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An Evidence-Based Approach to Augmentation and Combination Strategies for Treatment-Resistant Depression

ABSTRACT

Design, setting, participants: This paper is a review article that collects and synthesizes up-to-date information about the practice of augmenting and combining medications in regards to treatment resistant major depressive disorder. The authors have written the paper in an evidence-based model in order to show the reader where adequate data exists in regards to these strategies. A thorough MEDLINE search was utilized to collect many papers dedicated to this area of study spanning 1989-2005.

Measurements: Papers were divided based upon drug intervention and scientific merit, where randomized controlled trials were given the most evidence-based weight and case studies the least.

Results: The literature review data is divided into augmentation and combination strategies in descending order of scientific stringency. For augmentation, lithium, antipsychotic, and thyroid addition has the most empirical support. For combination strategies, heterocyclic addition is the best studied.

Conclusion: There is much literature regarding complex medication management of major depression that is generally supportive of this practice. However, much of the literature contains underpowered and uncontrolled studies.

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Key Words: major depression, antidepressant, augmentation, combination, polypharmacy

INTRODUCTION

Treatment-resistant depression (TRD) is, unfortunately, a common variant of major depressive disorder (MDD) and a significant source of referrals from primary care physicians to psychiatrists. Despite initial adequate antidepressant monotherapy of appropriate trial duration and dose optimization many patients will not fully respond or remit into a wellness state, possibly "due to varying degrees of resistance to treatment."[1,94] In fact, the longer a depressive episode lasts, as complicating factors increase, more treatments are failed, then resistance tends to increase and prognosis decreases.[2,3] Similar to other mental illnesses, such as psychotic processes and bipolar disorder, a failure to obtain remission of depressive symptoms may neurophysiologically predispose an individual to an increase in relapses with a worsening of symptoms in future major depressive episodes, making the initial treatment of a TRD patient an important one.

In order to combat TRD, many psychopharmacologists choose to switch antidepressant medications in order to continue a monotherapy approach, while others opt to add or combine agents together. For discussion purposes, an augmentation agent is used when said agent is not FDA approved for the treatment of MDD, but is used in an offlabel manner to gain remission. As the term *augmentation* suggests, an agent is prescribed and utilized simultaneously and in conjunction with an already therapeutically dosed, FDA-approved antidepressant. A combination strategy utilizes two FDA-approved antidepressants added together in order to gain better remission of symptoms. In general, augmentation and combination strategies do not usually involve the simultaneous start of two agents, but rather assumes that the first agent used has not yielded a remission of symptoms and, therefore, a second agent is added in an augmentation or combination fashion secondarily.

There is no definitive proof that either strategy is safer or more effective, but it appears in clinical practice that primary care clinicians are more likely to switch agents, while mental health clinicians are more likely to add or combine agents. Irrespective of the chosen treatment strategy, the goal in treatment of the TRD patient should be the remission of depressive symptoms and, ideally, recovery. Remission is defined as the elimination of all depressive symptoms, as defined by an inventory or scale, such as the Hamilton Depression Rating Scale (HDRS) or the Beck Depression Inventory (BDI), while recovery represents a state of "wellness" sustained for several months. Remission should be considered the goal of optimal treatment of depressive symptoms, as response, or a 50-percent reduction in symptoms similarly assessed, neither equates to patient's subjective sense of well health, nor does it optimally minimize a patient's risk for future depressive episodes.[3]

Given the tendency to combine agents without bona fide FDA approvals, in an effort to obtain symptom remission rather than settling for a patient treatment response, a clinician must examine the data available to support this practice. Unfortunately, these data rarely include double-blind, randomized, placebo-controlled trials that represent the gold standard and most stringent of study designs with the greatest minimization of bias in deriving results of high validity. It is often important for clinicians to participate in continuing medical education conferences and workgroups to remain abreast with the constantly evolving community standard of care regarding these practices, as rigorous studies are not often available in regards to these complex prescribing strategies.

We have written this article in order to describe the existing evidence base in regards to augmentation and combination strategies employed in the treatment of TRD. In addition, this review attempts to apply an evidence-based formulation with which to consider and evaluate TRD prescribing practices.

Despite initial adequate antidepressant monotherapy of appropriate trial duration and dose optimization, many patients will not fully respond or remit into a wellness state, possibly due to varying degrees of resistance to treatment.

METHODS

The authors chose to undertake a full MEDLINE literature review from 1989 to 2005. This timeline

was felt to be most applicable to current prescribing practice, despite the previous 35 years worth of data in regards to monoamine oxidase inhibitors and tricyclic antidepressants, which have largely fallen out of favor due to tolerability issues. This timeline allowed us to focus on newer antidepressants (i.e., SSRI, SNRI, etc.) and more timely augmentation practices as well. Over 200 papers were reviewed. Typical keyword searches included *antidepressant, depressive disorders, augmentation, combination, polypharmacy*, and individual drug names. The results were classified as either augmentation or combination strategies and were further ranked according to the strength of the study design. Double-blind, placebo-controlled, randomized, large-scale studies (RCTs) were considered the most rigorous and given the most weight in this text. Lack of placebo control (open-label trials), randomization and small sample size gave studies less weight. We tried to comment where there are mismatches in that some agents may have bountiful open-label, positive results in the face of a negative, small, underpowered RCT. Finally, meta-analyses and case series were given the least scientific weight as they are considered observational in nature. However, these are often presented first in an effort to summarize of range of treatment options.

The strength of each augmentation and combination class was based on the additive total of the strength of each individual study. These individual scores were based on the following parameters: Double-blind, placebo-controlled, randomized study = 8 strength; double-blind, randomized study without placebo control = 7 strength; single-blind, randomized study without placebo control = 6 strength; randomized study without placebo or blinding=5 strength; above studies without randomization=4 strength; meta-analyses=3 strength; case series=2 strength; case reports=1 strength.

Thase developed a similar approach for his evidence-based review that assigns a letter grade to each strategy based on supporting evidence and "level of TRD resistance" (Stage I–Stage V based on the sequential failure of different antidepressant class trials).[100] These evidence-based grades range from Level A, with RCT and meta-analytic support, as in Lithium (Li) augmentation of TCAs, through Level D, with anecdotal support but without endorsement from experts.

Within each class, we begin by providing an overview of the theorized mechanism of action. The "gestalt" of evidence, in the form of meta-analyses, for each class is discussed next, followed by individual studies of decreasing strength with newer data listed first.

The efficacy of the following strategies were then evaluated relative to treatment with Li augmentation, considered by this review and modern-day perspective to be the gold standard in TRD augmentation. The choice Li as a basis of comparison for other combination and augmentation strategies is borne out of positive data from over 10 randomized, double-blind, and other rigorously controlled trials, as documented in multiple publications, such as DeBattista's evidence-based review of combination and augmentation strategies.[95]

While this review intends to comment on the robust data for such well-studied augmentation agents as Li and thyroid hormone, it will also highlight the evidence pertaining to "en vogue" adjunctive agents being used today; namely psychostimulants, anticonvulsants, steroids, antipsychotics, amino acids and precursors, and other elemental compounds.

It is important, when reading this document, to be mindful that novel and less previously researched adjunctive strategies, such as neuroleptics, might be more represented in recent literature than older and more studied adjunctive strategies, such as thyroid hormone. This pattern is not to suggest greater efficacy, rather the drive to develop new combination and augmentation strategies for TRD that possess greater rapidity of effect, effectiveness, and tolerability.

There is a paucity of data-based reviews like Thase[100] and Debattista[95] that consider polypharmacy with an evidence-based focus. Counter-intuitively, as Dodd suggests in his review of combination treatment, it appears that it is this lack of data "to the contrary" that is driving today's clinician toward a preferred, "comfortable" dose-escalation monotherapy, switching, combination, or augmentation strategy for treating TRD, while neglecting the strategies that are most supported by the research.[96,100] We hope this review provides a preliminary template for clinicians to direct future polypharmacy research to apply to patient care.

RESULTS

AUGMENTATION STRATEGIES

As introduced earlier, an augmentation agent is used when said agent is not FDA approved for the treatment of MDD, but, rather, it is used in an off-label manner to enhance the effect of an initial antidepressant. The augmentation agent is added to a current therapeutically dosed FDA approved antidepressant to bolster effectiveness. Typically, the goal of augmentation strategies is to obtain symptom remission more rapidly when such remission cannot be obtained by optimizing monotherapy.

