Current Status of Augmentation and Combination Treatments for Major Depressive Disorder: A Literature Review and a Proposal for a Novel Approach to Improve Practice

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Abstract
Most patients with major depressive disorder (MDD) do not reach symptom remission. These patients with residual symptoms have worse function and worse prognosis than those who remit. Several augmentation and combination treatments are used to either increase the chances of achieving remission or to eliminate/minimize residual depressive symptoms. Evidence for these pharmacological approaches rests primarily on open, uncontrolled studies, and there are clearly not enough controlled studies. Clinicians should carefully weigh these different treatment options to increase their patients' chances of achieving and sustaining remission from depression. This paper will review the pertinent studies and will propose a novel approach to improve practice involving the use of augmentation or combination strategies at the outset of initial treatment to primarily enhance the chances of remission through synergy and/or a broader spectrum of action. This novel approach could potentially enhance retention and/or increase remission rates since the lack of response with antidepressant monotherapy may lead many depressed patients with little or no benefit to drop out of treatment, precluding the subsequent use of augmentation or combination strategies altogether. In addition, the emergence of certain side-effects (e.g., agitation, insomnia) or the persistence of some initial baseline symptoms (e.g., anxiety, insomnia) may lead to premature discontinuation from monotherapy in the absence of concomitant use of augmenting pharmacological options targeting these symptoms.

Treatment-resistant depression typically refers to the presence of an inadequate clinical response following adequate antidepressant therapy among patients suffering from major depressive disorder (MDD). While the more traditional view of treatment resistance has focused on nonresponse (i.e., patients with minimal or no improvement), ‘inadequate response’ is now viewed as the lack of symptom remission. Achieving remission is a significant clinical challenge [1], as a significant proportion of patients with MDD do not achieve full remission despite adequate treatment and (for some) significant symptom
improvement [2]. In fact, pooled analyses of double-blind antidepressant efficacy trials in typically uncomplicated (i.e., minimal general medical and psychiatric comorbidity), nonchronic depressions treated under research clinic conditions reveal that remission rates range between 30 and 45%, so that the majority of MDD patients are expected to fail to achieve remission with a single trial of monotherapy with antidepressants [3]. Patients who do not achieve remission, including those who respond (e.g., experience a ≥50% reduction of symptoms) but do not remit, continue to be affected by psychological, behavioral, and somatic residual symptoms [4], including depressed mood, reduced levels of interest, excessive guilt, fatigue, sleep disturbances, appetite changes, and pain. Even among 108 patients who had reached ‘remission’ based on the convention of a 17-item Hamilton Rating Scale for Depression (HAM-D) score <8, 25.9% had 1 residual symptom, and 56.5% had 2 or more symptoms [4].

Relapse and recurrence after successful treatment of MDD is both common and debilitating [5]. Patients with MDD who do not achieve complete symptom remission are particularly vulnerable to relapse [6–8]. For example, in a 15-month study of long-term outcome of treatment of depression, Paykel et al. [6] followed 60 patients with major depression in remission. Relapses occurred within the first 10 months of follow-up in 76% (13/17) of patients with residual symptoms but in only 25% (10/40) of patients without residual symptoms. Taken together, these data strongly support the need to improve the treatment of depression to achieve higher rates of remission and to eliminate residual symptoms.

Treatment Tactics to Increase Remission Rates with Antidepressant Monotherapy

Clinicians can employ several treatment tactics to increase the chances of achieving full remission with antidepressant monotherapy. These include (1) psycho-education, (2) enhancing treatment adherence, (3) ensuring adequacy of antidepressant dose, (4) ensuring adequacy of antidepressant treatment duration, (5) choosing antidepressant medications with relatively greater efficacy in specific subtypes or populations, and (6) adding psychotherapy.

(1) Psychoeducation. It is considered quite helpful to explain to patients that depression is a medical illness that is associated with changes in brain functioning and that antidepressants are used to help improve brain function. Psychoeducational materials and an emphasis on the importance of communication and collaboration may help set the stage for meaningful dialogue. Psychoeducation may therefore increase the degree of collaboration between the patient and the treating clinician and may enhance the acceptability of any subsequently proposed treatment approach.

(2) Enhancing treatment adherence. Adequate follow-up with patients (office visits or phone contacts) is known to lead to better adherence to treatment [9]. In certain settings (e.g., primary care), improved care management can greatly improve treatment adherence [10]. Antidepressants with relatively greater tolerability, fewer side-effects, or that require only once-a-day dosing, also can enhance adherence. It is important to discuss possible side-effects that may occur during antidepressant treatment and possible approaches to their management, should they occur, even before prescribing a treatment. Engaging the patient in the choice of the medication and in discussing the relative risk of potential side-effects is thought to also enhance patient engagement in the treatment process [11].

