tolerate fluoxetine were switched to sertraline. Of the 91 evaluable patients, 69 (76%) responded. Zarate et al.<sup>7</sup> found somewhat different results. They examined response to sertraline after failure or intolerance to fluoxetine in 31 patients with major depression who had been hospitalized. Unique to this study, patients were followed up afterwards to determine their long-term outcome. At discharge from the hospital, 13 (42%) of 31 patients were responders. However, at follow-up, on average 7 months later, only 8 (26%) of 31 were judged responders. Although this was a retrospective study, and suffered from several methodological limitations, it was a "real life" appraisal of the effectiveness of switching from one SSRI to another.

In the only study to limit the sample to patients who had failed to respond to prior treatment, Joffe et al.<sup>8</sup> evaluated the efficacy of a switch to a second SSRI in an open study of 55 patients with major depression. Criteria for prior failure included dose and duration of treatment. Patients must have received at least the minimum effective dose for at least 5 weeks. After 5 weeks of treatment with a new SSRI, 28 (51%) of the patients had a marked or complete antidepressant response.

Together, these studies provide evidence that switching to a second SSRI could be a useful alternative in some depressed patients who failed the initial SSRI trial. However, it is important to note that all of these studies were open-label, uncontrolled, and vulnerable to the possibility that continued time on the initial medication might also have had a positive effect. More importantly, they do not address the question of whether a within-class switch is as effective as switching to another antidepressant class.

#### SSRI to Tricyclic Antidepressant

Although the use of the tricyclic antidepressants (TCAs) has declined substantially in the past decade, there are limited data indicating that a switch from an SSRI to a TCA can be useful. The first such study<sup>9</sup> was a double-blind crossover study. Patients failing paroxetine were switched to imipramine. In this small sample, 11 (73%) of 15 patients responded. The second report was a larger study comparing sertraline and imipramine in chronic depression.<sup>10</sup> After 12 weeks of initial treatment, 117 patients who failed initial treatment with sertraline were crossed over, double-blind, to imipramine. In the intent-to-treat sample, 52 (44%) of the 117 patients were responders to imipramine.

Table 2. Summary of Clinical Studies of Switching From an SSRI in Major Depression<sup>a</sup>

Authors	Initial Treatment	Post-Switch Treatment	Design	Response Rate
Thase et al <sup>5</sup>	Sertraline	Fluoxetine	N = 106, open, nonresponse or intolerance	63%
Brown and Harrison <sup>6</sup>	Fluoxetine	Sertraline	N = 91, open, primarily intolerant	76%
Zarate et al <sup>7</sup>	Fluoxetine	Sertraline	N = 31, open, nonresponse or intolerance	42% at discharge 26% at follow up
Joffe et al <sup>8</sup>	Fluoxetine, sertraline, paroxetine	Second SSRI	N = 55, open, nonresponse only	51%
Peselow et al <sup>9</sup>	Paroxetine	Imipramine	N = 15, double-blind, prospective nonresponse	73%
Thase et al <sup>10</sup>	Sertraline	Imipramine	N = 117, double-blind, crossover, prospective nonresponse	44%
Nierenberg et al <sup>12</sup>	Various	Venlafaxine	N = 84, open, nonresponse to 3 prior trials	33%
DeMontigny et al <sup>14</sup>	Various	Venlafaxine	N = 152, open, nonresponse to at least 1 prior trial	58% response 28% remission
Kaplan et al <sup>15</sup>	Fluoxetine, sertraline, paroxetine	Venlafaxine	N = 73, open, nonresponse to one prior SSRI	87% full remission
Poirer and Boyer <sup>16</sup>	Various, two-thirds SSRIs	Venlafaxine or paroxetine	N = 122, double-blind, randomized, nonresponse to 2 prior trials, 1 prospective	Response 52% venlafaxine 33% paroxetine Remission 42% venlafaxine 20% paroxetine 28% response
McGrath et al <sup>17</sup>	Fluoxetine	Bupropion	N = 18, open, Nonresponse to prior prospective fluoxetine trial	28% response
Fava et al <sup>18</sup>	Various SSRIs	Mirtazapine	N = 69, open, Nonresponse to prior prospective SSRI trial	48% response
Thase et al <sup>19</sup>	Various SSRIs	Mirtazapine or sertraline	N = 243, double-blind, randomized, nonresponse to 1 prior SSRI, not sertraline	Response: At wk 3 and 4 mirtazapine > sertraline, p < .05 At week 8, mirtazapine and sertraline, p = NS