Lithium. The seminal work of De Montigny, et al., in the 1980s described the rapid antidepressant effects when lithium (Li) was added to tricyclic antidepressants in treatment-resistant patients and laid the path for augmentation

research.[4] While it was hypothesized that "short-term Li administration to 'TCA-resistant' depressive patients would unveil the sensitization of their 5-HT receptors induced by chronic TCA administration," recent evidence suggests that the phenomenon of Li augmentation of antidepressant effect may be secondary to a synergistic effect on second messenger systems related to monoamine production and perhaps transmission. Li as an augmentation agent continues to be the focus of much research and clinical application in TRD, and the literature continues to support its use in this capacity.

Bauer, et al., completed a meta-analysis in 1998 to investigate the efficacy of Li augmentation of conventional antidepressants in refractory depression.[14] Nine placebo-controlled, double-blind studies were included with 110 patients that used Li dosing of 250 to 1200mg/day for s minimum treatment duration of two weeks. The authors found the odds ratio of response during augmentation compared with placebo was 3.31 with 27-percent absolute improvement in response, with minimum dose of 800mg/day. A narrative review of 27 studies and 803 patients, completed by Bauer, noted an average response rate of 45 percent, in the Li group, versus 18 percent placebo, in acute-treatment trials.

The pooled data indicated that 50 percent of patients responded to Li augmentation within 2 to 6 weeks, corresponding with blood levels of 0.5–1.0mmol/liter. Rouillon adds in his 1998 review of 64 studies that it is beneficial to prescribe Li for at least 3 to 6 weeks, due to variability in response time. In 33 studies, 37.0 percent of patients responded within two days, 36.5 percent of patients responded from two days to two weeks, 27.5 percent of patients responded after two weeks. This inconsistency reported by Ontiveros, et al.,[11] as a function of SSRI versus TCA in a 14-week, open clinical of TRD and melancholia, in which the positive augmentation effect of Li occurred in about 60 percent of the patients, but 59 percent in desipramine arm were slow responders, and 72 percent on fluoxetine responded within one week.[10]

Further, regarding this variability in response time and effect duration, a randomized, double-blind study of 141 patients, both with and without previous treatment failure, conducted by Januel[5] compared clomipramine 150mg/day and placebo with Li (750mg/day) augmentation found that remission was three times higher in the Li group (15% versus 4%) by Day 7 and twofold on Day 11 versus placebo.[5] After six weeks, however, no statistical difference was found between the two groups clinically.[6]

On the other hand, in the nine-week, double-blinded Li augmentation study of 34 patients with tricyclic-resistant depressive disorder completed by Stein, et al.,[9] there was no significant difference between the groups during three weeks.[9] In Weeks 3 through 6, 22 percent responded to placebo, 18 percent to 250mg Li augmentation of the TCA, and 44 percent to 750mg based on the HAM-D.[9] Thus, not only did this study speak to the variability of latency of response to Li augmentation, it also supported the idea that response was dose-dependent, even up to the 1500mg/day used in the Nierenberg study.[16]

On the basis of such data, Bauer and Rouillon both recommend the continuation of Li augmentation for a minimum of 12 months in Li augmentation responders despite the suggestion by Nierenberg that long-term efficacy may be a function of acute response to Li augmentation versus duration of treatment augmentation.1[3,15,16] Regardless of duration, the meta-analyses and study data suggest an overall tolerability when Li and antidepressants are prescribed together, even in excess of 750mg/day where tremors are the most commonly reported side effect, central serotonin syndrome has been reported on occasion, and manic episode are rarely observed, likely due to the exacerbation of an underlying bipolar process.[6–10,102]

Unfortunately, only a few placebo-controlled trials in these meta-analyses examined lithium's efficacy with SSRIs or SNRIs, a point that, in addition to its perceived tolerability and side effect profile, might be undermining lithium's use as an augmentation agent today.

Randomized studies evaluating lithium's efficacy with SSRIs in TRD, such as those conducted by Baumann, et al.[7] and Katona, et al.,[8] using citalopram and fluoxetine,

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and lofepramine, respectively, have yielded similar effectiveness data versus placebo compared to older studies; 60 percent of patients responded to citalopram and Li, in the Baumann study, while 14 percent responded to the placebo arm, within five weeks.[7,8] Similarly, response was more frequently seen in the Katona study in patients taking Li (51.7%) versus monotherapy (25.0%) during the six-week trial period.[7,8] No significant differences were seen between groups with regard to adverse events in either study.[7,8]

In 1994, Fava, et al., completed a four-week, randomized, controlled study of 41 patients who had failed eight weeks of fluoxetine and were now assigned to high dose fluoxetine (40–60mg/day), fluoxetine (20mg/day) plus desipramine (25–50mg/day), or fluoxetine (20mg/day) plus Li (300–600mg/day).[10] Previous partial responders in the high dose fluoxetine study arm did significantly better than those treated with adjunct desipramine or Li, while high-dose fluoxetine and fluoxetine plus lithium were equally effective among non-responders.

This data intuitively supports the idea of monotherapy dosage optimization prior to switching, augmenting, or combining treatment modalities in partial responders, though it could not be replicated in a larger study conducted by Fava, et al., in 2002. There were no statistically significant differences in response rates when 101 fluoxetine partial and non-responders were randomized to the same treatment groups and evaluated on the basis of their delta HAM-D-17 scores after a period of eight weeks.[91]

A small, four-week 13-patient open trial conducted by Bertschy et al.[12] demonstrated the efficacy of Li added to an SNRI in previous non-responders.[12] Five patients became responders with (individually determined) Li augmented venlafaxine (300mg/day), three patients recovered; one patient presented a dramatic response (MADRS from 40 to 14 between Day 0 and Day 4), two patients a semi-rapid response (within 2 weeks). Two other patients became responders and six patients were non-responders.

Longer-term efficacy. Nierenberg, et al.,[16] conducted a follow-up study of 66 patients with documented refractoriness to antidepressants who were then treated with Li augmentation 900 to 1500mg/da, for 29±SD 15.3 months.[16] At follow-up, 29 percent had poor outcomes (hospitalization, suicide, death, or suicide attempt), 23 percent had fair outcomes (return of depressive symptoms for at least two weeks), and 48 percent had good outcomes (did not meet criteria for poor or fair). The authors noted that an acute positive response to Li augmentation predicted a good course, while acute partial and non-responders had a less benign course.[16]

In another long-term efficacy study, Bauer, et al.,[6] completed a four-month, randomized, double-blind, placebo-controlled trial of Li augmentation during continuation treatment for 30 patients with a refractory major depressive episode who had responded to acute Li augmentation (up to 1320mg/day based on tolerability) during a six-week study.[6] Relapses (including 1 suicide) occurred in 47 percent who had received placebo in addition to antidepressants. None of the patients who received lithium suffered a relapse.

Comments. Lithium remains a first-line augmentation strategy best supported by double-blind, randomized, placebo-controlled data. It is effective as both a response modulator and accelerant, often effecting a treatment response within two weeks of beginning treatment at doses between 750mg and 1500mg/day corresponding to serum levels >0.5mEq/L. Follow-up studies have shown Li augmentation of antidepressants to be efficacious with good tolerability when evaluated over three years later.

Antipsychotics. With their antipsychotic properties well documented and having contributed to the deinstitutionalization of many psychiatric asylums in the early 20th century, thioridazine and chlorpromazine were also studied for their antidepressant properties between 1960 and 1976 as well. While never considered suitable monotherapy agents for the treatment of pure mood symptoms, such neuroleptics were often utilized in the treatment of affective disorders with psychotic or agitated features.

With results of such studies as Stabl's double-blind study of thioridazine augmentation of moclobemide that showed no clinically significant difference in efficacy between antidepressant monotherapy and augmentation with a typical antipsychotic, the focus of recent research has shifted to augmentation using the newer, 'second generation' antipsychotics.[65] This newer, or atypical, class of antipsychotics that differ from the strictly D2 receptor antagonism of the predecessors theoretically lack the "cognitive blunting" effect of older antipsychotics, such as thioridazine.

Since the 1990s, the atypical antipsychotics have been more frequently utilized given recent approvals for the treatment of acute mania,[24] and their lesser risk of causing extrapyramidal symptoms and tardive dyskinesia compared to first generation antipsychotics. They do carry relatively minimal risks of these side effects and possibly a greater risk for metabolic syndrome or cerebrovascular disease.

It is postulated that these atypical antipsychotics have significantly more potent antagonism of the 5-HT2A serotonin receptor than the D2

receptor antagonism of their predecessors. This 5-HT2A antagonism ultimately facilitates serotonin activity comparable to the mechanism of nefazodone and mirtazapine, two FDA-approved antidepressants. Mesocortical dopmanine pathways may also be optimized and help the usual hypofrontality noted in depressed patients. Thus, the atypical antipsychotics appear to show much promise as potential augmentation agents, due to this serotonin antagonism.

