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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

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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 $\geq$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

with relatively greater efficacy in a specific depressive subtype. For example, dual-action antidepressants, acting to inhibit the reuptake of both serotonin and norepinephrine, have been associated with higher remission rates than certain single-action selective serotonin reuptake inhibitors (SSRIs) among patients with melancholic/endogenous depression [3, 14].

(6) Adding psychotherapy. Recent evidence indicates that for those who respond but do not remit to a medication, cognitive therapy not only removes the residual symptoms but is associated with an improved prognosis [15]. Beginning with a combination of depression-targeted psychotherapy and medication substantially increases remission rates in clinically depressed patient [16].

All these treatment tactics may increase the chance of a depressed patient achieving full remission with antidepressant monotherapy, although it is not clear whether there is synergy across them or whether each tactic affects treatment outcome independently. However, even with enhanced care, remission rates in 'real world' patients not preselected to be treatment resistant, as in the case of the IMPACT study (25% at 1 year) [10], remain rather modest. For these reasons, clinicians often choose to augment or combine antidepressant medications.

Augmenting or Combining Medications to Achieve Remission

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 Studies

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 antidepres-

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 monotherapy [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 ($5\text{-}HT_{1A}$) 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-

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-HT_{1A} 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-HT_{1A} 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], pramipexole (0.125–0.50 mg t.i.d.) [66–68], and ropinirole (0.5–1.5 mg t.i.d.) [69]. The dopamine D_2 and D_3 receptor agonists pramipexole 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 physiologic 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. Lormetazepam 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 zolpidem 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-

bination trial for those who respond or remit. Common practice 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 Fredman 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 α_2-adrenergic auto- and hetero-receptors and blocks the serotonergic 5-HT_2 and 5-HT_3 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 α_2-adrenoreceptor antagonism and blocks the serotonergic 5-HT_2 and 5-HT_3 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 (NRIs). 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-HT_2 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 lormetazepam 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 psychostimulants 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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References