<sup>a</sup>Prior treatment outcome was by history unless indicated. Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Although a switch to a tricyclic may be effective, the TCAs have been associated with substantial side effects, including adverse cardiac effects and death after overdose. Further, a rapid switch from paroxetine or fluoxetine can result in elevated blood TCA levels and the risk of toxicity. There may also be discontinuation effects from stopping the SSRI for those agents with shorter elimination half-lives.<sup>11</sup>

### SSRI to Venlafaxine

The studies reporting switching from an SSRI to venlafaxine are interesting, because in some, the subjects were clearly defined as being treatment refractory. For example, Nierenberg et al.<sup>12</sup> reported on a sample of 84 patients who had failed to respond to at least 3 adequate trials of antidepressants from at least 2 antidepressant classes or had failed electroconvulsive therapy and had attempted augmentation at least once. In this study, venlafaxine was effective for about one third of the patients after 12 weeks

of treatment. The study illustrates a previous observation<sup>13</sup> that the rate of response to a new agent is likely to decline as the number of prior failed trials increases. In another multicenter open-label study performed in Canada,<sup>14</sup> of the 152 patients who had failed at least 1 prior antidepressant trial (mean = 3.2 trials by history), 58% had at least 50% improvement on the HAM-D when switched to venlafaxine. In a third, recent, uncontrolled study<sup>15</sup> of 73 patients who had not responded or had experienced an unsustained response to SSRI treatment, 60 patients (87%) achieved full remission based on HAM-D scores after 6 to 8 weeks of venlafaxine treatment. These studies suggest that venlafaxine is an effective alternative treatment for outpatients with major depression who are SSRI nonresponders. The widely varying response rates may reflect differences in how treatment resistance was determined.

One of the most interesting studies of this switch was reported by Poirer and Boyer in 1999.<sup>16</sup> They described a double-blind randomized comparison of venlafaxine and

paroxetine in 122 patients with major depression who had failed 2 previous antidepressant trials. Each of the prior trials needed to be at least 4 weeks long, and the most recent trial had to be performed by the investigator. Two thirds of the patients had received an SSRI in one of the prior trials and about 70% had received a tricyclic. Venlafaxine was adjusted to a dose of 200 to 300 mg/day. Paroxetine was adjusted to a dose of 30 to 40 mg/day. The response rate in observed cases with venlafaxine was 52% versus 33% for paroxetine ( $p = .04$ ). Remission was achieved in 42% of venlafaxine-treated patients versus 20% of paroxetine-treated patients ( $p = .01$ ). This is one of the few studies to compare 2 agents following a switch. Although not all patients had received an SSRI during prior treatment, most had. Thus the results suggest that a switch outside of class might offer an advantage. The data also suggest a dual action agent might be superior to an SSRI. Although 2 prior trials were required, the duration required for prior treatment failure was only 4 weeks.

### SSRI to Bupropion

The evidence for a switch to bupropion in resistant patients is more limited. McGrath et al.<sup>17</sup> reported on 18 patients with major depression who failed prospective treatment with fluoxetine at a dose of 40 mg/day or greater and a duration of at least 8 weeks. Patients were directly switched to bupropion with no washout. Five (28%) of the 18 patients had at least 50% improvement at endpoint. Although this response rate is lower than in some studies, this may reflect the aggressive initial treatment received by all patients.

### SSRI to Mirtazapine

Mirtazapine is a safe and effective alternative when other antidepressant treatments fail. Fava et al.<sup>18</sup> conducted an open-label, 8-week study in outpatients with major depressive disorder. The patients had all failed a prospectively administered double-blind study with fluoxetine, paroxetine, or sertraline and were subsequently treated with mirtazapine. Of the 69 patients who were treatment resistant in the prior study, 33 (48%) responded to mirtazapine. Mirtazapine was well tolerated, with no apparent difference in efficacy, tolerability, or safety for patients undergoing an immediate switch from the various SSRIs versus those who had a brief washout.

In another study, Thase et al.<sup>19</sup> examined the advantage of switching from another class to mirtazapine in patients previously failing an SSRI. This was a randomized, double-blind study of 243 patients with major depression who had failed treatment with fluoxetine, paroxetine, or citalopram by history. Patients were then randomly assigned to sertraline (mean dose = 120 mg/day) or mirtazapine (mean dose = 30 mg/day). Mirtazapine was significantly more likely to result in 50% improvement at weeks 3 and 4 but was not significantly or meaningfully better

at the end of 8 weeks. Remission rates favored mirtazapine early in treatment but were not significantly different at the end (37% vs. 29%). This study failed to show an advantage for switching to mirtazapine in terms of final outcome, but it appeared that response occurred more quickly with mirtazapine.

