New Approaches to the Treatment of Refractory Depression

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Although the majority of patients with depression respond well to their initial pharmacologic treatment, as many as 30% to 45% fail to achieve an adequate response. In addition to the more traditional lithium and thyroid hormone augmentation strategies, a number of new pharmacotherapeutic approaches are currently being used to help manage refractory depression, including the addition of another agent or a switch to another antidepressant. Augmentation and switching strategies are often selected in order to obtain a different neurochemical effect (e.g., adding a relatively noradrenergic agent to a relatively serotonergic antidepressant). In particular, several studies have suggested that depressed patients refractory to treatment with selective serotonin reuptake inhibitors (SSRIs) may show a good response to newer agents that have a pharmacologic profile distinct from the SSRIs. Furthermore, preliminary studies have shown that the addition of SSRIs to either noradrenergic drugs such as the tricyclic antidepressants (TCAs) or dopaminergic agents may be efficacious, even though concerns about drug-drug interactions and tricyclic cardiac toxicity have limited the use of TCA-SSRI combinations. The introduction of reboxetine, a relatively selective norepinephrine reuptake inhibitor, may increase the use of the latter therapeutic approach because of its improved safety profile compared with the TCAs. The review of treatment options for refractory depression that follows will outline the advantages, disadvantages, and level of support for a number of new treatment strategies.

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Even though there are many effective treatments for major depressive disorder, including psychotherapy and electroconvulsive treatment, antidepressant therapy is considered the standard of care. Despite this emphasis on pharmacotherapy, 30% to 45% of depressed patients who are treated with antidepressants show only partial or no response.[1–3] Even among patients who are considered "responders" to antidepressant therapy, there may be residual symptoms.[4] Such incomplete responses are troubling because the presence of residual symptoms has been associated with a poorer prognosis and higher risk of relapse compared with the absence of residual symptoms.[5] While there are many good placebo- and comparator-controlled studies demonstrating the efficacy of antidepressants in the treatment of major depression in both outpatient and inpatient populations, there are only a few controlled clinical trials that specifically focus on the treatment of patients with refractory depression. For these patients, clinicians' decisions are most often guided by anecdotal reports, case series, and relatively small, uncontrolled clinical trials. Randomly assigning patients who have failed to respond to prior antidepressant treatment to placebo therapy is often perceived as unethical, making trials with a placebo arm difficult to implement. Even controlled trials that do not involve placebo can present significant challenges to investigators. It is often difficult to recruit patients for such studies, particularly when the criteria for refractoriness are established prospectively. The review of treatment options for refractory depression that follows will outline the advantages, disadvantages, and level of supporting documentation for a number of new augmentation strategies (Tables 1 and 2).

It is noteworthy that, when psychiatrists are asked what it takes to successfully treat patients with partial or no response to antidepressant therapy, their practices do not match the best-studied strategies for this population of depressed patients.[6] Although difficult to design, fund, and implement, studies are sorely needed to aid in the quest for improved strategies in the management of treatment-refractory patients.

Clinicians tend to use 2 types of pharmacologic strategies with patients who have failed to respond to antidepressant treatment: augmentation and switching. The augmentation strategy is relatively simple—one uses a pharmacologic agent to enhance the effect of an antide-

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Table 1. Advantages and Disadvantages of Augmentation Strategies for the Management of Refractory Depression[a]