Olanzapine. As Nemeroff and DeBattista note in their reviews, olanzapine-augmented fluoxetine has been found to be efficacious in TRD, possibly due to a "pharmodynamic synergy" that causes a greater increase in norepinephrine and dopamine effect than monotherapy alone.[103] This effect was most notably demonstrated in a eight-week, randomized, double-blind trial by Shelton, et al., in which olanzapine was titrated weekly within a range of 5 to 20mg/day based on response and tolerability in 28 TRD patients.[25] It was found that olanzapine plus fluoxetine produced significantly greater improvement than either monotherapy from baseline, with a particular improvement in patient apathy based on clinical global impression score (CGI-S), as noted in an eight-week open-label trial by Marangell, et al.[25,28]

There is also data that suggest that olanzapine-augmented fluotexine may show benefit as early as one-half week (mean decrease = 7 points) after starting treatment with response maintained at 76 weeks of treatment (mean decrease=22 points).[110] This data was based on MADRS scores from an open-label study conducted by Eli Lilly and Company. While increased appetite, sedation, tremor, and weight gain occurred in a disproportionate number of patients in the treatment groups, there were no significant differences with regard to extrapyramidal symptoms (EPS) or other adverse drug interactions.[25,28] There are much larger studies that helped gather FDA approval for olanzapine-fluoxetine combination in the treatment of acute bipolar depression. These are not discussed in this paper, as it is focused on unipolar TRD.

Given the tendency to combine agents without bona fide FDA approvals, in an effort to obtain symptom remission rather than settling for a patient treatment response, a clinician must examine the data available to support this.

Risperidone. Risperidone has been shown to be an effective add-on strategy of several SSRIs, perhaps, due to its antagonism of the serotonin (5-HT) 2A receptor, 100 times that of D2, that enhances the SSRI antidepressant effect at the serotonin 5-HT1A receptor.[103] This postulated mechanism has yielded remission rates that approach 75 percent in some studies of limited power.[97] In 2002, Hirose, et al., completed a six-week, 36-patient, open-pilot study of fluvoxamine plus risperidone, 0.5 or 1mg/day, as an initial antidepressant therapy.[26] Among the study completers, 76 percent achieved remission (versus 20–30-percent remission rate of six-week SSRI treatment alone), 17 percent achieved response, and two percent were not responsive.

In two separate case series, Viner[30] and Ostroff, et al.,[31] demonstrated CGI score improvement and remission, respectively. Patients received 0.5 to 1mg/day of risperidone in addition to their SSRI treatment for an average duration of 8 to 12 weeks with notable improvements seen in suicidal ideation, agitation, anxiety, sleep quality, sexual functioning, impulse control, and thought organization.[30,31] Furthermore, these benefits were maintained in the Viner study for a mean time of 12 months.[30] Adverse effects of nausea and vomiting were reported, while EPS was not noted in either study.[30,31]

Ziprasidone. In limited studies, ziprasidone has been found to be effective in augmenting selective serotonin reuptake inhibitors in refractory unipolar depression. In a small open-label trial conducted by Papakostas, et al., 20 patients with MDD who had failed an adequate trial of SSRI were treated with the addition of ziprasidone, titrated from 20 to 80mg two times/day based on efficacy and tolerability for an additional six-week period. At the trial's end, 61.5 percent of the subjects were classified as responders with 38.5 percent meeting remittance criteria.[27] Intent-to-treat analysis showed a 50-percent response and 25-

percent remittance. Ziprasidone appeared safe with no severe adverse events and no clinically significant QTc prolongation.

Aripiprazole. Simon, et al., conducted an eight-week, open-label study of 15 patients with either incomplete or no response to antidepressant monotherapy. With the addition of either 2.5 or 10mg of aripiprazole per day to the previous monotherapy, six out of 15 patients achieved remission by the end of Week 1, and nine of the 15 patients achieved remission by the end of Week 2. All eight study completers achieved remission by the end of Week 8.[98] Discontinuation was uniformly due to the development of akathisia in patients.[98]

Interestingly, a retrospective chart review completed by Barbee, et al., showed that of 30 TRD patients who had failed multiple antidepressant trials as well as augmentation with at least one other neuroleptic demonstrated, 14 (46.7%) of the patients improved with aripiprazole augmentation, based on intent-to-treat analysis and GAF score improvement.[99] Unfortunately, 6 of 14 patients who initially improved subsequently relapsed.[99]

Data from the Center for Anxiety and Traumatic Stress Disorders at Massachusetts General Hospital suggests that the addition of 15 to 30mg/day of aripiprazole augmentation in patients with or without anxiety comorbidity allowed for an effective response in as early as 1 to 5 weeks.[111] Worthington and colleagues reported that 59 percent of patients retrospectively showed "much" or "very much" improvement in symptoms at 12 weeks of augmentation treatment based on Clinical Global Impression of Improvement (CGI-I) criteria.[111]

In 2004, Barbee, et al., conducted a retrospective chart review of 76 medication trials in 49 patients to determine the effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in patients with treatment-resistant depression.[29] The overall response rate was 65 percent. The difference between baseline and final global assessment of functioning (GAF) scores was statistically significant only in the olanzapine (57%) and risperidone (33%) groups. With regard to side effects, weight gain was associated with olanzapine; nausea, anxiety, and depression were associated with risperidone; and sedation was associated with quetiapine and ziprasidone.

Comments. With data on quetiapine or clozapine adjunctive therapy either absent or forthcoming, strong data based on double-blind, randomized, placebo-controlled trials to support the use of atypical antipsychotics, as a class, as augmentation agents for TRD is lacking. What data does exist appears to support the use of olanzapine and, to a limited extent, risperidone as augmentation agents while remaining mindful of the metabolic, endocrine, and cardiovascular risks. Pharmacodynamically, ziprasidone and aripiprazole may have the most serotonergic and noradrenergic potential and require further study. Dosing may also be important in that low to moderate doses may be best suited for offlabel use in depression. Higher atypical doses may lose the dopamine-serotonin blockade ratio benefits to favor more dopamine blockade. This 'lowering' of dopamine activity could allow for less of an antidepressant effect at higher doses with an agent.

Thyroid hormone. Prange, et al., conducted the first of several studies in 1969, and similar to the research in lithium (Li) augmentation, this original study was conducted with TCA non-responders. In this pioneering study for thyroid hormone augmentation, the researchers demonstrated an "enhanced and accelerated recovery" when the more biologically active triiodo-thyronine (T3) was added to imipramine monotherapy.[17] Since that time, thyroid augmentation therapy has been the second most extensively studied augmentation strategy next to Li, with some studies, such as Joffe's two-week randomized trial suggesting that these two agents might be equipotent as augmenters (Li 9/17 response and T3 10/17 response vs. 3/16 placebo response in imipramine and desipramine nonresponders).[18]

While the exact mechanisms of action are still debated, it has been postulated that thyroid hormone acts in a number of ways including interacting with norepinephrine, acting directly on the pituitary-thyroid axis, modulating the T3 effect on thyroxine, or enhancing central beta-adrenergic receptor function. Research has demonstrated thyroid hormone to be an efficacious augmentation agent, effective in roughly 55 to 60 percent of patients who previously failed to respond to TCAs, making it a valuable option in a clinician's TRD armamentarium.[101]

In 1996, Aronson, et al., completed a meta-analysis of eight studies and 292 patients addressing the efficacy of hormone therapy in euthyroid, non-psychotic, depressed patients refractory to TCA therapy.[22] Patients treated with triiodothyronine (T3), or physiologic thyroid hormone, augmentation (ranging from 20–50 mcg/day) were twice as likely to respond than to placebo and 2.8 times more likely to respond than to thyroxine (T4) (53% vs. 19% response), based on a randomized study by Joffe.[19,102]

This pooled effect versus placebo corresponded to a 23.3-percent improvement in response rates and a moderately large improvement in depression, as was seen in the open clinical trial by Thase, et al.,[21] of 20 depressed patients who had failed greater than 11 weeks of imipramine and were given adjunctive treatment with 25mcg/day triiodothyronine (T3) for four weeks.[21] The overall

response rate after four weeks was 25 percent, based on HAM-D reduction greater than 50 percent. Furthermore, minimal adverse effects were noted in this and other pooled studies.