## AUGMENTING AND COMBINING SSRIs WITH OTHER AGENTS

Augmentation and combination strategies are particularly helpful in managing treatment-resistant patients who have had a partial response to treatment. These strategies allow the patient to maintain the improvement already achieved, and positive effects may appear rapidly. However, this rationale for augmentation or combinations in partial responders is based on practical considerations. In fact, other data suggest that these strategies are also effective in patients who show little response to initial treatment.<sup>20,21</sup>

Older strategies such as tryptophan, stimulant, thyroid, and lithium augmentation will not be extensively discussed here, because they have been reviewed previously.<sup>22</sup> Of all the augmentation strategies, lithium has been best researched. Seven of 9 placebo-controlled studies of lithium augmentation found lithium to be more effective than placebo, and lithium combined with SSRIs has been studied in at least 4 studies. Results for thyroid augmentation have been mixed with only case report data available on augmentation of SSRIs. No positive controlled studies of stimulant augmentation have been performed, and evidence for SSRI augmentation is quite limited. During the past decade, research has shifted to newer augmentation and combination strategies for patients who failed treatment with an SSRI.

### Buspirone

The successful addition of buspirone to SSRI treatment was reported in 5 open series of patients (see prior review).<sup>22</sup> Controlled studies of buspirone augmentation, however, have reported mixed results. One double-blind, placebo-controlled 4-week study<sup>23</sup> compared buspirone (mean dose = 49 mg/day) with placebo augmentation in 119 depressed patients who had not responded to 4 weeks of SSRI treatment. Response to buspirone, 51%, was not significantly or meaningfully greater than that for placebo, 47%. The high placebo rate may reflect the short duration of the prior trial and might have mitigated against a positive outcome.

In a second controlled study<sup>24</sup> of 102 patients who had failed 6 weeks of SSRI treatment, buspirone 10 to 30 mg b.i.d. or placebo was added to ongoing SSRI treatment. Greater improvement was seen with buspirone than placebo at 1 week of treatment (11.1% vs. 3.6% change, respectively;  $p = .03$ ), although at 6 weeks, improvement in

the 2 groups was very similar (30.5% vs. 30.8% change, respectively). In the most severe third of the sample, there was a significant advantage for buspirone (37.5% vs. 18.2% change,  $p = .03$ ).

### **Pindolol**

Augmentation with pindolol is rarely used in the United States but has received considerable attention in Canada and Europe. This agent has generated interest because it was proposed as a method for accelerating response to an SSRI.<sup>25</sup> In fact, 5 of 6 placebo-controlled studies previously reviewed elsewhere<sup>22</sup> demonstrated more rapid onset of effect with pindolol augmentation. Controlled studies in resistant patients, however, have not found pindolol useful. In a small crossover study of 10 resistant patients, Moreno et al.<sup>26</sup> found no advantage for pindolol. In a larger double-blind, placebo-controlled study, Perez et al.<sup>27</sup> randomly assigned 80 outpatients with major depression who had not responded to 6 weeks of SSRI treatment to receive placebo (3 times daily) or pindolol (2.5 mg, 3 times daily) for 10 days; the response rate was similar in both groups.

### **Noradrenergic Tricyclic Agents**

A series of studies has examined the combination of noradrenergic tricyclic agents and SSRIs. In 1989, Weilburg et al.<sup>28</sup> reported the effectiveness of adding fluoxetine to a variety of non-MAOI (monoamine oxidase inhibitor) antidepressants (usually a tricyclic) for 30 outpatients with treatment-resistant depression. They found that 26 (87%) of the 30 patients had a positive response. Another open study<sup>29</sup> involved 8 older patients for whom depression treatment had been very difficult; in fact, some of the patients had failed both electroconvulsive therapy and SSRI treatment. All 8 of the patients responded when a tricyclic (usually nortriptyline) was added to the SSRI.

Nelson et al.<sup>30</sup> compared 52 depressed patients previously treated with desipramine with 14 depressed patients who were treated with the combination of 20 mg/day of fluoxetine and a variable dose of desipramine. The desipramine dose was adjusted to achieve a therapeutic level by measuring 24-hour blood desipramine levels. The results of this open study showed that the rate and speed of response for the 14 patients receiving the combination treatment were superior to those observed in the patients receiving desipramine alone. This study was not specifically a study of resistant depression but did suggest greater efficacy for the combination. Subsequently, a prospective study<sup>31</sup> comparing the combination of desipramine and fluoxetine with either drug alone found the combination significantly more likely to result in remission. In that study, speed of response did not appear to be more rapid if final efficacy was taken into account. Although this was not specifically a study of treatment resistance, half of the patients had a history of treatment resistance, and the same

trends were observed in those resistant patients as in the full sample. When this type of augmentation treatment is administered, it is advisable to monitor the blood level of the tricyclic in order to avoid toxicity, especially if the TCA is given with fluoxetine or paroxetine. These SSRIs inhibit the cytochrome P450 2D6 pathway and thus can raise desipramine concentrations 3- to 4-fold.