1 Fava M: Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53:649–659.
2 Fava M, Davidson KG: Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200.
3 Thase ME, Entsuah AR, Rudolph RL: Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–241.
4 Nierenberg AA, Keefe BR, Leslie VC, Alpert JE, Pava JA, Worthington JJ 3rd, Rosenbaum JF, Fava M: Residual symptoms in depressed patients who respond acutely to fluoxetine. J Clin Psychiatry 1999;60:221–225.
5 Fava M, Kaji J: Continuation and maintenance treatments of major depressive disorder. Psychiatr Ann 1994;24:281–290.
6 Paykel ES, Ramana R, Cooper Z, Hayhurst H, Kerr J, Barocka A: Residual symptoms after partial remission: an important outcome in depression. Psychol Med 1995;25:1171–1180.
7 Ramana R, Paykel ES, Cooper Z, Hayhurst H, Saxty M, Surtees PG: Remission and relapse in major depression: a two-year prospective follow-up study. Psychol Med 1995;25:1161–1170.
8 Judd LL, Paulus MJ, Schettler PJ, Akiskal HS, Endicott J, Leon AC, Maser JD, Mueller T, Solomon DA, Keller MB: Does incomplete recovery from first lifetime major depressive episode herald a chronic course of illness? Am J Psychiatry 2000;157:1501–1504.
9 Wells K, Sherbourne C, Schoenbaum M, Ettner S, Duan N, Miranda J, Unutzer J, Rubenstein L: Five-year impact of quality improvement for depression: results of a group-level randomized controlled trial. Arch Gen Psychiatry 2004;61:378–386.
10 Unützer J, Katon W, Callahan CM, Williams JW, Hunkeler E, Harpole L, Hoffing M, Della Penna RD, Noel PH, Lin EH, Arean PA, Hegel MT, Tang L, Belin TR, Oishi S, Langston C. IMPACT Investigators: Improving mood-promoting access to collaborative treatment: collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. JAMA 2002;288:2836–2845.
11 Crismon ML, Trivedi M, Pigott TA, Rush AJ, Hirschfel RM, Kahn DA, DeBattista C, Nelson JC, Nierenberg AA, Sackeim HA, Thase ME: The Texas medication algorithm project: report of the Texas consensus conference panel on medication treatment of major depressive disorder. J Clin Psychiatry 1999;60:142–156.
12 Quitkin FM, McGrath PJ, Stewart JW, Ocepek-Welikson K, Taylor BP, Nunes E, Deliyannides D, Agosti V, Donovan SJ, Petkova E, Klein DF: Chronological milestones to guide drug change. When should clinicians switch antidepressants? Arch Gen Psychiatry 1996;53:785–792.
13 Nierenberg AA, McLean NE, Alpert JE, Worthington JJ, Rosenbaum JF, Fava M: Early nonresponse to fluoxetine as a predictor of poor 8-week outcome. Am J Psychiatry 1995;152:1500–1503.
14 Anonymous: Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. Danish University Antidepressant Group. J Affect Disord 1990;18:289–299.
15 Fava GA, Rafanelli C, Grandi S, Conti S, Belluardo P: Prevention of recurrent depression with cognitive therapy: preliminary findings. Arch Gen Psychiatry 1998;55:816–820.
16 Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, Markowitz JC, Nemeroff CB, Russell JM, Thase ME, Trivedi MH, Zajecka J: A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342:1462–1470.
17 Fava M: Augmentation and combination strategies in treatment-resistant depression. J Clin Psychiatry 2001;62(suppl 18):4–11.
18 Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, Worthington J, Baer L, Rosenbaum JF: Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J Clin Psychopharmacol 2002;22:379–387.
19 Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM: Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. Am J Psychiatry1994;151:1372–1374.
20 Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, Jonzier-Perey M: A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. J Clin Psychopharmacol 1996;16:307–314.
21 Cournoyer G, De Montigny C, Oulette J, et al: Lithium addition in tricyclic-resistant unipolar depression: a placebo-controlled study. Presented at the XIVth Congress of the Collegium Internationale Neuropsychopharmacologicum, Florence, Italy, June 19–23, 1984.
22 de Montigny C, Cournoyer G, Morissette R, Langlois R, Caille G: Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression. Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. Arch Gen Psychiatry 1983;40:1327–1334.
23 Heninger GR, Charney DS, Sternberg DE: Lithium carbonate augmentation of antidepressant action: An effective prescription for treatment-refractory depression. Arch Gen Psychiatry 1983;40:1335–1342.
24 Joffe RT, Schuller DR: An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. J Clin Psychiatry 1993;54:269–271.
25 Kantor D, McNeven S, Leichner P, Harper D, Krenn M: The benefit of lithium carbonate adjunct in refractory depression: fact or fiction? Can J Psychiatry 1996;31:416–418.
26 Katona CL, Abou-Saleh M, Harrison DA, Nairac BA, Edwards DR, Lock T, Burns RA, Robertson MM: Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. Br J Psychiatry 1995;166:80–86.
27 Schopf J, Baumann P, Lemarchand T, Rey M: Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Pharmacopsychiatry 1989;22:183–187.
28 Stein G, Bernadt M: Double-blind trial of lithium carbonate in tricyclic-resistant depression; in NJ Birch (ed): Lithium: Inorganic Pharmacology and Psychiatric Use. Oxford, IRL Press, 1988, p 35.
29 Stein G, Bernadt M: Lithium augmentation therapy in tricyclic-resistant depression: a controlled trial using lithium in low and normal doses. Br J Psychiatry 1993;162:634–640.