(3) Ensuring adequacy of antidepressant dose. Although antidepressant medications are typically administered at doses within recommended therapeutic ranges, some patients may require doses well above the therapeutic range in order to remit. Monitoring antidepressant blood levels may be useful for patients who are not responding and do not report side-effects, even with the newer antidepressants for which there is no clear blood level-response relationship.

(4) Ensuring adequacy of antidepressant treatment duration. Most patients require 6–12 weeks of treatment to achieve adequate response [12]. On the other hand, studies have shown that minimal improvement by week 4 or 5 leads to a very small chance of response [12, 13]. In fact, a study from our group has demonstrated that nonresponse as early as week 4 or 6 predicted poor outcome at week 8 [13]. These findings suggest that, in general, clinicians must consider taking action, if at least minimal symptom improvement has not occurred by weeks 5 or 6 with an adequate dose. Improved longer-term outcomes may be achieved with longer courses of treatment, perhaps especially for the chronic or comorbidly ill patients.

(5) Choosing antidepressant treatments with relatively greater efficacy in specific subtypes or populations. Remission rates tend to be comparable across the different antidepressant medications and classes. The chances of remission, however, may be enhanced by choosing agents
Augmentation and Combination Treatments for MDD

Augmentation strategies involve the use of medications that are not standard antidepressant monotherapies in order to enhance the antidepressant effect. Combination strategies involve the use of two antidepressant medications, typically of different classes. Augmentation and combination treatments may be implemented either: (a) at the onset of treatments to enhance the chances of achieving remission or (b) following the use of antidepressant monotherapy initially, if it did not result in remission. Most augmentation and combination studies have used the latter approach. Despite this fact and the fact that current treatment guidelines recommend a single medication to initially treat MDD, several reasons support the use of augmented or combined treatment at treatment initiation to either enhance retention or to increase remission rates. (1) First, most patients with MDD do not remit with initial antidepressant monotherapy; (2) no initial monotherapy medication is robustly different from others in achieving remission [3]; (3) the lack of response with antidepressant monotherapy may lead many depressed patients with little or no benefit to drop out of treatment, precluding the use of augmentation or combination altogether, and (4) the emergence of certain side-effects (e.g., agitation, insomnia) or persistence of some initial baseline symptoms (e.g., anxiety, insomnia) may lead to premature discontinuation from monotherapy without pharmacological options to deal with these symptoms. In addition, such initial combinations may create a broader spectrum of action (i.e., a larger proportion of patients initially treated may at least respond if not remit). Finally, the pharmacological synergism achieved with combinations may convert monotherapy responders into combination treatment remitters. In the following sections, we are going to review the studies concerning the efficacy of combination and augmentation strategies in the treatment of MDD. All these strategies are off-label as no treatment has been approved for augmentation of antidepressants in MDD.

Augmentation Strategies

Over the past few decades, numerous compounds have been used to augment antidepressant medications. Most of these studies are uncontrolled and open label, though some investigations are double blind and placebo-controlled. The latter studies allow us to draw relatively firm conclusions about the efficacy of some augmenting agents (e.g., lithium and thyroid hormones). When the augmentation strategy is implemented after the patient with MDD has not achieved remission with antidepressant monotherapy, improvement, if it is to occur, will follow initiation of antidepressant augmentation within 3–4 weeks. Thus it is premature to decide about the efficacy of augmentation within less than several weeks. Nearly all augmentation studies have focused on the short-term outcomes (4–8 weeks). Little is known about the minimum duration of the augmentation trial for responders to such a strategy. Augmentation strategies have also been used to hasten the onset of antidepressant effect. A plethora of augmentation strategies has been reported [17], but the most-studied strategies for depression are lithium, thyroid hormone, pindolol, and buspirone.

Lithium

Lithium augmentation, most popular in the 1980s, is supported by controlled studies that have clearly shown that the addition of a dose of 600 mg/day or more of lithium, typically in divided doses, and with reasonably good blood levels, leads to robust increases in response chances in patients not responding to tricyclic antidepressants.
sants (TCAs), monoamine oxidase inhibitors (MAOIs), or SSRIs. Twelve double-blind controlled trials of lithium augmentation in depression have reported response rates that averaged 52% in a total of 255 lithium-augmented patients [18–32]. A meta-analysis of placebo-controlled trials by Bauer et al. [33] revealed a response rate in the lithium-augmented group of 45 vs. only 18% in the placebo group (p < 0.001). This meta-analysis, however, did not include the largest placebo-controlled study of lithium augmentation so far. In this study among 142 MDD patients who had not responded to clomipramine mono-therapy [32], study exit remission and response rates were not statistically different between lithium and placebo augmentation. Lithium augmentation was not particularly effective when added to SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs) [18, 19, 26, 32]. Similarly, the efficacy of lithium augmentation in the only two double-blind studies in partial responders to SSRIs in the literature is rather modest, with an overall response rate of 27% (7/26) [18, 19]. Therefore, the role of lithium augmentation among MDD patients treated with the newer antidepressants remains to be established. Furthermore, despite the relative robust early findings concerning lithium augmentation of TCAs in the literature, the three most recent double-blind studies of lithium augmentation have all failed [18, 31, 32], suggesting that perhaps lithium’s therapeutic success in the 1980s might have been partly due to the fact that bipolar spectrum patients may have been enrolled in some of the early studies of unipolar depression. The use of lithium is further limited by high rates of side-effects (e.g., sedation and weight gain), its potential toxicity (e.g., renal and thyroid), frequent blood monitoring requirements, and significant toxicity or death in overdose. Perhaps for these reasons, there are no placebo-controlled studies to assess the efficacy of lithium augmentation in nonresistant depressed patients to enhance the chances of achieving remission (i.e., at the start of initial treatment).