Limited by a paucity of data pertaining to thyroid hormone augmentation of SSRIs, Joffe published three cases in 1993 in which triiodothyronine (T3) was used to successfully augment an antidepressant response to fluoxetine.[23] These cases were similar in that the patient experienced improvement in depressive symptoms when given either a tricyclic or MAOI antidepressant as well. However, residual dysthymia and lack of energy persisted similar to fluoxetine used as a monotherapy. These symptoms dissipated within weeks of adding T3 to augment fluoxetine, with no adverse effects noted.[23]

Comments. Based on pooled data and randomized controlled trials, thyroid hormone has been found to be an effective augmenter in TCA non-responders.[22] While it is believed that a favorable response to T3 is most likely to occur within 2 to 3 weeks of treatment when associated with lower pretreatment levels of TSH and higher T4 and FTI, based on the prospective study of Sokolov et al., there is a paucity of rigorous data evaluating optimal treatment duration, adverse effects, and most importantly, efficacy regarding SSRI and SNRI augmentation.[20,101]

Buspirone. Similar to pindolol, buspirone likely exerts its effects as a partial 5HT1A receptor agonist.[32] The addition of buspirone to an SSRI or TCA may result in an enhanced serotinergic effect and improvement of depressive symptoms. This was the case in The Sequenced Treatment Alternatives to Relieve Depression (STAR*D), a randomized NIMH study, that demonstrated the efficacy of buspirone augmented SSRIs in previous SSRI monotherapy nonresponders.[103]

In three separate, open-label studies, buspirone, dosed 20–30mg/day, was found to be an effective augmentation agent in TRD patients who had previously failed an SSRI or TCA trial. Statistically significant differences versus baseline were found in all three studies, with a 68-percent response to buspirone plus fluoxetine and 76.5 percent of these patients sustaining the response over three months in the Joffe study.[44] Sixty-three percent and 68 percent of patients in the Dimitriou[50] and Joffe[51] studies, respectively, showed complete or marked response.[45,46] A chart review by Bouwer, et al.,[52] also reported a statistically significant improvement of 43 percent with buspirone augmentation of SSRI versus baseline.[47] In each of these studies, no differences in side effects were reported.

Despite this positive data, two RCTs by Appelberg[53] and Landen, et al.,[54] failed to demonstrate statistically significant efficacy, versus placebo, as augmentation agents in SSRI non-responders. Buspirone was dosed from 20 to 30mg/day and up to 60mg/day, in these studies, respectively, without any difference from placebo at the study end-points at four weeks and six weeks.[53,54]

Comments. In addition, the STAR*D randomized study and multiple smaller open-label trials have supported the efficacy of buspirone 20 to 30mg/day as an augmentation agent.[44–46,53,54] These positive findings are unfortunately confounded by non-replicated more stringent RCT data. In light of buspirone's favorable side effect profile, which includes occasional dizziness, nervousness, restlessness, headache, and rarely mania, euphoria, and serotonin syndrome (at higher than prescribed doses), further randomized controlled trials may need to be conducted to further assess buspirone's short- and long-term efficacy and tolerability as an augmentation agent.[102] It does have less evidence base per our evaluation, but its open OLT and Star*D outcomes should carry clinical weight.

Steroids. The data for steroid augmentation of antidepressants is founded in interrelationships between gonadal steroids and their modulation of central nervous system serotinergic function, blocking 5-HT reuptake, or possibly as direct activators of transcription at the level of the genome.[32] In

A clinician must weigh the availability of FDA approvals, strength of evidence-based combination/augmentation data, and pharmacodynamic theory before prescribing.

addition to the male and female gonadotropins, steroids, such as prednisone, may function to suppress a dysregulation of the hypothalamic-pituitary-adrenal axis that is believed to occur in depression. This postulated dysregulation results in the hypersecretion of cortisol and may be effectively blunted by a feedback mechanism with the addition of exogenous steroids to a TRD antidepressant treatment regimen.

Estrogen. The most significant data regarding the role of estrogen in TRD was borne out of study data pooled by Schneider, et al., from two 12-week, randomized, double-blind, multicenter trials that evaluated 127 women over 60 years old who were treated with sertraline with and without estrogen-replacement therapy for the treatment major depression.[36] At the end-point, sertraline-treated women taking estrogen replacement therapy (ERT) with a mean dose of 0.625mg/day had significantly greater global improvement (79% vs. 58%) and improved quality of life than those not receiving ERT.[31]

In 2003, Soares, et al., conducted two open label trials of peri- and postmenopausal women with depression and menopause-related symptoms.[34] Patients received either citalopram monotherapy for 12 weeks (n=22) or citalopram plus 100mcg/day-estrogen therapy for eight weeks (n=13). Of the 92.3 percent of the patients who completed the adjunctive treatment trial, 91.6 percent achieved full remission with ERT.

Symptoms that had persisted after an initial four-week treatment with estrogen alone (tension, anxiety, tiredness, and difficulty concentrating) improved significantly. Fifteen subjects from the monotherapy group (68.2%) concluded the treatment with 86.6 percent showing full remission. Anxiety and somatic complaints had significant improvement (p<0.05). There was a trend toward improvement in vasomotor symptoms in those receiving monotherapy with citalopram. In both the Schneider and Soares subject groups there were no significant differences in tolerability and adverse events between the monotherapy and adjunctive estrogen arms.

Testosterone. Nineteen subjects completed an eight-week, randomized, placebo-controlled study in which Pope, Jr. et al., administered either 10g/day transdermal testosterone gel or equivalent placebo in men with refractory depression and low or normal testosterone levels.[33] Each subject continued his existing antidepressant regimen. Efficacy analysis revealed that the testosterone-treated patients had a significantly greater rate of decrease in scores on both the HAM-D and CGI than the placebo-treated patients. There were no significant differences between the placebo and testosterone with regard to changes in body fat or muscle mass. One subject receiving testosterone reported increased nocturia and urinary hesitancy with no other reported differences in side effects between the groups.

Contrary to the positive results of the Pope study, no statistically significant differences between the placebo and testosterone gel or intramuscular testosterone augmentation arms of the Orengo[108] and Seidman[109] studies, respectively, were appreciated. While no significant group differences separated out in either the eugonadal or hypogonadal patient populations of the studies, the results suggest that testosterone may be effective in improving mood symptoms in hypogonadal males with depression.[108,109]

Prednisone. In 2000, Bouwer, et al., completed a nonplacebo-controlled, naturalistic, retrospective study of six patients with TRD with severe fatigue and low cortisol levels.[35] Prednisone 7.5mg/day was added to their antidepressant regimens for four weeks. Significant improvement in depression was seen in 83.3 percent of the patients treated with predisone augmentation, and 66.6 percent demonstrated a greater than 50-percent reduction in HAM-D scores.[30] Prednisone augmentation resulted in weight gain in all six patients, and gastrointestinal side effects occurred in two thirds of the patients.

Comments. The available data suggests a possible role of adjunctive estrogen in the treatment of peri- and post-menopausal depression in woman with and without vasomotor symptoms. With limited data at this point, one should be mindful of the positive efficacy and tolerability data and weigh it against potential long-term risks of uterine and breast cancer and thromboembolism.[95] Similarly, studies suggest a possible role for adjunctive testosterone and prednisone in TRD patients who are testosterone and cortisol deficient, respectively. However, the clinician and patient must weigh the potential risks when evaluating the limited steroid-TRD data.[35,95]

Pindolol. The structural homology of the β-blocker pindolol to serotonin is likely to underlie its capacity to act as an antidepressant-augmenting agent at the level of the serotonin receptor.[32] Similar to buspirone, an FDA-approved drug for anxiety disorders, pindolol likely exerts its effect by acting on the 5-HT1A serotonin receptor. By agonizing these autoreceptors, serotonin effectively builds up within the presynaptic axon and nerve terminal of presumably serotonin-depleted TRD patients until it is ultimately released in increased force once the 5-HT 1B/1D receptors are desensitized by the TCA or SSRI being taken by the patient in addition to the pindolol.[32]

Randomized trials conducted by

Isaac, et al.,[40] and Perez, et al.,[41] demonstrated statistically significant response rate when 80 milnacipran-resistant and 111 fluoxetine-resistant patients, respectively, were given 7.5mg/day of pindolol for six weeks in addition to their previous treatment.[40,41] These studies noted significant CGI score improvement in the pindolol (97.2%) versus placebo arm (60.6%), as earlier as seven days into the study.[40] Sustained response scores were noted in the latter study at Day 19 versus Day 29 in the placebo group.[40] Study endpoint response rates and remittance in the fluoxetine/pindolol group were 15.6-percent and 15.4-percent greater than the placebo arm, respectively.[41] There were no differences in side effects between groups, with nausea, diarrhea, and headache being the most common adverse effects that were mostly transiently noted.[40,41,102]