30 Zusky PM, Biederman J, Rosenbaum JF, Manschreck TC, Gross CC, Weilberg JB, Gastfriend DR: Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. J Clin Psychopharmacol 1988;8:120–124.
31 Nierenberg AA, Papakostas GI, Petersen T, Montoya HD, Worthington JJ, Tedlow J, Alpert JE, Fava M: Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol 2003; 23:92–95.
32 Januel D, Poirier MF, D'alche-Biree F, Dib M, Olie JP: Multicenter double-blind randomized parallel-group clinical trial of efficacy of the combination clomipramine (150 mg/day) plus lithium carbonate (750 mg/day) versus clomipramine (150 mg/day) plus placebo in the treatment of unipolar major depression. J Affect Disord 2003;76:191–200.
33 Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfmer S, Bschor T: Lithium augmentation therapy in refractory depression-update 2002. Eur Arch Psychiatry Clin Neurosci 2003;253:132–139.
34 Joffe RT, Singer W: A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. Psychiatry Res 1990; 32:241–251.
35 Aronson R, Offman HJ, Joffe T, Naylor CD: Triiodothyronine augmentation in the treatment of refractory depression: A meta-analysis. Arch Gen Psychiatry 1996;53:842–848.
36 Agid O, Lerer B: Algorithm-based treatment of major depression in an outpatient clinic: clinical correlates of response to a specific serotonin reuptake inhibitor and to triiodothyronine augmentation. Int J Neuropsychopharmacol 2003;6:41–49.
37 Clayton AH, Shen C: T4 augmentation in partial responders with major depression. NCDEU Annu Meet, Boca Raton, Fla., USA, June 2002.
38 Iosifescu DV, Nierenberg AA, Mischoulon D, Perlis RH, Papakostas GI, Ryan JL, Alpert JE, Fava M: An open study of triiodothyronine augmentation of selective serotonin reuptake inhibitors in treatment-resistant major depressive disorder. J Clin Psychiatry 2005;66:1038–1042.
39 Appelhof BC, Brouwer JP, Van Dyck R, Fliers E, Hoogendijk WJ, Huyser J, Schene AH, Tijssen JG, Wiersinga WM: Triiodothyronine addition to paroxetine in the treatment of major depressive disorder. J Clin Endocrinol Metab 2004;89:6271–6276.
40 Altshuler LL, Bauer M, Frye MA, Gitlin MJ, Mintz J, Szuba MP, Leight KL, Whybrow PC: Does thyroid supplementation accelerate tricyclic antidepressant response? A review and meta-analysis of the literature. Am J Psychiatry 2001;158:1617–1622.
41 Bouwer C, Stein DJ: Buspirone is an effective augmenting agent of serotonin selective reuptake inhibitors in severe treatment-refractory depression. South Afr Med J 1997;87(suppl 4):534–537, 540.
42 Dimitriou EC, Dimitriou CE: Buspirone augmentation of antidepressant therapy. J Clin Psychopharmacol 1998;18:465–469.
43 Jacobsen FM: A possible augmentation of antidepressant response by buspirone. J Clin Psychiatry 1991;52:217–220.
44 Landen M, Bjorling GB, Agren H, Fahlen T: A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998;59:664–668.
45 Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH: Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J Clin Psychiatry 2001; 62:448–452.
46 Onder E, Tural U: Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. J Affect Disord 2003;76:223–227.
47 Cohn JB, Rickels K: A pooled, double-blind comparison of the effects of buspirone, diazepam and placebo in women with chronic anxiety. Curr Med Res Opin 1989;11:304–320.
48 Fava M, Alpert JE, Carmin CN, Wisniewski SR, Trivedi MH, Biggs MM, Shores-Wilson K, Morgan D, Schwartz T, Balasubramani GK, Rush AJ: Clinical correlates and symptom patterns of anxious depression among patients with major depressive disorder in STAR*D. Psychol Med 2004;34:1299–1308.