**Thyroid Hormone**

In treatment-resistant depression studies, L-triiodothyronine (T3) has been shown to be superior in efficacy to thyroxine (T4) [34]. Among four randomized double-blind studies of T3 augmentation of antidepressants, pooled effects were not significant (relative response, 1.53; 95% CI, 0.70–3.35; p = 0.29), but one study with negative results accounted for most of this effect [35]. Since all published controlled studies involved T3 augmentation of TCAs, the efficacy of T3 augmentation in SSRI-resistant patients is unknown. Only uncontrolled studies of thyroid hormone augmentation with SSRIs have been carried out this far [36–38]. Common side-effects with thyroid hormone augmentation include palpitations, sweating, nervousness, and tremor [39]. Six double-blind, placebo-controlled studies assessed the efficacy of concomitant administration of T3 and TCAs in accelerating clinical response among patients with nonrefractory depression. Five of the six studies found T3 to be significantly more effective than placebo in accelerating clinical response, with the pooled, weighted effect size index being 0.58, and the average effect being highly significant [40]. Despite apparent acceleration of response with T3, there are no published placebo-controlled studies assessing the efficacy of thyroid hormone augmentation in nonresistant depressed patients to enhance the chances of achieving remission as a first-step treatment.

**Buspirone**

Buspirone is typically a well-tolerated anti-anxiety drug, with serotonin (5-HT1A) receptor partial agonist properties. Open studies using 5–15 mg b.i.d. of buspirone have shown significant improvement in refractory patients [24, 41–43]. The first placebo-controlled study in resistant depression compared buspirone and placebo augmentation among 117 patients who had not responded to a minimum of 4 weeks of treatment with either paroxetine or citalopram (mean treatment duration prior to augmentations: 5 months) and found no statistically significant difference in response rates between these two treatments (51% buspirone versus 47% placebo) [44]. However, the extremely long duration of SSRI treatment prior to randomization raises the possibility that many of the randomized patients may have been relapsers and not nonresponders to SSRIs. A more recent double-blind study showed that, among 102 depressed outpatients who had failed to respond to a minimum of 6 weeks of treatment with either fluoxetine or citalopram, in the SSRI-resistant patients with severe depression buspirone (20–60 mg/day) augmentation was more effective than placebo and very well tolerated, even though the difference between buspirone and placebo was not significant in the overall sample [45]. A randomized, open-label study in 120 nonresistant depressed patients showed comparable response rates among patients treated with fluoxetine alone versus fluoxetine plus buspirone [46]. However, there are no placebo-controlled studies in the literature assessing the efficacy of buspirone augmentation in nonresistant depressed patients to enhance the chances of achieving remission. This is somewhat surprising, as buspirone has shown efficacy in anxiety dis-

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orders such as generalized anxiety [47], and anxious depression accounts for approximately half of depressed outpatients [48].

Pindolol

Pindolol augmentation, while rarely used in clinical practice in the US, is relatively more popular in Europe and Canada in the management of resistant depression. Pindolol is a β-blocker and a serotonin 5-HT₁A antagonist. A dose of 2.5 mg t.i.d. has been used in most depression studies, yet PET imaging studies suggest that this dose is likely suboptimal for an adequate occupancy of 5-HT₁A receptor [49]. This agent has generated a lot of interest because it has been shown to accelerate antidepressant response when combined with SSRIs in most [50–55], but not all [56] studies. In some studies, higher response rates were reported at endpoint with pindolol augmentation than with placebo augmentation [50, 52, 55, 57, 58]. However, a study by Moreno et al. [59] found no response among 10 treatment-resistant depressed patients, and two separate studies [60, 61] showed no difference from placebo in augmenting antidepressants in resistant depressed populations, despite good tolerability [61]. On the other hand, a study in 31 hospitalized depressed patients showed a 60% response rate in patients treated with fluoxetine plus pindolol compared with a 9% response rate in patients treated with fluoxetine alone [58].