Augmentor	Augmented	Advantages	Disadvantages	Clinical Evidence
Lithium	Current antidepressant	Increased chance of response in patients unresponsive to TCAs, MAOIs, or SSRIs	Low response rates with SSRIs; increased risk of toxicity; bothersome side effects; need for blood monitoring	Clinical studies[8–17]
Thyroid hormone	Current antidepressant	Successful among patients refractory to TCAs	Published studies concern only TCAs; potential for developing nervousness, insomnia	Clinical studies with TCAs[18]
Buspirone	Current antidepressant	Good antidepressant response in some nonresponsive patients	Extremely low response rate in 1 study[23]	Small open-label studies[19–23]
	SSRI or placebo		Placebo-controlled trial showed no statistically significant difference between buspirone and placebo	Large placebo-controlled trial[24]
Pindolol	Current antidepressant	Accelerates response to SSRIs in some studies	Not different from placebo, but trial was very short (10 days)[32]	Anecdotal[25–32]
Nefazodone	SSRI	May help manage SSRI-induced sexual dysfunction	Potential risk for serotonin syndrome; risk for worsening anxiety and irritability; potential for drug interactions	Case report,[33] anecdotal[34]
Dopaminergics	Current antidepressant	Pramipexole and amantadine used to treat SSRI-induced sexual dysfunction	Lack of prospective studies	Studies limited in scope[35–37]
Psychostimulants	Current antidepressant	Rapid onset of action	Abuse potential in patients with history of substance abuse; may worsen anxiety, irritability; response may be transient	Small clinical studies[38–41]
Bupropion	Current antidepressant	Effect on dopamine, NE systems; may help manage SSRI-induced sexual dysfunction	Tremor and panic attacks	Anecdotal, case reports, small open-label studies[7,42–48]
Venlafaxine	SSRI	Dual action (on 5-HT, NE systems)	Potential risk for serotonin syndrome, blood pressure elevation, and severe anticholinergic side effects	Anecdotal, case reports[49,50]
SSRIs	SSRI	Drug-drug interactions may lead to favorable effects in some cases	Theoretical increased side effect severity; potential risk of serotonin syndrome	Case reports[53,54]
Mirtazapine	SSRI	Dual action (on 5-HT, NE systems); may help manage SSRI-induced sexual dysfunction	Weight gain, sedation	Small open-label trial[55]
Desipramine (TCAs)	SSRI	Combination causes increased rapid onset of action	TCAs are substrates of CYP2D6 system	Small clinical studies[15,57–61]
		Remission rates much higher with desipramine + fluoxetine than with either drug alone	Low response rate in 1 study	
Reboxetine	SSRI	Combination may be used in severely depressed patients; increased safety, tolerability than TCAs; fluoxetine-reboxetine combination seems well tolerated, presents no pharmacokinetic or pharmacodynamic interactions	Lack of pertinent studies	Anecdotal
Atypical antipsychotics	SSRI	May help manage anxiety, insomnia	Sedation, weight gain	Two small open-label studies[63,64]
Anticonvulsants	Current antidepressant	May help manage anxiety, irritability, insomnia	Sedation; lack of studies	Anecdotal

[a]Abbreviations: CYP2D6 = cytochrome P450 2D6, 5-HT = serotonin, MAOI = monoamine oxidase inhibitor, NE = norepinephrine, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

pressant—whereas the switching strategy involves the substitution of the failed agent with another antidepressant, often one with a different mechanism of action. This article will review some of the studies that address both augmentation and switching strategies.

Our group at the Massachusetts General Hospital recently surveyed 402 psychiatrists from across the country and queried them about the treatment strategies they use for patients who have not responded to ≥ 8 weeks of an adequate dose of a selective serotonin reuptake inhibitor (SSRI). Interestingly, switching to a non-SSRI agent was the most popular recommendation.[7] Even though there are no published, controlled trials of such practices, switching to another agent is what clinicians seem to choose. Most augmentation studies have been done with lithium or one of the thyroid hormones as the augmentor. Despite the evidence supporting lithium or thyroid hormone augmentation, those responding to our survey of psychopharmacology practices ranked bupropion as their first choice for augmentation.[7] These findings confirm the impression that

Table 2. Advantages and Disadvantages of Switching Strategies for the Management of Refractory Depression