49 Martinez D, Broft A, Laruelle M: Pindolol augmentation of antidepressant treatment: recent contributions from brain imaging studies. Biol Psychiatry 2000;48:844–853.
50 Perez V, Gilaberte I, Faries D, Alvarez E, Artigas F: Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. Lancet 1997;349:1594–1597.
51 Tome MB, Isaac MT, Harte R, Holland C: Paroxetine and pindolol: a randomized trial of serotoninergic autoreceptor blockade in the reduction of antidepressant latency. Int Clin Psychopharmacol 1997;12:81–89.
52 Zanardi R, Artigas F, Franchini L, Sforzini L, Gasperini M, Smeraldi E, Perez J: How long should pindolol be associated with paroxetine to improve the antidepressant response? J Clin Psychopharmacol 1997;17:446–450.
53 Bordet R, Thomas P, Dupuis B: Effect of pindolol on onset of action of paroxetine in the treatment of major depression: intermediate analysis of a double-blind, placebo-controlled trial. Am J Psychiatry 1998;155:1346–1351.
54 Blier P, Bergeron R: The use of pindolol to potentiate antidepressant medication. J Clin Psychiatry 1998;59(suppl 5):16–23.
55 Isaac MT, Isaac MB, Gallo F, Tournoux A: Milnacipran and pindolol: a randomized trial of reduction of antidepressant latency. Hum Psychopharmacol 2003;18:595–601.
56 Berman RM, Anand A, Cappiello A, Miller HL, Hu XS, Oren DA, Charney DS: The use of pindolol with fluoxetine in the treatment of major depression: final results from a double-blind, placebo-controlled trial. Biol Psychiatry 1999;45:1170–1177.
57 Sacristan JA, Gilaberte I, Boto B, Buesching DP, Obenchain RL, Demitrack M, Perez Sola V, Alvarez E, Artigas F: Cost-effectiveness of fluoxetine plus pindolol in patients with major depressive disorder: results from a randomized, double-blind clinical trial. Int Clin Psychopharmacol 2000;15:107–113.
58 Maes M, Libbrecht I, van Hunsel F, Campens D, Meltzer HY: Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. J Clin Psychopharmacol 1999;19:177–182.
59 Moreno F, Gelenberg AJ, Bachar K, Delgado P: Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry 1997;58:437–439.
60 Perez V, Soler J, Puigdemont D, Alvarez E, Artigas F: A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. Arch Gen Psychiatry 1999;56: 375–379.
61 Perry EB, Berman RM, Sanacora G, Anand A, Lynch-Colonese K, Charney DS: Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. J Clin Psychiatry 2004;65:238–243.
62 Fava M, Kendler KS: Major depressive disorder. Neuron 2000;28:335–341.
63 Bouckoms A, Mangini LP: An antidepressant adjuvant for mood disorders? Psychopharmacol Bull 1993;29:207–211.
64 Stryjer R, Strous RD, Shaked G, Bar F, Feldman B, Kotler M, Polak L, Rosenzcwaig S, Weizman A: Amantadine as augmentation therapy in the management of treatment-resistant depression. Int Clin Psychopharmacol 2003;18:93–96.
65 Rogoz Z, Dziedzicka-Wasylewska M, Daniel WA, Wojcikowski J, Dudek D, Wrobel A, Zieba A: Effects of joint administration of imipramine and amantadine in patients with drug-resistant unipolar depression. Pol J Pharmacol 2004;6:735–742.
66 Sporn J, Ghaemi SN, Sambur MR, Rankin MA, Recht J, Sachs GS, Rosenbaum JF, Fava M: Pramipexole augmentation in the treatment of unipolar and bipolar depression: a retrospective chart review. Ann Clin Psychiatry 2000;12:137–140.
67 Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, Gemignani A, Battistini G, Bassi A, Abelli M, Cassano GB: Pramipexole in treatment-resistant depression: a 16-week naturalistic study. Bipolar Disord 2002;4:307–314.
68 Cassano P, Lattanzi L, Soldani F, Navari S, Battistini G, Gemignani A, Cassano GB: Pramipexole in treatment-resistant depression: an extended follow-up. Depress Anxiety 2004;20:131–138.