Dopaminergic Drugs

Given the putative role of dopaminergic neurotransmission in MDD [62], augmentation with dopaminergic drugs is a potentially useful strategy. In an open trial (n = 20), Bouckoms and Mangini [63] used, with some success, the antiparkinsonian drug pergolide (0.25–2 mg/day) in resistant unipolar and bipolar depression. Similarly, there are uncontrolled, small studies of antidepressant augmentation with the dopaminergic drugs amantadine (100–200 mg b.i.d.) [64, 65], pemoline (0.125–0.50 mg t.i.d.) [66–68], and ropinirole (0.5–1.5 mg t.i.d.) [69]. The dopamine D₂ and D₃ receptor agonists pemoline and ropinirole are typically much better tolerated than the older dopaminergic drugs and are associated primarily with somnolence and very mild nausea [69, 70]. Without controlled studies, the effectiveness of antidepressant augmentation with dopaminergic agents remains to be established for treatment resistant depression for residual symptoms of depression, and as a treatment for nonresistant depressed patients to enhance remission rates.

Psychostimulants

Psychostimulants also have significant effects on dopamine neurotransmission, and they have been used to augment TCAs, MAOIs, SSRIs, and SNRIs [71–77]. Clinicians typically use methylphenidate (20–80 mg/day) or dextroamphetamine (10–40 mg/day) in divided doses. A small, uncontrolled study (n = 11) suggested the usefulness of methylphenidate in accelerating antidepressant response [78]. The main issues concerning the use of psychostimulant augmentation are the potential for abuse in some patients with history of substance abuse, the possible emergence of anxiety and irritability, and their relatively short half-life [17]. There are no controlled data on the effectiveness of these augmenting agents in treatment-resistant MDD or in nonresistant MDD to enhance the chances of achieving remission at the onset of treatment.

Modafinil

Modafinil, a novel psychostimulant, has pharmacological actions that are distinct from those of amphetamines. In a small (n = 7) retrospective case series, Menza et al. [79] first reported the usefulness of modafinil (in doses up to 200 mg/day) as an adjunct to antidepressants in resistant depression. More recently [80], 8 of 14 patients not responsive to SSRIs or venlafaxine rated themselves as much improved following augmentation with up to 400 mg/day of modafinil. A preliminary double-blind, placebo-controlled, 6-week study found that modafinil rapidly improved fatigue and daytime wakefulness, with significantly greater mean improvements from baseline than placebo in fatigue (Fatigue Severity Scale) scores at week 2 (p < 0.05) and sleepiness (Epworth Sleepiness Scale) scores at week 1 (p < 0.01), but no significant differences between modafinil and placebo at endpoint [81]. A subsequent, placebo-controlled multicenter study evaluated the efficacy of modafinil augmentation in MDD patients with fatigue and excessive sleepiness despite SSRI monotherapy. Of the 311 patients who received at least 1 dose of study drug, modafinil significantly improved patients’ overall clinical condition compared with placebo (based on CGI-I scores, p = 0.02), with trends toward greater reductions in sleepiness and depression (HAM-D and MADRS) severity scores versus placebo. Modafinil also significantly reduced Brief Fatigue Inventory scores for worst fatigue at exit (p < 0.05 versus placebo). Only nausea and jitteriness were significantly more common with modafinil than placebo [82]. A small, uncontrolled study of modafinil has also suggested its usefulness in accelerating response and enhancing the chances of achieving remission [83]. The relatively greater user
friendliness of modafinil (compared to psychostimulants) has made it a relatively popular augmentor of antidepressants for MDD residual symptoms, especially fatigue, sleepiness, and lethargy [80, 82].

Atypical Antipsychotics
Risperidone [84], olanzapine [85], quetiapine [86], aripiprazole [87, 88] and ziprasidone [89, 90] have all shown good responses in small, uncontrolled trials with SSRI nonresponders, with the exception of the Shelton et al. study [85]. The typical doses in augmentation of antidepressants are 0.5–2 mg/day for risperidone, 5–20 mg/day for olanzapine, 50–300 mg/day for quetiapine, 10–30 mg/day for aripiprazole, and 40–160 mg/day for ziprasidone. A large study (n = 386) of citalopram monotherapy nonresponders showed a 63% remission rate after 4–6 weeks open phase of risperidone augmentation (0.5–2 mg/day). During the double-blind discontinuation phase (n = 241), however, 53% of patients randomized to remain on risperidone relapsed versus 55% of those switched to placebo (ns) [91]. A meta-analysis of two large controlled studies found olanzapine augmentation of fluoxetine to be effective over 8 weeks [92]. The apparently rapid onset of olanzapine augmentation [85] has made it relatively popular among clinicians for treatment-resistant depression, although very little is known about its efficacy in managing residual symptoms of MDD or in its use for nonresistant depressed patients to enhance the chances of achieving remission. The potential risk for treatment-emergent weight gain, sedation, extrapyramidal symptoms, metabolic disturbances (e.g., diabetes, and hyperlipidemia), and hyperprolactinemia [93–95], although variable among atypical antipsychotic drugs, has somewhat limited the use of these drugs for nonpsychotic depression. Whether these agents are needed in the longer term is unknown. The above-mentioned risperidone augmentation results suggest they may not be effective in the long term.