Switch to:	Advantages	Disadvantages	Clinical Evidence
MAOI	Useful in atypical unipolar depression and anergic bipolar depression	Dietary restrictions; risk of hypertensive crisis	Small clinical studies[65,66]
TCA	Useful in SSRI nonresponders	Greater side effect burden than with newer agents	Crossover study[67]
Bupropion	Less weight gain, sexual dysfunction than with other antidepressants	Lack of pertinent studies	Small clinical studies[68,69]
Venlafaxine	Dose-response curve	Response rates to SSRI nonresponders less than TCA, MAOI nonresponders	Clinical studies[70,71]
Nefazodone	SSRI intolerance not a predictor of nefazodone intolerance; associated with fewer sexual side effects than SSRIs	Often underdosed; b.i.d. dosing	Large clinical study[72]
Mirtazapine	May prevent SSRI discontinuation–emergent adverse events by blocking 5-HT_2 and 5-HT_3 receptors, and immediate switch is therefore safe; may improve SSRI-induced sexual dysfunction	Sedation and weight gain	Large clinical study[74]
Reboxetine	Potentially distinctive effects on social functioning	Lack of studies	Anecdotal

Table 3. Limitations of Lithium Augmentation

Several studies with SSRIs have shown poor results
Increased risk of toxicity when added to SSRIs
Increases risk of bothersome side effects (e.g., weight gain, thirst)
Less user-friendly (e.g., multiple daily doses, requirement for blood monitoring) than other augmentation strategies

there is a discrepancy between what clinicians do and what is recommended in the literature.

AUGMENTATION STRATEGIES

Lithium Augmentation

The augmentation of antidepressants with lithium has recently lost favor, despite studies showing robust improvements in patients who have not previously responded to a tricyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI), or SSRI.[8–14] In such cases, lithium is typically administered in dosages of ≥ 600 mg/day in divided doses. Such an augmentation strategy would, of course, necessitate careful monitoring of plasma lithium concentrations. In view of the documentation from these studies, it is curious that lithium is not more widely used (Table 3). In several studies, lithium was associated with very modest improvements when added to an SSRI.[15,16] Furthermore, lithium augmentation is likely to increase the risk of toxicity,[17] and a significant proportion of patients may report bothersome side effects. The reports of side effects are particularly likely among those who are used to the fairly benign side effect profile associated with the SSRIs. Because of the need for blood monitoring, lithium augmentation is less user-friendly than other augmentation strategies. All of these reasons are likely to contribute to lithium's lack of popularity among clinicians as an augmentor.

Thyroid Hormone Augmentation

Augmentation strategies using doses of 25–50 μg/day of levothyroxine or triiodothyronine have been used successfully among depressed patients refractory to TCAs.[18] However, thyroid hormone augmentation is currently even less popular than lithium augmentation, probably because the studies involving this strategy were conducted with TCAs and not SSRIs,[18] or perhaps because of the potential for developing side effects such as nervousness and insomnia.

Buspirone Augmentation

The addition of buspirone is a relatively popular augmentation strategy. Buspirone is considered a well-tolerated antianxiety drug with partial agonist properties for the serotonin-1A (5-HT_{1A}) receptor. Small, open-label studies using buspirone, 5–15 mg twice daily, have demonstrated a marked or complete antidepressant response in patients considered treatment resistant.[19–22] However, not all studies have been this promising. In one study, the response rate was very low among participants with refractory depression,[23] and the only placebo-controlled study comparing buspirone with placebo augmentation in refractory depression did not find statistically significant differences in response rates between buspirone and placebo augmentation (51% vs. 47%, respectively).[24]

Pindolol Augmentation

Pindolol augmentation is infrequently used in the United States, but is a relatively common augmentor in Europe and Canada. Pindolol is a β-blocker and a 5-HT_{1A} antagonist. Most studies have evaluated pindolol doses of 2.5 mg 3 times daily. Interest in pindolol augmentation probably stems from data showing an accelerated response to SSRIs in some,[25–29] but not all,[30] studies. A study by Moreno and colleagues[31] found no significant improvement in depressive symptoms in 10 treatment-refractory depressed patients; similarly, a study by Perez and colleagues[32] showed no difference from placebo in a very short (10-day) trial of augmentation in a treatment-refractory depressed population. Blier and Bergeron[29] have raised a concern about this augmentation strategy, because they found that some patients experienced increased irritability with pindolol.