69 Perugi G, Toni C, Ruffolo G, Frare F, Akiskal H: Adjunctive dopamine agonists in treatment-resistant bipolar II depression: an open case series. Pharmacopsychiatry 2001;34:137–141.
70 Zarate CA, Payne JL, Singh J, Quiroz JA, Luckenbaugh DA, Denicoff KD, Charney DS, Manji HK: Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol Psychiatry 2004;56:54–60.
71 Fawcett J, Kravitz HM, Zajecka JM, Schaff MR: CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. J Clin Psychopharmacol 1991; 11:127–132.
72 Feighner JP, Herbstein J, Damlouji N: Combined MAOI, TCA, and direct stimulant therapy of treatment-resistant depression. J Clin Psychiatry 1985;46:206–209.
73 Linet LS: Treatment of a refractory depression with a combination of fluoxetine and d-amphetamine. Am J Psychiatry 1989;146:803–804.
74 Masand PS, Anand VS, Tanquary JF: Psychostimulant augmentation of second generation antidepressants: a case series. Depress Anxiety 1998;7:89–91.
75 Metz A, Shader RI: Combination of fluoxetine with pemoline in the treatment of major depressive disorder. Int Clin Psychopharmacol 1991;6:93–96.
76 Stoll AL, Pillay SS, Diamond L, Workum SB, Cole JO: Methylphenidate augmentation of serotonin selective reuptake inhibitors: a case series. J Clin Psychiatry 1996;57:72–76.
77 Wharton RN, Perel JM, Dayton PG, Malitz S: A potential clinical use for methylphenidate with tricyclic antidepressants. Am J Psychiatry 1971;127:1619–1625.
78 Lavretsky H, Kim MD, Kumar A, Reynolds CF: Combined treatment with methylphenidate and citalopram for accelerated response in the elderly: an open trial. J Clin Psychiatry 2003;64:1410–1414.
79 Menza MA, Kaufman KR, Castellanos AM: Modafinil augmentation of antidepressant treatment in depression. J Clin Psychiatry 2000;61:378–381.
80 DeBattista C, Solvason HB, Flores BH, et al: Modafinil as an adjunctive agent in the treatment of fatigue and hypersomnia associated with depression. 39th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2000.
81 DeBattista C, Doghramji K, Menza MA, Rosenthal MH, Fieve RR: Adjunct modafinil for the short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. J Clin Psychiatry 2003;64: 1057–1064.
82 Fava M, Thase ME, DeBattista C: A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2000; 66:85–93.
83 Ninan PT, Hassman HA, Glass SJ, McManus FC: Adjunctive modafinil at initiation of treatment with a selective serotonin reuptake inhibitor enhances the degree and onset of therapeutic effects in patients with major depressive disorder and fatigue. J Clin Psychiatry 2004; 65:414–420.
84 Ostroff RB, Nelson JC: Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. J Clin Psychiatry 1999;60:256–259.
85 Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, Buras WR, Bymaster FP, Zhang W, Spencer KA, Feldman PD, Meltzer HY: A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158:131–134.
86 Adson DE, Kushner MG, Eiben KM, Schulz SC: Preliminary experience with adjunctive quetiapine in patients receiving selective serotonin reuptake inhibitors. Depress Anxiety 2004;19:121–126.
87 Worthington JJ 3rd, Kinrys G, Wygant LE, Pollack MH: Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol 2005;20:9–11.
88 Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, Alpert JE, Fava M, Nierenberg AA: Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. J Clin Psychiatry 2005;66:1326–1330.
89 Papakostas GI, Petersen TJ, Nierenberg AA, Murakami JL, Alpert JE, Rosenbaum JF, Fava M: Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. J Clin Psychiatry 2004;65:217–221.