### **Bupropion**

Adding bupropion to an SSRI to enhance response is a very popular strategy, even though all the supportive data come from uncontrolled studies. The rationale for this combination is that the catecholamine effects of bupropion would complement the serotonin effects of the SSRI. Three open series, which included a total of 65 cases, suggested beneficial effects.<sup>32-34</sup> The usual dose of bupropion was between 200 and 300 mg/day. Although clinical practice suggests this combination is no more likely to cause adverse reactions than others, drug interactions can occur. Recently some SSRIs have been found to inhibit bupropion metabolism but the magnitude of this effect is not well described.<sup>35</sup>

### **$\alpha_2$ Antagonists**

Adding an  $\alpha_2$  antagonist to SSRI treatment is another approach to managing resistant unipolar depression. A preclinical study suggested that the combination of mirtazapine and paroxetine more rapidly and effectively enhanced serotonin neurotransmission.<sup>36</sup> In human subjects, controlled studies of yohimbine and mianserin, 2  $\alpha_2$  antagonists, demonstrated beneficial effects in depressed patients.<sup>37,38</sup> In the United States, the marketed  $\alpha_2$  antagonist is mirtazapine. In one controlled study by Debonnel et al.,<sup>39</sup> mirtazapine combined with paroxetine demonstrated a significantly higher response rate, 60%, than monotherapy with either drug alone, 49%. Patients in this study were not necessarily treatment resistant; however, the non-responders to initial monotherapy were switched to combined treatment and 50% responded. Although suggestive, this switch was made after 6 weeks and without a comparison group, it is not possible to determine the effect of continued duration of initial treatment. In a second controlled study of mirtazapine, Carpenter and Yasmin<sup>40</sup> conducted a double-blind trial in which 26 adult outpatients who had failed adequate antidepressant monotherapy were randomly assigned to receive 4 weeks of mirtazapine or placebo augmentation. At the end of the trial, response rates were significantly higher in the mirtazapine group (45% vs. 13%;  $p = .04$ ).

### **Atypical Antipsychotics**

The use of antipsychotics to treat depression has a long history. Several controlled studies suggested superiority over placebo or benzodiazepines, and some studies found comparability with tricyclic antidepressants.<sup>41</sup> Four of the

typical antipsychotics were marketed with labeling suggesting efficacy in depression. However, the possible risk of tardive dyskinesia, coupled with the finding that patients with affective disorder were at increased risk for tardive dyskinesia, rapidly curtailed the use of the typical antipsychotics in depression.

The introduction of the atypical antipsychotic agents renewed interest in the possible use of this drug class. In particular, the possibility was raised that combining these agents with SSRIs might enhance response. Ostroff and Nelson<sup>42</sup> postulated that risperidone might be useful as augmentation in patients who had failed SSRIs based on the idea that the addition of a serotonin-2 antagonist—the principle effect of risperidone in a low dose—may enhance the serotonergic effects of an SSRI, as a previous preclinical study suggested.<sup>43</sup> In their study, risperidone was added to the ongoing treatment of 8 patients with major depressive disorder without psychotic features who had not responded to adequate SSRI therapy. All 8 patients improved within 1 week of risperidone augmentation. Additionally, risperidone appeared to have beneficial effects on sleep disturbance and sexual dysfunction. Recently, a prospective open study was reported adding risperidone to fluvoxamine from the start of treatment.<sup>44</sup> Thirty-two (89%) of the 36 patients responded (50% improvement) within 4 weeks. Although only 5 of these patients had failed prior therapy, the results suggested the combination might be a very effective and rapid treatment.

Another combination, olanzapine and fluoxetine, has received considerable attention for treatment of resistant patients. Preclinical data suggest that the combination of olanzapine and fluoxetine may have a unique effect on extracellular concentrations of norepinephrine and dopamine.<sup>45</sup> Although increased levels of serotonin might be expected with fluoxetine, the addition of olanzapine produced marked increases in the levels of dopamine and norepinephrine in the prefrontal cortex. If the combination of olanzapine and fluoxetine enhances all 3 major neurotransmitters, it might prove to be very effective in resistant depression.