Nefazodone Augmentation

Only anecdotal reports have so far suggested that nefazodone augmentation of SSRIs is a viable option. Augmentation doses of nefazodone are typically 100 mg or 200 mg administered twice daily. One possible concern with this strategy stems from a case report of apparent serotonin syndrome by John and colleagues.[33] Nefazodone is a mildly potent uptake blocker of serotonin and thus increases serotonin levels in brain synapses. But the main concern is over the accumulation of an active metabolite of nefazodone, *m*-chlorophenylpiperazine (*m*-CPP), that is metabolized by the cytochrome P450 2D6 (CYP2D6) isoenzyme. The concern is that a drug-drug interaction may occur when nefazodone is coadministered with an SSRI that inhibits the same cytochrome P450 pathway. Such an interaction would likely lead to an increase in anxiety and irritability due to an accumulation of *m*-CPP. The advantage of adding nefazodone to an SSRI in the event of treatment failure is that anecdotally it has been shown to mitigate sexual dysfunction related to SSRIs.[34]

Dopaminergic Drug Augmentation

Dopaminergic drug augmentation is another interesting strategy for treating refractory depression. Bouckoms and Mangini[35] used the antiparkinsonian drug pergolide, 0.25–2 mg/day, with some success. Similarly, improvement has been reported for the combination of an antidepressant and the dopaminergic drugs amantadine, 100–200 mg twice daily,[36] and pramipexole, 0.125–0.25 mg 3 times daily.[37] Unfortunately, studies to date that have evaluated the augmentation of an SSRI with a dopaminergic agent have been limited in scope; true effectiveness has not yet been established. A potential advantage for dopaminergic drug augmentation stems from animal studies showing that these drugs are associated with some stimulation of sexual function and anecdotal reports of benefits in alleviating sexual dysfunction induced by SSRIs.[37]

Psychostimulant Augmentation

In line with the potential role of dopaminergic agents as augmentors of antidepressants, there are published studies showing improvement in antidepressant efficacy with psychostimulants as augmentors to TCAs,[38] MAOIs,[39] SSRIs,[40] and venlafaxine.[41] Clinicians typically use methylphenidate, 10–40 mg/day; dextroamphetamine, 5–20 mg/day; or pemoline, 8.75–112.5 mg/day in a divided dose. The main concern over psychostimulant augmentation is the potential for abuse, especially in patients who have a history of substance abuse. Psychostimulants may also worsen anxiety or irritability and may cause significant insomnia. Therefore, it is important to administer the dose of the psychostimulant early in the day. Even though the response may be transient,[39] the augmentation effect is often quite rapid.

Bupropion Augmentation

As mentioned earlier, augmentation with bupropion, 100–150 mg as sustained-released tablets once or twice daily, was the top choice of the psychiatrists participating in the Massachusetts General Hospital Augmentation Strategy Survey for Refractory Depression.[7] The evidence in favor of bupropion augmentation is predominantly based on anecdotal reports, case series, or small open trials.[42–45] Potential disadvantages of bupropion augmentation are found in reports that the combination of bupropion and SSRIs can sometimes lead to tremor[44] or panic attacks.[46] However, the positive effects of bupropion amelioration of SSRI-induced sexual dysfunction reported in some augmentation studies[47,48] may be a significant advantage for this strategy.

Venlafaxine Augmentation

Benefits for augmentation with venlafaxine, 75–300 mg/day, in SSRI nonresponders are suggested by a few anecdotal reports. The main disadvantage to this augmentation strategy stems from its metabolism by the CYP2D6 system. Increased plasma levels of venlafaxine have been reported in cases in which venlafaxine has been combined with an SSRI that also inhibits the CYP2D6 pathway. Reports included a patient who experienced serotonin syndrome[49] and another with marked blood pressure elevation and severe anticholinergic side effects.[50]

SSRI Augmentation of SSRIs

Since venlafaxine is considered by some to be more of an SSRI than a true serotonin-norepinephrine reuptake inhibitor (SNRI) when used at lower doses,[51,52] it is not surprising that SSRIs have been anecdotally reported to be useful in augmenting other SSRIs.[53] The main disadvantages of such an approach are an increase in the intensity of serotonergic side effects and a theoretical risk of developing serotonin syndrome.[54] Although this is not a widely used treatment option, Bondolfi and colleagues[53] suggest that there may be an unusual drug-drug interaction when certain SSRIs are combined. The authors argue that fluvoxamine augmentation of citalopram increases the ratio of S-citalopram versus R-citalopram, and since S-citalopram is a more potent uptake inhibitor of serotonin, this drug-drug interaction may lead to an increase in the more active form of citalopram.