90 Dunner DL, Amsterdam JD, Shelton RC, Romano SJ, Loebel A: Adjunctive ziprasidone in treatment-resistant depression: randomized, double-blind, 8-week pilot study. 44th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2004.
91 Nemeroff CB, Gharabawi GM, Canuso CM, Mahmoud R, Loescher A, Turkoz I, Rapaport MH, Gharabawi GM: Augmentation with risperidone in chronic resistant depression: A double-blind placebo-controlled maintenance trial. 44th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2004.
92 Dube S, Andersen S, Paul S: Meta-analysis of olanzapine-fluoxetine use in treatment-resistant depression (abstract P.1.021). J Eur Coll Neuropsychopharmacol 2002;12(suppl 3):S182.
93 Casey DE: Dyslipidemia and atypical antipsychotic drugs. J Clin Psychiatry. 2004;6(suppl 18):27–35.
94 Newcomer JW: Abnormalities of glucose metabolism associated with atypical antipsychotic drugs. J Clin Psychiatry 2004;65(suppl 18):36–46.
95 Cheng-Shannon J, McGough JJ, Pataki C, McCracken JT: Second-generation antipsychotic medications in children and adolescents. J Child Adolesc Psychopharmacol 2004;14:372–394.
96 Nemets B, Mishory A, Levine J, Belmaker RH: Inositol addition does not improve depression in SSRI treatment failures. J Neural Transm 1999;106:795–798.
97 Levine J, Mishori A, Susnosky M, Martin M, Belmaker RH: Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. Biol Psychiatry 1999;45: 270–273.
98 Stoll AL, Rueter S: Treatment augmentation with opiates in severe and refractory major depression. Am J Psychiatry 1999;156:2017.
99 Bodkin JA, Zornberg GL, Lukas SE, Cole JO: Buprenorphine treatment of refractory depression. J Clin Psychopharmacol 1995;15: 49–57.
100 Stahl SM: Basic psychopharmacology of antidepressants. Part 2: estrogen as an adjunct to antidepressant treatment. J Clin Psychiatry 1998;59(suppl 4):15–24.
101 Shapira B, Oppenheim G, Zohar J, Segal M, Malach D, Belmaker RH: Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. Biol Psychiatry 1985;20:576–579.
102 Zohar J, Shapira B, Oppenheim G, Ayd FJ, Belmaker RH: Addition of estrogen to imipramine in female-resistant depressives. Psychopharmacol Bull 1985;21:705–706.
103 Amsterdam J, Garcia-Espana F, Fawcett J, Quitkin F, Reimherr F, Rosenbaum J, Beasley C: Fluoxetine efficacy in menopausal women with and without estrogen replacement. J Affect Disord 1999;55:11–17.
104 Rasgon NL, Altshuler LL, Fairbanks LA, Dunkin JJ, Davtyan C, Elman S, Rapkin AJ: Estrogen replacement therapy in the treatment of major depressive disorder in perimenopausal women. J Clin Psychiatry 2002; 63(suppl 7):45–48.
105 Schneider LS, Small GW, Hamilton SH, Bystritsky A, Nemeroff CB, Meyers BS: Estrogen replacement and response to fluoxetine in a multicenter geriatric depression trial. Am J Geriatr Psychiatry 1997;5:97–106.
106 Schneider LS, Small GW, Clary CM: Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. Am J Geriatr Psychiatry 2001;9: 393–399.
107 Stahl SM: Augmentation of antidepressants by estrogen. Psychopharmacol Bull 1998b;34: 319–321.
108 Wolkowitz OM, Reus VI, Keebler A, Nelson N, Friedland M, Brizendine L, Roberts E: Double-blind treatment of major depression with dehydroepiandrosterone. Am J Psychiatry 1999;156:646–649.
109 Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JI: Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. Am J Psychiatry 2003;160:105–111.