Inositol
Despite initial anecdotal positive reports of inositol (up to 12 g/day) to augment antidepressants, a controlled, double-blind augmentation trial did not support its use in SSRI nonresponders [96]. Another study assessed the ability of inositol augmentation in enhancing or speeding up response to SSRIs [97] and found no difference in outcome between patients treated with SSRIs and placebo versus those treated with SSRIs and inositol.

Opiates
Minimal evidence (mostly case reports and case series) suggests a role for antidepressant augmentation with opiates, such as oxycodone, oxymorphone [98], and buprenorphine [99]. The lack of definitive evidence and the potential risk of abuse do not recommend the use of these agents presently.

Estrogen
Estrogen exerts profound effects on behavior by interacting with neuronal estrogen receptors [100]. Mostly anecdotal evidence suggests the efficacy of estrogen augmentation of antidepressants in resistant depression among postmenopausal women. Two early studies [101, 102] failed to find a benefit of estrogen augmentation of TCAs. Four nonrandomized studies of hormone replacement therapy (HRT) to treat SSRI nonresponse [103–106] suggested that estrogen may augment the antidepressant effect of SSRIs. In addition, as pointed out by Stahl [107], there are no guidelines on how to optimize antidepressant administration with estrogen, especially in women insufficiently responsive to antidepressants.

Dehydroepiandrosterone and Testosterone
Dehydroepiandrosterone (DHEA), a major circulating adrenal androgen in humans, plays an unclear physiological role. In addition to serving as a precursor to testosterone and estrogen, DHEA and its sulfated metabolite, DHEA-S, most likely play important biological roles and have been hypothesized to be involved in regulating mood and sense of well-being [108]. A very small (n = 22), preliminary, double-blind study suggested the utility of up to 90 mg/day as an adjunct to antidepressants in resistant depression [108]. Further studies are clearly necessary, given the small number of patients studied. Similarly, in an 8-week randomized, placebo-controlled trial of testosterone transdermal gel among 23 men, aged 30–65 years, with resistant depression and low or borderline testosterone levels, testosterone was significantly better than placebo in treating depressive symptoms [109]. A subsequent small study [110] did not show significant differences between testosterone and placebo in the augmentation of antidepressants among older hypogonadal men. However, there are no published studies that have examined specifically the role of DHEA or testosterone augmentation in the management of residual MDD symptoms or in nonresistant depressed patients to enhance the chances of achieving remission with initial treatment. The need to monitor the neuroendocrine effects of these treatments limits their use in depression.
Folate and S-Adenosyl-Methionine

Folate, in particular its active form methyltetrahydrofolate, and S-adenosyl-methionine (SAMe) are compounds closely involved in the one carbon cycle and in methylation processes in the brain. These compounds have been studied extensively in depression. Literature suggests that they have antidepressant properties [111, 112]. An open trial of methylfolate (up to 30 mg/day) in SSRI-refractory patients suggested its usefulness as an adjunct [113]. A large randomized study of 127 patients who received either 500 µg/day of folic acid or placebo (in addition to 20 mg/day of fluoxetine) revealed a significantly greater improvement in the fluoxetine plus folic acid group, primarily among women [114]. A recent open study with SAMe [115] has also shown the usefulness of this augmenting agent in SSRI nonresponders. A placebo-controlled study of SAMe augmentation of imipramine had previously shown an acceleration of the response [116]. The availability of SAMe over the counter and the favorable side-effect profile (most-common side-effects are gastrointestinal symptoms and headaches) [115] have made this agent a relatively popular augmentation agent among MDD patients with residual symptoms. However, there are no controlled studies of SAMe or methyltetrahydrofolate augmentation in the management of residual MDD symptoms or in nonresistant depressed patients to enhance the chances of achieving remission.