Perez,[42] Berman,[43] and Moreno, et al.,[44] each conducted additional double-blind, randomized, controlled trials to evaluate the efficacy of 7.5mg of daily pindolol as an SSRI-augmentation. Each study conducted with the TRD-patient population failed to demonstrate any statistically significant differences versus placebo in response, remittance, or change in Hamilton and Montgomery-Asberg by their study endpoints.[42–44]

Comments. Given pindolol's conflicting open-label vs randomized controlled trial efficacy data, Thase considers pindolol to be at best a "C" level augmentation agent.[95] The effectiveness story is similar to the busprione date presented above, and both medications may use the same mechanism of antidepressant action. While short-term side effects appear to be limited to headache, nausea, and diarrhea, little is known about pindolol's longer-term tolerability.[102] Additional efficacy data from powered studies is also warranted to determine whether pindolol dosed higher than 5 to 10mg/day (where brain 5-HT1A receptor occupancy has been found to be low) would be effective and tolerable augmentation agent, or the postulated "depressant" qualities of β-blockers, such as pindolol, warrant its grade.[95]

Omega-3 fatty acids. There is some evidence that omega-3 acids may have an effect on human CSF serotonin metabolites, a property that may be utilized to augment the effects of an antidepressant agent.[63] Thus, in 2001, Nemets, et al., completed a 20-patient, four-week, parallel-group, double-blind study adding either 2g/day of placebo or eicosapentaenoic acid (E-EPA) to ongoing antidepressant therapy.[75] The mean reduction in HAM-D score in patients receiving E-EPA was 12.4 versus 1.6 in patients receiving placebo. No clinically relevant side effects were reported.[75]

The efficacy data reported by Nemets was reproduced in a double-blind trial conducted by Peet, et al., with 70 treatment refractory patients. They were randomized to receive placebo, 1, 2, or 4g/d of ethyl-eicosapentaenoate for 12 weeks in addition to their current medication.[92] While the 2g/day failed to show much efficacy, and the 4g/day showed nonstatistically significant improvement, and the 1g/day group showed statistically significant improvement versus placebo along all three of the objective depression rating scales. This group showed particular improvement in depression, anxiety, sleep, lassitude, libido, and suicidality subscales.[92]

Comments. With limited research, that suggests efficacy as an augmentation agent dosed at 1 to 2g/day, the innocuousness of nutriceuticals, such as omega 3 fatty acids, warrants further investigation.[75,92] Based on speculated pleiomorphic effects on depression and cardiovascular disease, future trials may yet prove "fish oil" to be an effective TRD treatment option.[95]

Modafinil. Despite its need for an intact dopamine reuptake carrier side, this "stimulant" exerts much of its wakefulness effects in a manner completely unlike stimulants or dopamine agonists. Modafinil appears to increase histamine activity in the tuberomammilary nucleus with its projections to the frontal cortex. In addition, it is believed that some of modafinil's augmentation effects may be ascribed to its reduction of alpha-aminobutyric acid release.[55] Much clinical research is being done to further explore modafinil's utility as an augmentation agent, as its lesser dopamine effect may make it a more attractive adjunct than stimulants, for whom they may be warranted, to minimize abuse potential.

In 2004, DeBattista, et al.,[55] completed a six-week, double-blind, placebo study of 136 patients with a partial response to six-week antidepressant therapy.[56] Patients received once-daily modafinil (100–400 mg) or matching placebo in addition to their antidepressant therapy. Modafinil rapidly improved fatigue and daytime wakefulness from Weeks 2 through 6 versus placebo. Overall Hamilton and Beck Scale changes that were significant ($p<0.001$ for BDI and HAM-D) were noted in Battista's prospective open-label study[56] from baseline to Week 2, as well.

Unfortunately, augmentation effects in these studies and the Menza, et al., case series were not significant versus placebo in reducing global Hamilton Scores beyond 2 to 4 weeks.[55–57] It has been postulated from such results that modafinil may not be an 'antidepressant' though it is effective as an accelerant in reducing the depressive target symptoms of low energy, fatigue, and concentration.

In 2005, Fava, et al., demonstrated the efficacy of modafinil augmentation in 311 SSRI partial responders with excessive fatigue and sleepiness randomly assigned to either 200mg/day

modafinil or placebo for eight weeks as part of a multicenter study.[93] While there were no statistically significant differences between placebo and modafinil at the final visit, on two fatigue scales, global improvement of function was improved in the modafinil trial group.[93]

Comments. Certain study results support the idea that modafinil dosed at 100 to 400mg/day is a reasonable antidepressant accelerant or adjunct used to treat target symptoms of depression, such as fatigue, rather than the core mood and anhedonia components of the disease. Recent studies suggest that modafinil, with its benign side effect profile (some reported jitteriness and nausea), might be more appropriately considered an augmentation agent in the treatment antidepressant partial responders with excessive fatigue.

Stimulants. Psychostimulants, such as methylphenidate, are typically utilized in the treatment of attention disorders, most notably in the pediatric and adolescent patient population. The efficacy of stimulants is based in their actions as either inhibitors of dopamine/norepinephrine reuptake, or release of these monoamines into the synaptic cleft.[32] This dopaminergic boost acting on the level of mesolimbic dopaminergic projections is believed to contribute to an enhanced and rapid antidepressant effect and possibly addictive potential.[32]

Open-label studies by Lavretsky and colleagues[45,46] and Gwirtsman[47] showed methylphenidate (MPH) 5 to 20mg/day to be an effective augment of citalopram and TCAs, respectively, with 20- to 60-percent treatment response by the end of Week 2. In both the Gwirtsman study and Fawcett and colleagues' retrospective pemoline or dextroampthetamine augmentation of MAOi study, 70 to 80 pecent of the study populations that were not limited to the elderly as in Lavretsky trials showed "good responses" and improvement in CGI scores by the end of the trials.[47,48]

While side effects were generally mild in these studies, usually limited to sedation, nausea, and anxiety, more significant adverse events were reported. Three patients developed manic episodes, three patients required the cessation of the stimulant, and several patients required dosage adjustments to maintain tolerability.[45–48]

Comments. While there remains to be any positive data from randomized double-blind trials, multiple open-label trials have suggested that methylphenidate at doses between 5 to 20mg/day and other stimulants are efficacious antidepressant augments and treatment accelerators, notably in depressed elderly patients. Unfortunately, well-documented adverse effects, such as anxiety, insomnia, dose-dependent hypertension, abuse potential, and exacerbation of psychosis and mania, could continue to limit their use in the absence of more robust data regarding both long-term efficacy and tolerability.

Yohimbine. Asakura, et al., originally postulated that the 5-HT system is associated with antidepressant-induced down-regulation of beta receptors.[58] Based on this concept, it has been suggested that α2-antagonists, such as yohimbine, may further disinhibit norepinephrine autoreceptors and serotonin heteroreceptors resulting in a net release of both monoamines.[32] This effect would augment the serotonin effect of long-term SSRI or TCA treatment.

Sanacora and colleagues conducted a six-week, 50-patient, randomized, double-blind, controlled trial of α2-antagonist (yohimbine) augmentation of fluoxetine.[59] Yohimbine was titrated up from 16.2 to 32.4mg/day. At the final visit, 65 percent and 42 percent were responders in the treatment and placebo groups, respectively, based on HAM-D criteria. In a small single-blind, randomized study, Cappiello and colleagues[60] found yohimbine at doses of 90 to 120mg/day to be similarly efficacious as an augmentation agent to fluvoxamine.

Yohimbine dose increases were limited in four subjects in the Sanacora study, due to increases in blood pressure, tremulousness, and light-headedness. It was, otherwise, generally well tolerated in both studies.

Comments. Despite positive data, yohimbine's efficacy as an augmentation agent is still questionable given the limited power of the studies. Additional randomized trials with larger subject numbers are necessary to better address dosage, efficacy, and tolerability considerations.

Benzodiazepines. The utility of anti-anxiety sedative agents like the benzodiazepines as augmentation agents in TRD may be most beneficial for atypical depression accompanied by significant anxiety, mood reactivity/lability, and hyperactivity versus vegetative symptoms.[32] Furukawa, et al., completed a meta-analysis in 2001 of nine randomized control studies with 679 adult patients who were followed for up to eight weeks to determine whether antidepressant-benzodiazepine treatment or antidepressant alone was more efficacious in treating TRD.[62] Seven of 9 studies involved benzodiazepine augmentation of a TCA, while one study by Smith and colleagues involved 0.5 to 1mg clonazepam augmentation of fluoxetine.[61,62]

Based on intent-to-treat analysis, the benzodiazepine-augmented antidepressant group was more likely (63% vs. 38%) to show response in four weeks. In addition, the number needed to treat (NNT) for four weeks to make one patient show 50-percent or greater reduction in depressive severity from baseline was 7.[62] There were no reported differences in adverse events.