110 Orengo CA, Fullerton L, Kunik ME: Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. J Geriatr Psychiatry Neurol 2005;18:20–24.
111 Alpert JE, Mischoulon D, Nierenberg AA, et al: Nutrition and depression: focus on folate. Nutrition 2000;16:544–546.
112 Spillmann M, Fava M: S-adenosylmethionine (Ademetionine) in psychiatric disorders: historical perspective and current status. CNS Drugs 1996;6:416–425.
113 Alpert JE, Mischoulon D, Rubenstein GE, Bottonari K, Nierenberg AA, Fava M: Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry 2002;14:33–38.
114 Coppen A, Bailey J: Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo-controlled trial. J Affect Disord 2000;60:121–130.
115 Alpert JE, Papakostas G, Mischoulon D, Worthington JJ 3rd, Petersen T, Mahal Y, Burns A, Bottiglieri T, Nierenberg AA, Fava M: S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 2004;24:661–664.
116 Berlanga C, Ortega-Soto HA, Ontiveros M, Senties H: Efficacy of S-adenosyl-L-methionine in speeding the onset of action of imipramine. Psychiatry Res 1992;44:257–262.
117 Yasmin S, Carpenter LL, Leon Z, Siniscalchi JM, Price LH: Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. J Affect Disord 2001;63:243–247.
118 Schmidt do Prado-Lima PA, Bacaltchuck J: Topiramate in treatment-resistant depression and binge-eating disorder. Bipolar Disord 2002;4:271–273.
119 Otani K, Yasui N, Kaneko S, Ohkubo T, Osanai T, Sugawara K: Carbamazepine augmentation therapy in three patients with trazodone-resistant unipolar depression. Int Clin Psychopharmacol 1996;11:55–57.
120 Varney NR, Garvey MJ, Cook BL, Campbell DA, Roberts RJ: Identification of treatment-resistant depressives who respond favorably to carbamazepine. Ann Clin Psychiatry 1993;5:117–122.
121 De la Fuente JM, Mendlewicz J: Carbamazepine addition in tricyclic antidepressant-resistant unipolar depression. Biol Psychiatry 1992;32:369–374.
122 Hantouche EG, Akiskal HS, Lancrenon S, Chatenet-Duchene L: Mood stabilizer augmentation in apparently 'unipolar' MDD: predictors of response in the naturalistic French national EPIDEP study. J Affect Disord 2005;84:243–249.
123 Rybakowski JK, Suwalska A, Chlopocka-Wozniak M: Potentiation of antidepressants with lithium or carbamazepine in treatment-resistant depression. Neuropsychobiology 1999;40:134–139.
124 Normann C, Hummel B, Scharer LO, Horn M, Grunze H, Walden J: Lamotrigine as adjunct to paroxetine in acute depression: a placebo-controlled, double-blind study. J Clin Psychiatry 2002;63:337–344.
125 Barbosa L, Berk M, Vorster M: A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. J Clin Psychiatry 2003;64:403–407.
126 Wong IC, Lhatoo SD: Adverse reactions to new anticonvulsant drugs. Drug Saf 2000;23:35–56.
127 Cates M, Powers R: Concomitant rash and blood dyscrasias in geriatric psychiatry patients treated with carbamazepine. Ann Pharmacother 1998;32:884–887.
128 Nolen WA, Haffmans PM, Bouvy PF, Duivenvoorden HJ: Hypnotics as concurrent medication in depression. A placebo-controlled, double-blind comparison of flunitrazepam and lormetazepam in patients with major depression, treated with a (tri)cyclic antidepressant. J Affect Disord 1993;28:179–188.
129 Smith WT, Londborg PD, Glaudin V, Painter JR: Is extended clonazepam cotherapy of fluoxetine effective for outpatients with major depression? J Affect Disord 2002;70:251–259.
130 Asnis GM, Chakraburtty A, DuBoff EA, Krystal A, Londborg PD, Rosenberg R, Roth-Schechter B, Scharf MB, Walsh JK: Zolpidem for persistent insomnia in SSRI-treated depressed patients. J Clin Psychiatry 1999;60:668–676.
131 Fava M, Buysse DJ, Rubens R, Wessel T, Caron J, Roth T: Eszopiclone coadministered with fluoxetine for insomnia-associated with major depressive disorder (MDD): Effects on sleep and depression. 45th Annu NCDEU Meet, Boca Raton, Fla., USA, 2005.
132 Terzano MG, Rossi M, Palomba V, Smerieri A, Parrino L: New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. Drug Saf 2003;26:261–282.
133 Roehrs T, Roth T: Hypnotics: an update. Curr Neurol Neurosci Rep 2003;3:181–184.
134 Moller HJ: Effectiveness and safety of benzodiazepines. J Clin Psychopharmacol 1999;19(suppl 2):S2–S11.
135 Fredman SJ, Fava M, Kienke AS, White CN, Nierenberg AA, Rosenbaum JF: Partial response, non-response, and relapse on SSRIs in major depression: a survey of current 'next-step' practices. J Clin Psychiatry 2000;61:403–407.
136 Bodkin JA, Lasser RA, Wines JD Jr, Gardner DM, Baldessarini RJ: Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. J Clin Psychiatry 1997;58:137–145.
137 Ramasubbu R: Treatment of resistant depression by adding noradrenergic agents to lithium augmentation of SSRIs. Ann Pharmacother 2002;36:634–640.
138 Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G, Baker GB: Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. J Clin Psychiatry 2002;63:181–186.
139 DeBattista C, Solvason HB, Poirier J, Kendrick E, Schatzberg AF: A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. J Clin Psychopharmacol 2003;23:27–30.
140 Lam RW, Hossie H, Solomons K, Yatham LN: Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry 2004;65:337–340.
141 Carpenter LL, Jocic Z, Hall JM, Rasmussen SA, Price LH: Mirtazapine augmentation in the treatment of refractory depression. J Clin Psychiatry 1999;60:45–49.
142 Carpenter LL, Yasmin S, Price LH: A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol Psychiatry 2002;51:183–188.
143 Debonnel G, Gobbi G, Turcotte J, DeMontigny C, Blier P: The alpha-2 antagonist mirtazapine combined with the SSRI paroxetine induces a greater antidepressant response: a double-blind controlled study. 39th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2000.
144 Lauritzen L, Clemmesen L, Klysner R, Loldrup D, Lunde M, Schaumburg E, Waarst S, Bech P: Combined treatment with imipramine and mianserin. A controlled pilot study. Pharmacopsychiatry 1992;25:182–186.
145 Medhus A, Heskestad S, Thue JF: Mianserin added to tricyclic antidepressants in depressed patients not responding to a tricyclic antidepressant alone. A randomized, placebo-controlled, double blind study. Nord J Psychiatry 1994;48:355–358.
146 Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ: Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr Scand 2001;103:66–72.
147 Licht RW, Qvitzau S: Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology (Berl) 2002;161:143–151.
148 Nelson JC, Mazure CM, Bowers MB, Jatlow P: A preliminary open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. Arch Gen Psychiatry 1991;48:303–307.
149 Nelson JC, Mazure CM, Jatlow PI, Bowers MB Jr, Price LH: Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol Psychiatry 2004;55:296–300.