Anticonvulsants

There are uncontrolled and anecdotal reports of the usefulness of anticonvulsant augmentation of antidepressants in major depression, with drugs such as gabapentin [117], topiramate [118], carbamazepine [119–121], and valproic acid [122]. In a study of 59 treatment-resistant depressed patients randomly assigned to the addition of either lithium or carbamazepine to ongoing antidepressant treatment, the therapeutic efficacy of both strategies, assessed after 28 days, was not significantly different [123]. Two small, placebo-controlled trials of lamotrigine vs. placebo as an adjunctive treatment to paroxetine [124] or fluoxetine [125] in treatment-resistant depression were suggestive of efficacy, but neither study was definitive because of the inadequate sample size. Therefore, there are no adequately powered, prospective controlled studies of anticonvulsant augmentation in the management of nonremission of MDD, nor as initial treatment with nonresistant depressed patients. In addition, the risk of significant side-effects (e.g., hepatotoxicity with valproic acid; hypersensitivity reactions with lamotrigine; sedation and cognitive side-effects with topiramate and gabapentin; blood dyscrasias with carbamazepine) [126, 127] further limits the use of these drugs in treatment-resistant depression.

Benzodiazepines/Hypnotics

Benzodiazepine and sedative hypnotic augmentation in depression has been used primarily to reduce attrition during antidepressant treatment (partly by managing side-effects such as insomnia and agitation) or to enhance antidepressant response. Lorzepam has been shown to be more effective than placebo in enhancing the antidepressant effect of maprotiline or nortriptyline [128]. Similarly, clonazepam augmentation of fluoxetine was associated with nonsignificantly higher remission rates than placebo augmentation in an 8-week acute trial with 80 depressed patients [129]. A 4-week study on 190 patients with a history of depression and of effective and stable treatment with SSRIs showed that augmentation with the nonbenzodiazepine hypnotic eszopiclone was significantly more effective than placebo in treating residual symptoms of insomnia [130]. A recent, large, double-blind study has shown significantly higher remission rates at 8 weeks among patients treated with fluoxetine plus the non-benzodiazepine hypnotic eszopiclone than for patients treated with fluoxetine plus placebo (42 versus 32.8% remission rates, respectively) [131]. Further studies are needed to evaluate the usefulness of hypnotic and benzodiazepine augmentation to enhance the chances of achieving and/or sustaining remission among nonresistant depressed patients, particularly given the fact that these drugs tend to be very well tolerated and to be widely used, despite concerns about possible benzodiazepine dependence and abuse [132–134].

Combination Studies

While double-blind controlled studies of augmentation strategies are scarce, there are even fewer double-blind studies of combination strategies, reflecting the need for further studies in this area. Since improvement following the initiation of antidepressant combinations tends to occur within 4–6 weeks, it is premature to decide on the efficacy of a combination before that time. Almost all efficacy studies of combination treatments have focused on short-term outcomes with patients who had initially not remitted and often not responded to an initial antidepressant monotherapy. Most combination strategies employ full doses of both antidepressant agents. Very little is known about the minimum duration of the com-

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Combination therapy entails maintaining the combination for 6–9 months following remission, followed by an attempt to gradually discontinue one of the two antidepressants. Combination strategies for resistant depression entail the use of two different antidepressants. Thus one cannot determine whether the efficacy achieved is due to the combination (perhaps due to the synergy) or to the simple exposure to another antidepressant. Combination strategies have also been used to speed up the onset of the antidepressant effect.

**Bupropion plus SSRIs**

Bupropion in sustained release formulations (SR or XL) (100–300 mg once a day or 150 mg b.i.d.) combined with SSRIs was the most popular combination strategy chosen by 400 psychiatrists surveyed by Friedman et al. [135]. Even so, the evidence for this combination is primarily based on anecdotal reports, case series, or small open trials that also suggest that this strategy is relatively well tolerated [136–139]. In a small, nonrandomized, open-label trial, the combination of bupropion-SR and citalopram was more effective than switching to other medication in patients who had not responded to either one of these two medications [140]. Future studies need to systematically assess the effectiveness of this combination in MDD patients with residual symptoms or the enhancement of initial therapeutic efficacy.

**Mirtazapine or Mianserin plus SSRIs**

Mirtazapine, a dual-action antidepressant, increases both serotonergic and noradrenergic activity by blocking the α2-adrenergic auto- and hetero-receptors and blocks the serotonergic 5-HT2 and 5-HT3 receptors. Mirtazapine (15–30 mg q.h.s.) combined with SSRIs has been reported to be helpful in an open study of nonresponders to SSRIs [141], and to be more effective than placebo plus SSRIs in a subsequent double-blind study among 20 SSRI-resistant depressed patients, although sedation and weight gain were significant issues among mirtazapine-treated patients [142]. A study in nonresistant depressed patients [143] found a significantly higher response rate to the combination of paroxetine and mirtazapine than monotherapy with either drug alone, and a 64% response rate after the switch to combination therapy for patients not responding to monotherapy.