TABLE 1. Augmentation strategies head to head

Augmentation Agent	DBPCRX (8)	DBRX-P (7)	SBRX-P (6)	RX–P-B (5)	- R (4)	MA (3)	CS (2)	CR (1)	Total Score	Relative Efficacy
Lithium	5	1	0	1	1	3	0	0	65	1
Antipsychotics	0	1	0	0	4	0	5	0	33	0.51
Thyroid Hormone	1	1	0	0	2	1	0	0	28	0.43
Buspirone	0	0	0	1	2	0	1	0	23	0.35
Steroids	1	0	0	0	2	1	0	0	19	0.29
Pindolol	2	0	0	0	0	0	0	0	16	0.25
Omega 3-Fatty Acids	2	0	0	0	0	0	0	0	16	0.25
Modafinil	1	0	0	0	1	0	1	0	14	0.22
Stimulants	0	0	0	0	3	0	1	0	14	0.22
Yohimbine	1	0	1	0	0	0	0	0	14	0.22
BZO	1	0	0	0	0	1	0	0	11	0.17
Pergolide	0	0	0	0	2	0	0	0	8	0.12
Lamotrigine	0	0	0	0	0	0	3	0	6	0.09

Regarding the data supporting benzodiazepines as augmentation agents, Furakawa notes that the meta-analysis cannot discern whether the data is a product of reducing patient insomnia and anxiety versus "some synergistic effect on the core depressive symptoms."[62]

Comments. Until longer-term, randomized-controlled trials with "continued combination" and "withdrawing benzodiazepine" arms versus monotherapy can be done, the clinician should be mindful of the association between benzodiazepines and dependence and accident proneness, especially falls in the elderly.[62] The prescribing doctor should also consider the tendency of benzodiazepines to disinhibit the patient with organic neurological illness.[62] Similar to modafinil targeting a specific set of vegetative depressive symptoms, the sedatives may preferentially target the spectrum of hyperarousal symptoms of depression.

Pergolide. There is a growing body of evidence that dopamine agonists, such as pergolide, as well as others drugs currently being used in the treatment of Parkinson's disease may have utility as adjuncts in the treatment of depression.[37,38] While most of this data is founded in open studies, new data based on RCTs have supported the concept that optimizing dopamine, like other monoamines, is important in the treatment of patient's with TRD.

In an attempt to confirm an earlier study reporting the efficacy of pergolide as an augmenting agent, Mattes, et al., administered pergolide from 0.05mg/day up to 2mg/day or placebo for three weeks in a double-blind manner to eight treatment-refractory patients receiving antidepressants.[37] The results of the study demonstrated

no long-term benefit of the addition of pergolide, as the mean time to relapse in the improvers was found to be less than six weeks. Therefore, the study was discontinued. Side effects related to nausea and headache contributed to significant study dropout within Week 1.[37]

Izumi[38] and Bouckoms[39] completed separate open-label trials of 0.15 to 2mg/day pergolide to augment antidepressants in treatment non-responders. By the end of the trials, Week 4 and Week 7, respectively, 40 to 55 percent of patients were "much or very much improved" based on CGI measures. In 30 percent of patients of both studies, there was no change or worsening of symptoms.[38,39] Subjects of both studies reported nausea and anxiety, with one patient discontinuing pergolide in the first study due to nausea and another secondary to the development of hypomanic symptoms.[38]

Comments. Based on conflicting negative data from a double-blind study and marginally positive data from two open-label studies, further efficacy and tolerability data from randomized trials is needed before pergolide should be reasonably considered for antidepressant augmentation.

Lamotrigine. One proposed neurophysiogical mechanism of depressive processes involves the cytotoxic effects of glutamate on the central nervous system.[32] Thus, it has been speculated that a final pathway for efficacious antidepressant effect is the modulation or dampening of glutamate and its NMDA receptor. To this end, anticonvulsants that inhibit glutamate release, such as lamotrigine, may be effective augmentation agents.[32]

The only randomized, controlled trial of lamotrigine augmentation was completed in a heterogeneous study population of patients with bipolar II disorder (n=8) and TRD (n=15).[105] Conducted by Barbosa and colleagues, the addition of 25 to 100mg/day of lamotrigine to 20mg fluoxetine yielded response in 84 percent of previous treatment nonresponders, based on CGI-S criteria but failed to yield statistically significant results versus placebo in the primary outcome measures of MADRS and Hamilton scores.[105]

Three retrospective chart reviews of lamotrigine augmentation were conducted by Gutierrez[106] Rocha,[107] and Barbee.[72] They demonstrated that the addition of lamotrigine (mean dose 113mg/day) to antidepressant monotherapy, in previous treatment non-responders, yielded significant symptom improvement in 62 to 76 percent of patients. Common side effects were tiredness, headache, dizziness, nausea, and malaise.[106]

Comments. The results of such trials suggest that anticonvulsants, such as lamotrigine, may be efficacious as augmentation agents, especially in patients with shorter duration depression and fewer antidepressant trials. Positive efficacy and tolerability data is necessary from randomized-control trials where better dosing may be offered.

Augmentation Strategies in the "Pipeline." One theory suggests that the amino-acid precursor of serotonin L-tryptophan may be a viable adjunct in the treatment of TRD. An eight-week randomized, double-blind, placebo-controlled study conducted by Levitan and colleagues found 2 to 4g of tryptophan augmented fluoxetine to yield a statistically significant decrease in HAM-D scores versus fluoxetine and placebo with only mild daytime drowsiness reported in the tryptophan arm.[64]

S-adenosyl-methionine (SAMe) is distributed throughout the brain and is related to vitamin B12, folate, and homocysteine by a one-carbon cycle that exchanges methyl groups to synthesize neuronal messengers. SAMe is a natural compound and is available to a wide variety of acceptors (catecholamines, biogenic amines, phospholipids, proteins, and nucleic acids) in the central nervous system, some of which are implicated in the pathogenesis of depression.[65] Consequently, deviations in these compounds could predispose neuropsychiatric disorders. Berlanga and colleagues demonstrated SAMe to be an effective antidepressant "accelerant" in their eight-week, double-blind study. SAMe-augmented imipramine 200mg/day decreased depressive symptoms versus imipramine monotherapy, but this difference was only significant through two weeks.[66] No adverse effects were noted.

On the premise of the "one-carbon cycle," Taylor, et al., examined three randomized trials of 247 patients that compared treatment with folic acid or 5'-methyltetrahydrofolic acid 500mcg/day and an antidepressant medication to antidepressant monotherapy.[68] Two studies found that fewer patients treated with folate experienced a reduction in their HAM-D score of less than 50 percent at 10 weeks. One study of 96 people found no significant benefit of added folic acid than trazodone alone.[69] No side effects were reported in any study.

Zinc is also a naturally occurring compound whose pro-monoamine and amino-acidergic neurotransmission properties may contribute to the persistence of mood disorders in TRD patients.[67] Nowak, et al., published a small 12-week, placebo-controlled, double-blind pilot study of zinc (25mg/day) versus placebo supplementation of standard antidepressant therapy. Treatment significantly reduced HAM-D and BDI scores as early as the second through the 12th week of the study versus placebo treatment (40% relative reduction). There were no reported side effects in either the zinc or placebo groups.

Melatonin is a hormone secreted by the pineal gland that is essential

to the regulation of sleep-wake cycle by supposedly dampening arousal signals from the suprachiasmatic nucleus at nighttime. Given its role in the maintenance of biological rhythms, mood disorders and basal melatonin levels may be interrelated.[71] In addition, there is data to suggest that insomnia may be one of the most significant predictors of future depressive episodes, making research into melatonin augmentation particularly valuable.[112]

Dalton conducted a small open-label trial of 5 to 10mg/day SR-melatonin given with antidepressants in outpatients who had failed two or more trials of antidepressant medication.[71] There was a 36-percent decrease in scores related to insomnia, with 50 percent of patients showing at least 50 percent improvement by the end of the study.[71] Limited side effects were noted.