Shelton et al.<sup>46</sup> conducted an 8-week double-blind study with 28 patients having recurrent, unipolar depression that had failed to respond to an initial course of fluoxetine treatment. Patients were then randomly assigned to olanzapine (5 mg/day titrated weekly within a range of 5–20 mg/day) plus placebo; fluoxetine (20 mg/day titrated to the maximum tolerable dose, up to 60 mg/day) plus placebo; or olanzapine plus fluoxetine (varied dosing determined at investigators' discretion). The combination group (N = 10) achieved greater improvement from baseline on the Montgomery-Asberg Depression Rating Scale (MADRS) and the HAM-D scale than either monotherapy group. In addition, substantial improvement occurred within 1 week on the combination. Both drugs were well tolerated alone or in combination.

Another recent study<sup>47</sup> suggested the addition of olanzapine to ongoing SSRI treatment substantially reduced SSRI-induced apathy. In this study of 21 patients, the symptoms of depression had improved but apathy remained or was induced. Olanzapine was added and the dose increased by 2.5-mg increments (mean final dose 5.4 mg/day). The mean MADRS scores dropped substantially (10.2 to 4.6), item 8 (inability to feel) improved (2.6 to 0.5), and the Scale for Assessment of Negative Symptoms (SANS) score declined (30.6 to 10.2). All these changes were significant at  $p = .001$  or better. This is a very interesting finding because it suggested that olanzapine has a positive effect on mood and interest.

One of the shortcomings of the typical neuroleptics in depression was that while they were associated with improvement of depression in many areas, e.g., sleep, agitation, they did not have as great an effect on loss of interest as the antidepressants did.<sup>48</sup> In fact, this may have been one of the reasons the neuroleptics were never viewed as true antidepressants despite several positive placebo-controlled studies. Further, the finding that olanzapine reduced apathy runs counter to the idea that olanzapine is just sedating. This finding would be consistent with the hypothesis that apathy during SSRI treatment may be secondary to attenuation of dopamine functioning by chronic serotonin stimulation<sup>49</sup> and that this effect is reversed by olanzapine, which, when added to an SSRI, increases extracellular dopamine.<sup>45</sup> Other studies<sup>50,51</sup> demonstrating an advantage of this combination in bipolar depression and psychotic depression suggest the combination of olanzapine and fluoxetine may be very useful across a range of difficult-to-treat depressions.

### **SSRI Plus SSRI or SSRI Plus Venlafaxine Combinations**

Although there are anecdotal reports, reviewed elsewhere,<sup>52</sup> of combining SSRIs with each other or combining SSRIs with venlafaxine, it is this author's view that this does not represent rational polypharmacy. The aim in rational polypharmacy is to combine drugs with different mechanisms of action in order to enhance response. Combining agents whose primary mechanism is similar does not achieve that goal. It has been argued that some secondary effects of the SSRIs differ—for example, that paroxetine has weak norepinephrine effects or that sertraline has weak dopamine effects. But these secondary effects appear weak at best and have not been shown to be clinically meaningful. The best established dual-action agent is venlafaxine, which at higher doses does block uptake of norepinephrine. From a practical perspective, however, it makes more sense to add a second drug whose primary mechanism differs or, in the case of venlafaxine, switch to that drug and raise the dose. If a second SSRI or venlafaxine is added to an SSRI, the dose of the second agent must be raised in order to engage the secondary effect of that

agent. However, at that point, serotonin side effects, which are dose dependent, will increase and may be severe. It makes much more sense to add a drug with a different mechanism, and avoid increasing serotonin blockade.

### SUMMARY

A variety of switching, augmentation, and combination treatment options are available for treatment-resistant depression. Each offers a different neurochemical effect than that which can be obtained with antidepressant monotherapy. The empirical evidence supporting these various approaches is inconsistent, however. Ironically, some of these studies support the importance of a longer duration of initial treatment. Clinicians want to know which strategy is most likely to be effective, and it is tempting to compare response rates from different studies. Yet, this is particularly hazardous because the level of prior treatment resistance is often not well described but will clearly affect outcome. Currently there are almost no studies that compare alternative strategies. Clinicians also want to know if there are predictors of response to specific interventions. Again these data are lacking. Despite these obvious deficiencies, effective treatments have emerged that can aid the clinician in the treatment of resistant depressions.

*Drug names:* bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), mirtazapine (Remeron), nortriptyline (Aventyl, Pamelor, and others), olanzapine (Zyprexa), paroxetine (Paxil), pindolol (Viskin and others), risperidone (Risperdal), sertraline (Zoloft), venlafaxine (Effexor).

*Disclosure of off-label usage:* The author of this article has determined that, to the best of his knowledge, fluvoxamine, olanzapine, pindolol, risperidone, tryptophan, and yohimbine mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of depression; and mianserin is not approved for use in the U.S.

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