Mianserin hydrochloride, a tetracyclic antidepressant, also enhances noradrenergic and serotonergic transmission by presynaptic α2-adrenoreceptor antagonism and blocks the serotonergic 5-HT2 and 5-HT3 receptors. The combination of mianserin with tricyclic antidepressants at initiation of treatment has been shown to augment therapeutic efficacy in 40 depressed patients, with 77% of the imipramine-plus-mianserin group being considered responders compared with 27% of the imipramine-only group [144]. Another double-blind study (n = 31) has shown higher response rates among patients treated with fluoxetine plus mianserin than among those treated with fluoxetine alone at initiation of treatment [58]. Mianserin augmentation has been reported anecdotally to be effective in depressed patients unresponsive to TCA alone [145], and fluoxetine nonresponders achieved greater efficacy when mianserin was added to fluoxetine than when placebo was added [146]. A more recent study found adding mianserin in sertraline nonresponders had no advantage over adding placebo [147], but the initial trial with sertraline monotherapy was too brief and a dose increase of sertraline was carried out 2 weeks prior to randomization, thereby confounding the results. All these studies suggest the potential usefulness of combining mirtazapine or mianserin with SSRIs when remission is not achieved with antidepressant monotherapy or when residual symptoms persist (especially insomnia and weight loss) or even to enhance therapeutic efficacy as an initial treatment.

**TCAs plus SSRIs**

An early study using a historical control [148] suggested that a combination of TCA plus SSRI may produce a more rapid onset of action. A more recent, prospective randomized trial [149] found remission rates were significantly higher with desipramine plus fluoxetine than with either drug alone. The results are consistent with uncontrolled findings that desipramine and other TCAs are effective in combination with SSRIs in small cohorts of resistant patients [150, 151]. The efficacy of TCAs combined with SSRIs has been put into question by two studies that found that adding low-dose desipramine to fluoxetine was less effective than increasing the dose of fluoxetine in patients unresponsive to 8 weeks of treatment with fluoxetine 20 mg/day [18, 19]. Since TCAs are substrates of the cytochrome P450 2D6 isoenzyme, TCA blood levels may rise when coadministered with SSRIs that inhibit this pathway, with the potential for cardiac toxicity, anticholinergic side-effects, and orthostatic hypotension. Low doses of TCAs (25–75 mg/day) are therefore typically used, and monitoring of TCA blood levels is necessary.
Reboxetine/Atomoxetine plus SSRIs

Reboxetine and atomoxetine are norepinephrine reuptake inhibitors (NRIIs). Reboxetine is available in Europe for the treatment of depression; atomoxetine is marketed in the US for the treatment of attention-deficit disorder. Three open trials of reboxetine, using doses up to 8 mg/day, have suggested the usefulness of combining this agent with SSRIs in resistant depression [152–154]. Given the fact that reboxetine is not available in the US, a number of clinicians have been using atomoxetine in combination with SSRIs. An open trial suggests its efficacy in antidepressant nonresponders [155]. Future studies are needed to evaluate this off-label use of atomoxetine.

Nefazodone/Trazodone plus SSRIs

Only anecdotal reports or case series suggest efficacy for combining SSRIs with nefazodone [156] or trazodone [157], which are antidepressants with significant serotonin 5-HT2 receptor antagonism. One controlled study of nonresistant depressed patients has shown higher response rates among patients treated with trazodone plus fluoxetine than among those receiving trazodone plus placebo [158]. Furthermore, a study on patients with residual symptoms of insomnia taking fluoxetine or bupropion has shown greater efficacy of trazodone than placebo in treating residual sleep disturbances [159]. Nefazodone augmentation of SSRIs has been associated with serotonin syndrome [160] and nefazodone treatment with rare fatal cases of hepatotoxicity [161]. Trazodone augmentation may be limited by the risk of sedation and orthostatic hypotension [162].

Summary of the Literature Review

Augmentation and combination strategies have been primarily used to manage treatment-resistant depression and/or residual symptoms in MDD patients, and, in some cases, to enhance therapeutic efficacy at the initiation of treatment in nonresistant patients. Most of these studies are uncontrolled and open label. There is a clear shortage of double-blind placebo-controlled studies.