Researchers have speculated that amantidine's dopamine agonistic properties as well as monoamine oxidase activity and NMDA effects may be beneficial in TRD when it was used in the treatment of numerous medical conditions, such as influenza, Parkinson's disease, and cocaine withdrawal.[70] Stryjer, et al., treated eight patients with TRD with 300mg/day of amantadine in a non-blinded fashion for four weeks. Improvement of depressive and anxiety scores of up to 49 percent was noted by study completion. Side effects included dry mouth and sedation.[70]

Inositol is an intermediate in the possible lithium carbonate-induced second messenger system when treating bipolar patients. It has been hypothesized that since it operates in a similar common pathway as lithium, that inositol, too, might be effective in the regulation of gene expression and synergy with other antidepressants in treating affective dysfunction.[74] However, Levine and colleagues were unable to demonstrate any significant difference in treatment response between the inositol augmentation arm and antidepressant monotherapy arms of their double-blinded trial.[73,74]

Comments. The above agents have little study data to support their efficacy as antidepressant augment agents. While predominantly "niche" or academic agents at this time, there novel mechanisms of action and pharmacodynamic interactions with antidepressants may one day prove them to be useful in the realm of TRD.

Combination therapy is widely popular, as is highlighted by a study in which approximately 25 percent of discharged patients from a psychiatric hospital were on more than one antidepressant.

COMBINATION STRATEGIES

As discussed earlier, a "combination" strategy utilizes two FDA approved antidepressants added together (usually in sequence) to obtain better symptom remission in a depressed patient. Combination therapy is widely popular, as highlighted by a study in which approximately 25 percent of discharged patients from a psychiatric hospital were on more than one antidepressant.[96] Despite its popularity, combination treatment remains an under-researched treatment modality for TRD, Typically, the clinician will carefully select two agents, based on their pharmacodynamic synergism, to optimize treatment of particularly troubling neuro-vegetative or agitated mood symptoms, or to mitigate drug-induced side effects.

Heterocyclic antidepressants. Between 1980 and 1996, several agents referred to as second and third-generation heterocyclic antidepressants were introduced. Similar in pharmacokinetic properties to the older tricyclics (TCAs or first-generation heterocyclics), heterocyclic antidepressants, such as trazodone, mirtazapine, and nefazodone, were developed and utilized as both monotherapy and secondarily as combination agents for TRD.

Within the class of heterocyclic antidepressants, the alpha-2 antagonism of mirtazapine and 5HT2A blockade and serotonin reuptake inhibition of nefazodone and trazodone should effectively boost both serotonin and norepinephrine. This effect, when combined with a TCA or SSRI, could create a synergistic response, in compensating for depleted monoamines in depressed patients, as theory offers.

In an open-label study conducted by Zajecka, 35 percent of subjects who demonstrated a

partial response to fluoxetine responded when an HCA was added to the SSRI. Also, 20 percent of subjects who demonstrated significant improvement with fluoxetine, but had residual depression symptoms experienced further improvement with the addition of a HCA, such as amitripyline, amoxapine, doxepin, desipramine, maprotiline, or trazodone (42.7% HAM-D change).[85]

Mirtazapine. Following an open-label study that showed a 55-percent treatment response rate, Carpenter and colleagues completed a 26-subject, four-week, double-blind, placebo-controlled combination study where mirtazapine (15–30mg/day) was added to SSRI monotherapy for major depression.[87,88] Forty-four percent had an acute clinical response over placebo. There was no difference in side effects between groups, despite a 15-percent discontinuance in the prior study due to weight gain and sedation.[87,88]

Trazodone. Frequently used as a sleep agent, Maes and colleagues completed a five-week, double-blind, placebo-controlled study in which 75 percent of TRD patients treated with trazodone 100mg/day and fluoxetine 20mg/day had a 50-percent reduction in HAM-D score by the trial's end versus 20 percent in the trazodone and placebo arm.[84] All combination strategies were effective with no unique adverse effects noted.[84]

Nefazodone. In 2003, Taylor, et al., completed a non-placebo controlled, non-randomized cohort study of 11 patients who were given increasing dosages of nefazodone from 50 to 300mg/day (mean effective dose of 200mg/day) in addition to their previous antidepressant regimen.[90] After the addition of nefazodone, 63 percent achieved complete remission of depressive symptoms. In each of the 11 cases, nefazodone was efficacious and well tolerated.[90]

Comments. Studies have documented the efficacy of combining the above agents with SSRI's in TRD. More robust data is needed to specify dosing parameters, as well as demonstrate long-term efficacy and tolerability, especially considering the hepatotoxicity of nefazodone. These strategies may be particularly useful in TRD patients who have difficulty with appetite and insomnia, in the case of mirtazapine.

Despite its popularity, combination treatment remains an under-researched treatment modality for TRD.

Tricyclic antidepressants. Studies in animal models have suggested that TCAs when combined with SSRIs in previous treatment nonresponders effect a quicker, β-receptor down-regulation than does monotherapy alone. This norepinephrine-enhancing effect should allow for a more robust antidepressant effect at lower treatment doses of both agents.

In 2002, Fava, et al., completed a double-blind study of 101 patients who were previously treated with eight weeks of fluoxetine treatment.[75] These patients were then randomized to four weeks of either high-dose fluoxetine, fluoxetine and lithium, or a fluoxetine and desipramine combination. As reported above, at the end of the study, there were no significant differences in efficacy among these treatment strategies in patients who failed to respond to the eight-week treatment with fluoxetine. The high-dose fluoxetine group was associated with non-significantly higher response rates in both partial and non-responders. This is one of the only studies showing little effect from noradrenergic TCA combination with SSRI. It also academically outlines the need for aggressive full-dose monotherapy prior to considering combination strategies.

An earlier double-blind study conducted by Fava and colleagues focused on patients who had previously failed trials of 20mg of fluoxetine. They were randomly assigned to the above treatment arms for four weeks. While, the patients with high-dose fluoxetine did significantly better (53%), the response rates in the lithium and desipramine arms were nearly similar, 29 percent and 25 percent, suggesting efficacy in TRD comparable to lithium augmentation.[76]

In a small non-controlled study of 13 patients, Levitt and colleagues demonstrated the synergism of two different antidepressant classes.[77] Of these patients, who had serially failed SSRI and TCA trials, 30 percent had greater than 50 percent reductions in HAM-D scores when they were given together.[77]

An open trial conducted by Nelson and colleagues[78] and a case series reported by Seth, et al.,[79] also demonstrated the efficacy of combination SSRI-TCA treatment versus monotherapy. In the Nelson

TABLE 2. Combination strategies head to head

Combination Agent	DBPCRX (8)	DBRX - P (7)	SBRX - P (6)	RX –P - B (5)	- R (4)	MA (3)	CS (2)	CR (1)	Total Score	Relative Efficacy
Heterocyclic Antidepressant	2	0	0	1	2	0	0	0	29	0.45
Tricyclic Antidepressant	0	2	0	0	2	0	1	0	24	0.37
Bupropion	1	0	0	0	3	0	1	0	22	0.34
SNRIs	0	0	0	0	0	0	2	0	4	0.06

study, this difference in response between combination and TCA monotherapy was profound; it differed by a factor of two favoring combination response. Of note, in each study responders had a higher mean tricyclic level than non-responders.

Comments. The majority of studies suggest an increase in efficacy when TC's are combined with other antidepressants (i.e., SSRIs). In addition to the pharmacodynamic effects, a pharmacokinetic synergism exists, as well when some SSRI inhibit p450 2D6 enzymes that may result in increased plasma TCA levels that raise dose-dependent tolerability and safety concerns. Thus, given the inherent epileptogenic and procardioarrhythmic properties of TCAs, clear monitoring must be recommended.

Bupropion. Bupropion, an antidepressant that is structurally similar to amphetamine, is classified as a norepinephrine and dopamine reuptake inhibitor. Its lack of serotonergic activity and minimal sexual side effects has made it an attractive alternative for those patients who are intolerant of these effects. Unlike stimulants, it is not addictive. It is also an option in combination therapy to modulate the adverse effect properties (weight gain, fatigue, sexual dysfunction) of other antidepressants as it does not effect serotonin and at the same time offers complete facilitation of all three major monamine systems implicated in the pathophysiology of TRD.