Mirtazapine Augmentation

Mirtazapine is a dual-action antidepressant that increases both serotonergic and noradrenergic activity by blocking the α_2 adrenergic autoreceptors and heteroreceptors and blocking the serotonergic 5-HT_2 and 5-HT_3 receptors. A favorable effect of mirtazapine, 15–30 mg at bedtime, as an augmentor of an SSRI has been reported by Price and colleagues.[55] This augmentation may also serve to ameliorate SSRI-induced sexual dysfunction.[56] The main

disadvantages of this strategy are the potential for weight gain and sedation associated with the combination.[55]

Desipramine or TCA Augmentation

An early study by Nelson and colleagues[57] showed that a combination of desipramine or other TCA with an SSRI may produce a more rapid onset of action. Furthermore, a more recent study by the same author[58] has shown significantly higher remission rates for patients taking a desipramine/fluoxetine combination than either drug alone. This finding is consistent with reports that desipramine and other TCAs were effective in augmenting SSRIs in small cohorts of patients.[59–61] The main issue related to the TCA augmentation strategy is that TCAs are substrates of the CYP2D6 isoenzyme—a common metabolic pathway for drug metabolism. Should a TCA be coadministered with an SSRI that also inhibits CYP2D6, plasma concentrations of the TCA are likely to increase. This occurrence may increase the risk of cardiac toxicity from the TCA. For this reason, physicians tend to use low doses (25–75 mg/day) of a TCA and also monitor blood drug concentrations. In a double-blind study from our center,[15] we observed fairly low response rates with desipramine augmentation (up to 50 mg/day) of fluoxetine.

Reboxetine Augmentation

Harkin and colleagues[62] found, in a number of animal models of depression, that a combination of reboxetine, a relatively selective norepinephrine reuptake inhibitor, and sertraline yielded a more rapid onset of responses than with either reboxetine or sertraline treatments alone. Studies in humans are warranted to investigate this interesting finding.

Our group at Massachusetts General Hospital has anecdotally observed that the addition of reboxetine to SSRIs was helpful with patients who were refractory to SSRI treatment alone. We have typically used reboxetine, 8–12 mg/day, in divided doses. As the use of reboxetine will increase with its release in the United States, we are likely to learn more about this augmentation scheme. Nelson[58] has hypothesized that combining drugs that affect both serotonin and norepinephrine may be especially effective for patients who have not responded to drugs that affect only one or the other neurotransmitter system. In this regard, we are likely to see more use of this combination of medications. One drug-drug interaction study of fluoxetine and reboxetine suggests the safety of this particular drug combination (data on file, Pharmacia & Upjohn, 1999).

Atypical Antipsychotic Drug Augmentation

In small trials of SSRI nonresponders, positive findings have been noted with both risperidone[63] and olanzapine[64] augmentation of an SSRI. The main disadvantage of such a strategy is the risk of sedation and weight gain, although this drug combination may improve symptoms such as anxiety and insomnia.

Anticonvulsant Augmentation

Many of the anticonvulsants used in bipolar illness (i.e., divalproex, carbamazepine, lamotrigine, gabapentin, and topiramate) are also used as adjunctive medications in refractory, unipolar depression, although there are no published studies to support this strategy. The main concern with an anticonvulsant augmentation strategy is the potential for sedation and, in the case of divalproex and carbamazepine, the need for blood monitoring.