Among the augmentation strategies, lithium and thyroid hormone have shown robust effects with TCA nonresponders and, in the case of thyroid hormone augmentation, acceleration of response with TCAs. However, the usefulness of these strategies in patients with inadequate responses to the newer antidepressants and in enhancing remission rates remains to be established. Pindolol augmentation seems to accelerate response to SSRIs and perhaps enhance their efficacy, but its usefulness in SSRI nonresponders has been questioned. Buspirone augmentation in SSRI nonresponders certainly merits further study, but evidence for enhancing remission rates with SSRI nonresponders is lacking. Benzodiazepine and nonbenzodiazepine hypnotics have clear value in treating residual sleep disturbances in antidepressant-treated patients. Placebo-controlled, 6- to 8-week trials indicate enhanced remission rates with the benzodiazepine lorazepam and the nonbenzodiazepine hypnotic eszopiclone compared to placebo. Whether differential remission rates would be present after 12–14 weeks is unknown, however. Dopaminergic drugs and psycho-stimulants have shown to help antidepressant nonresponders in uncontrolled studies in unipolar depression, but their ability to enhance remission at initiation of treatment has not been tested yet in a controlled fashion. Controlled studies have shown modafinil augmentation to be helpful in treating residual symptoms in SSRI partial responders with excessive sleepiness and fatigue. Modafinil augmentation to enhance remission rates clearly merits further investigation, given a preliminary, positive open study. The one-carbon cycle compounds folate, methylfolate, and, in particular, SAMe are promising augmentation strategies to enhance remission rates and help antidepressant nonresponders, but additional adequately powered studies are needed. Atypical antipsychotic and anticonvulsant augmentations, while promising, clearly need adequately powered studies to assess their acute and longer-term efficacy and safety in resistant depressed populations. Finally, there is no clear evidence yet favoring the adjunctive use of estrogen, opiates, and inositol.

As for combination strategies, bupropion augmentation, while widely used in practice, is supported by only uncontrolled studies. Systematic, controlled prospective evaluations of its ability to enhance remission rates and to help antidepressant nonresponders are needed. Mirtazapine or mianserin augmentation of SSRIs is supported by controlled studies suggesting that they enhance remission rates and help antidepressant nonresponders. Further studies are needed for these two agents. TCA and NRI augmentations of SSRIs have modest data that indicate they may both enhance remission rates and help antidepressant nonresponders. Finally, the evidence in favor of the use of nefazodone and trazodone augmentation is very limited.

Clinicians must choose among the different combination or augmentation treatment options to increase the
chances of achieving sustained remission from depression and resolution of residual symptoms. The ongoing NIMH-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study [163, 164] is comparing augmentation and combination treatment options for patients not benefiting adequately from an initial treatment with an SSRI. The results of STAR*D will hopefully inform and guide future treatment options for psychiatrists and primary care physicians alike in the medication management of depressed patients who do not achieve remission with an initial adequately delivered antidepressant monotherapy. STAR*D does not, however, evaluate the use of augmentation or combination strategies at the outset of initial treatment to enhance the chances of remission.

**A Proposal for a Novel Approach to Improve Practice**

Given the relatively low remission rates with antidepressant monotherapy in practice [10], the use of augmentation or combination strategies at the initiation of treatment to enhance the chances of remission seems quite reasonable, at least from a theoretical standpoint. Although in practice clinicians typically augment and combine antidepressants only after there is incomplete response to monotherapy, there is enough preliminary evidence from controlled studies that combination [58, 144, 150] and augmentation [50, 52, 55, 57, 58, 128, 131] strategies used at the beginning of antidepressant therapy may indeed increase the rates of remission compared to antidepressant monotherapy. Therefore, despite the fact that current treatment guidelines recommend a single medication to initially treat MDD, the use of augmented or combined antidepressant treatment at treatment initiation could potentially improve practice and treatment outcome, since most patients with MDD do not remit with initial antidepressant monotherapy and no initial monotherapy medication is robustly different from others in achieving remission [3]. In fact, this novel approach could potentially enhance retention and/or increase remission rates, since the lack of response with antidepressant monotherapy may lead many depressed patients with little or no benefit to drop out of treatment, thus precluding the subsequent use of augmentation or combination strategies altogether. In addition, the emergence of certain side-effects (e.g., agitation, insomnia) or the persistence of some initial baseline symptoms (e.g., anxiety, insomnia) may lead to premature discontinuation from monotherapy in the absence of concomitant augmentation of pharmacological options targeting these symptoms. Finally, since crossover studies have clearly shown that the spectrum of efficacy of antidepressant treatments does not typically fully overlap and that depressed patients who do not respond to an antidepressant may respond to the switch to another [165, 166], augmenting and combining antidepressants at treatment initiation may lead to synergy and to a broader spectrum of action (i.e., a larger proportion of patients initially treated may at least respond if not remit). This novel approach is clearly different from the sequential approach, which has been recently outlined [167]. In the sequential approach, monotherapy is carried out in two different phases of treatment (acute and residual) and the addition of a second pharmacological treatment substitutes the first one, with the aims of improving the level of remission and preventing relapse. With this novel approach, clinicians would not wait to combine drugs until one of the two alone is proven ineffective or in a second phase of therapy, but instead they would use augmented or combined antidepressant treatments right from the start of treatment. Moncrieff and Cohen [168] have recently suggested that we need to rethink our models of antidepressant drug action. We also need to rethink whether monotherapy with antidepressants is still a justified first-line treatment for MDD or whether a more aggressive treatment from the outset is justified. Given the strong rationale and the preliminary support from the literature, a systematic evaluation of this novel approach is clearly called for.

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