150 Weilburg JB, Rosenbaum JF, Meltzer-Brody S, Shushtari J: Tricyclic augmentation of fluoxetine. Ann Clin Psychiatry 1991;3:209–214.
151 Zajecka JM, Jeffries H, Fawcett J: The efficacy of fluoxetine combined with heterocyclic antidepressant in treatment-resistant depression: a retrospective analysis. J Clin Psychiatry 1995;56:338–343.
152 Hawley CJ, Sivakumaran T, Ochocki M, Bevan J: Co-administration of reboxetine and serotonin selective reuptake inhibitors in treatment-resistant patients with major depression. 39th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2000.
153 Dursun SM, Devarajan S: The efficacy and safety of reboxetine plus citalopram in treatment-resistant depression – An open, naturalistic case series. 39th Annu Meet Am Coll Neuropsychopharmacol, San Juan, P.R., USA, 2000.
154 Lucca A, Serretti A, Smeraldi E: Effect of reboxetine augmentation in SSRI resistant patients. Hum Psychopharmacol 2000;15:143–145.
155 Milosavljevic N, Schecter JM, Price LH, Carpenter LL: Antidepressant augmentation with open-label atomoxetine. APA Annu Meet, New York, N.Y., USA, 2004.
156 Taylor FB, Prather MR: The efficacy of nefazodone augmentation for treatment-resistant depression with anxiety symptoms or anxiety disorder. Depress Anxiety 2003;18:83–88.
157 Nierenberg AA, Cole JO, Glass L: Possible trazodone potentiation of fluoxetine: a case series. J Clin Psychiatry 1992;53:83–85.
158 Maes M, Vandoolaeghe E, Desnyder R: Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. J Affect Disord 1996;41:201–210.
159 Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M: Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994;151:1069–1072.
160 Smith DL, Wenegrat BG: A case report of serotonin syndrome associated with combined nefazodone and fluoxetine. J Clin Psychiatry 2000;61:146.
161 Stewart DE: Hepatic adverse reactions associated with nefazodone. Can J Psychiatry 2002;47:375–377.
162 Cassano P, Fava M: Tolerability issues during long-term treatment with antidepressants. Ann Clin Psychiatry 2004;16:15–25.
163 Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, Quitkin FM, Wisniewski S, Lavori PW, Rosenbaum JF, Kupfer DJ; for the STAR*D Investigators Group: Background and rationale for the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study. Psych Clin North Am 2003;26:1–38.
164 Rush AJ, Fava M, Wisniewski SR, Lavori PW, Trivedi MH, Sackeim HA, Thase ME, Nierenberg AA, Quitkin FM, Kashner TM, Kupfer DJ, Rosenbaum JF, Alpert J, Stewart JW, McGrath PJ, Biggs MM, Shores-Wilson K, Lebowitz BD, Ritz L, Niederehe G; STAR*D Investigators Group: Sequenced Treatment Alternatives to Relieve Depression (STAR*D): rationale and design. Control Clin Trials 2004;25:119–142.
165 Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, Schatzberg AF, Koran LM, Keller MB, Russell JM, Hirschfeld RM, La Vange LM, Klein DN, Fawcett J, Harrison W: Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry 2002;59:233–239.
166 McGrath PJ, Stewart JW, Nunes EV, Ocepek-Welikson K, Rabkin JG, Quitkin FM, Klein DF: A double-blind crossover trial of imipramine and phenelizine for outpatients with treatment-refractory depression. Am J Psychiatry 1993;150:118–123.
167 Fava GA, Ruini C: What is the optimal treatment of mood and anxiety disorders? Clin Psychol Sci Pract 2005;12:92–96.
168 Moncrieff J, Cohen D: Rethinking models of psychotropic drug action. Psychother Psychosom 2005;74:145–153.