SWITCHING STRATEGIES

Switching to MAOIs and TCAs

In the 1970s and 1980s, it was popular to switch patients who had a poor response to an MAOI to another antidepressant. Currently, this option is among the least attractive, primarily because of the dietary restrictions necessary with MAOIs and the risk of spontaneous and nonspontaneous hypertensive crisis. However, the MAOIs may be particularly effective in the treatment of atypical unipolar depression[65] and anergic bipolar depression[66] and therefore should not be ruled out.

Although the switch to a TCA has also been shown to be effective among SSRI nonresponders,[67] the popularity of this strategy has declined because of the improved safety profile and, consequently, the favor of the newer agents.

Switching to Bupropion

Even though switching to bupropion appears to be a very popular strategy among psychiatrists,[7] documentation for this strategy is limited. There are 2 small studies, one by Goodnick and colleagues[68] and the other by Walker and colleagues,[69] that show significant improvement on switching patients to bupropion who have not done well taking an SSRI. The main advantage of such a strategy is the decreased risk of weight gain and sexual dysfunction.[69]

Switching to Venlafaxine

Nierenberg and colleagues[70] showed improvements in depressive symptoms in a group of 84 treatment-refractory patients switched to venlafaxine. These patients had failed to respond to at least 3 adequate trials of antidepressants from at least 2 different antidepressant classes or electroconvulsive therapy, plus at least 1 attempt at augmentation. A potential disadvantage of the broad use of this strategy is that venlafaxine may work better in TCA and MAOI nonresponders than SSRI nonresponders.[71]

Switching to Nefazodone

Thase and colleagues[72] recently presented results of a multicenter study in which patients with poor response to

SSRIs improved when switched to nefazodone. The main disadvantage of the nefazodone conversion is that this drug is frequently underdosed and must be administered in divided doses. On the other hand, nefazodone therapy is associated with fewer sexual side effects than the SSRIs.[73]

Switching to Mirtazapine

A multicenter study involving switching treatment-refractory patients to mirtazapine has recently been completed.[74] In this study involving 102 patients, our group demonstrated a 47% response rate for patients treated with mirtazapine, 15–45 mg/day. Each of the patients had previously failed an adequate trial of an SSRI. Sedation and weight gain were the main disadvantages to mirtazapine therapy. We were able to abruptly switch from a short-acting SSRI to mirtazapine with few discontinuation-emergent symptoms, obviating a long washout period.[74] In addition, there was significant improvement in sexual functioning in a substantial number of patients who were previously troubled by SSRI-induced sexual dysfunction.[74]

Switching to Reboxetine

There are only unpublished reports about the efficacy of reboxetine, the newest of the antidepressants, in refractory patients. However, a multicenter study of the efficacy of switching to reboxetine for patients who have failed to respond to an SSRI is currently underway, and an interim analysis has shown promising results. A potential advantage of such a switch may be reboxetine's positive effects on social functioning.[75]

CONCLUSION

In conclusion, new switching and augmentation strategies are now available. These treatment strategies offer safe and effective approaches to treatment-refractory or treatment-intolerant patients. Most of the strategies aim at obtaining a different neurochemical effect or at reducing the likelihood of encountering a specific side effect (e.g., sexual dysfunction). Some augmentation strategies may be limited by drug-drug interactions, and some switching strategies may be limited by the loss of partial benefits from the previous medication. Further studies are needed to evaluate the efficacy and tolerability of each of the strategies described.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin), buspirone (BuSpar), carbamazepine (Tegretol and others), citalopram (Celexa), desipramine (Norpramin and others), dextroamphetamine (Dexedrine and others), divalproex sodium (Depakote), fluoxetine (Prozac), fluvoxamine (Luvox), gabapentin (Neurontin), lamotrigine (Lamictal), levothyroxine (Synthroid and others), methylphenidate (Ritalin), mirtazapine (Remeron), nefazodone (Serzone), olanzapine (Zyprexa), pemoline (Cylert), pergolide (Permax), pramipexole (Mirapex), reboxetine (Vestra), risperidone (Risperdal), sertraline (Zoloft), triiodothyronine (Cytomel), venlafaxine (Effexor).

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