The most significant data for bupropion as a combination agent was borne out of a randomized study of a 565-patient subset of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) initiative. In patients with previous citalopram failure, up to 400mg/day of sustained release bupropion (SR) or up to 60mg/day of buspirone was combined with citalopram.[103] By study's end there was a 29.7- to 39-percent remission rate (depending on the scale used) in the bupropion arm.[103] While the difference between the bupropion and buspirone remission rates was not statistically significant, the bupropion arm had a greater reduction in scores from baseline, and a lower dropout rate due to intolerance, than the buspirone group.[103]

Earlier cohort and open-label studies initially demonstrated the efficacy of 150 to 300mg/day of bupropion SR as a combination agent with SSRIs (predominantly citalopram) or SNRIs (venlafaxine), in previous monotherapy partial or nonresponders.[80–83] Between 50 to 80 percent of patients in these studies noted symptomatic improvement and/or treatment response within 1.5 to 10 months of treatment initiation.[80–82] Side effects were generally mild and not different from monotherapy; they were documented in some studies to include: headache, insomnia, diaphoresis.[81–83]

Comments. The STAR*D trial revealed bupropion to be an efficacious combination agent that at doses of 150 to 400mg/day can be reasonably combined with other antidepressants to obtain depressive symptom improvement in treatment nonresponders. It may also be used to minimize unwarranted sexual side effects common to SSRIs. Despite limited side effects,that are mostly gastrointestinal bupropion should be used extremely cautiously in those patients who are susceptible to seizure disorders (i.e./ epilepsy or eating disorder patients).

SNRIs. *Venlafaxine.* Venlafaxine, like duloxetine, is a dual-action serotonin and norepinephrine reuptake inhibitor (SNRI). It has more potent serotonin reuptake inhibition at lower doses and better norepinephrine reuptake inhibition at higher doses, thus contributing to its dose-dependent effects on blood pressure. In 2000, Gomez, et al., submitted three-year data from an ongoing non-controlled case series in which venlafaxine was added to either clomipramine or imipramine in 11 partial responders with major and/or chronic

depression.[86] Nine out of 11 patients experienced a sustained improvement (>50% decrease in HAM-D score), as well as sustained full remission. There were no dropouts and tolerability was felt to be good in this small study.

Duloxetine. A retrospective chart review completed by Papakostas and colleagues showed the combination of bupropion and duloxetine to be effective in patients who had failed trials for either of the two antidepressants.[104] Bupropion and duloxetine combined at mean doses of 330 and 90mg/day, respectively, yielded remittance in 30 percent and response in 60 percent of patients based on CGI criteria at 4 to 16 weeks follow-up. Side effects included nausea, jitteriness, fatigue, sweating, and insomnia.[104]

Comments. Given the inherent duality of the SNRI mechanism of action, and the similar duality of monoamine depletion presumed to occur in depression, the added "jolt" of serotonin provided when combined with an SSRI would likely benefit certain TRD patient. However, dynamically speaking, blocking the serotonin pump twice could be accomplished with a fair dose of SSRI monotherapy. The SNRI may allow for better norepinephrine activity in combination. One must watch for serotonin toxicity when SSRI and SNRI are combined. Unfortunately, study data is limited at this time, as is information regarding long-term efficacy and tolerability. This should be the subject of future randomized controlled trials.

MISCELLANEOUS

Further back in the TRD pipeline are various agents that have benefited from very few clinical studies to date but may ultimately be added to conventional antidepressants to expand the clinician's TRD armamentarium. These agents include the N-Methyl d-aspartate (NMDA) receptor partial agonist antibiotic d-cycloserine; NMDA receptor antagonist ketamine; the glutamate antagonist and brain-derived growth factor promoter, riluzole, approved for the treatment of amyotrophic lateral sclerosis (ALS); AMPA receptor potentiators; repetitive transcranial magnetic stimulation (rTMS); dopamine agonist ropinirole used in Parkinson's disease; pramipexole, a D2 and D3 dopamine agonist; perospirone, a novel atypical antipsychotic with 5-HT1A agonism and 5-HT2A and D2 receptor antagonism; and CRF receptor antagonists.

It appears to be the standard of care that psychiatrists will often add medications together in order to better treat major depressive disorder to full remission.

DISCUSSION

There is a wide range of literature available in regards to treating resistant major depression by way of augmentation or combination strategies. The heterogeneity exists in regards to type of agents used and the scientific merit behind the evidence base that is currently available. It appears to be the standard of care that psychiatrists will often add medications together in order to better treat major depressive disorder to full remission.[113] Interestingly, the large literature base briefly reviewed above often demonstrates that, "the most common augmentation strategies in depression are those with the least controlled evidence."[95] The best studied approaches, i.e., Li augmentation, may be the least used due to adverse effects such as end organ damage risk.

We suggest given the imbalance between usual polypharmacy practices and the amount of available controlled data that some standards of accepted rational polypharmacy be developed. It may be possible to use pharmacodynamic theory (how each drug works based on neurotransmitter and receptor profile) in order to predict which agents may be most likely to be safe and effective when used together. Obviously many of the agents individually have safety and tolerability data given that they have gone through an FDA-approval process, which suggests reasonable efficacy, tolerability, and safety data from multiple clinical research trials. When there is little controlled data and no clear pharmacodynamic rationale available to support combining or augmenting drugs, then at least the available monotherapy efficacy and safety data must be consulted and weighed before prescribing occurs.

A clinician must weigh the availability of FDA approvals, strength of evidence-based combination/augmentation data, and pharmacodynamic theory before prescribing. When there is a lack of evidence in any of these areas, clinicians should be aware of the usual clinical practices in their community or even nationally. This is usually accomplished by participating in local and national continuing medical education (CME) events, attending area grand rounds, or APA branch meetings.

Concurrently though the idea that "the most common augmentation strategies in depression are those with the least controlled evidence" highlights the fact that much of psychopharmacology is also an "art" in which clinicians prescribe based on anecdotal experience of positive patient responses based on particular depressive symptoms. Similar to the idea of nature and nurture, where both are necessary to adequately explain human processes, a consideration of both the clinician's subjective experience and more objective evidence-based data is necessary. Weighing all of these issues and with the goal of gaining depressive remission in our patients, clinicians may then make well-rounded decisions when prescribing for their patients with resistant major depressive disorder.

REFERENCES

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin of N Am* 1996; 19(2):179–200
2. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA* 1997;277:333–40.
3. Thase ME. Defining remission in patients treated with antidepressants. *J Clin Psychiatry* 1999;60(suppl 22):3–6.
4. De Montigny C, Grunberg F, Mayer A. Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *Br J Psychiatry* 1981;138:252–6.
5. Januel D, Poirier MF, D'alche-Biree F, et al. Multicenter, double-blind, randomized parallel group, clinical trial of efficacy of the combination clomipramine (150mg/day) plus lithium carbonate (750mg/day) versus clomipramine (150mg /day) plus placebo in the treatment of unipolar major depression. J Affective Dis 2003; 76:191- 200.
6. Bauer M, Bschor T, Kunz D, et al. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *Am J Psychiatry* 2000;157:1429–35.
7. Baumann P, Nil R, Souche A, et al. 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(4):307–14.
8. Katona CL, Abou-Saleh MT, Harrison DA, et al. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *Br J Psychiatry* 1995;166(1):80-6. Erratum in: *Br J Psychiatry* 1995;166(4):544.
9. 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;162:634–40.
10. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: A double-blind, controlled study. *Am J Psychiatry* 1994;151(9):1372–4.
11. Ontiveros A, Fontaine R, Elie R. Refractory depression: The addition of lithium to fluoxetine or desipramine. *Acta Psychiatrica Scandinavica* 1991;83:188–92.
12. Bertschy G, Ragama-Pardos E, Ait-Ameur A, et al. Lithium augmentation in venlafaxine non-responders: An open study. *Eur Psychiatry* 2003;18:314–17.
13. Bauer M, Forsthoff A, Baethge C, et al. Lithium augmentation therapy in refractory depression: Clinical evidence and neurobiological mechanisms. *Can J Psychiatry* 2003;48(7):440–6.
14. Bauer M. Dopmer S. Lithium augmentation in treatment-resistant depression: Meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 1999;19(5):427–34.
15. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. *J Clin Psychiatry* 1998;59(suppl 5):32–9.
16. Nierenberg AA, Price LH, Charney DS, Heninger GR. After lithium augmentation: A retrospective follow-up of patients with antidepressant refractory depression. *J Affect Dis* 1990;18:167–75.
17. Prange AJ, Loosen PT. Hormone therapy in depressive diseases. *Adv Biochem Psychopharmacol* 1982;32:289–96
18. Joffe R, Singer W, Levitt AJ, MacDonald C. A placebo-controlled comparison of lithium and triidothryonine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry* 1993;50:387–93.
19. Joffe R, Singer W. A comparison of triiodothyronine and thyroxine in the potentiation of tricyclic antidepressants. *Psychiatry Res* 1990;32:241–51.
20. Sokolov ST, Levitt AJ, Joffe RT. Thyroid hormone levels before unsuccessful antidepressant therapy are associated with later response to T3 augmentation. *Psychiatry Res* 1997;69(2-3):203–6.
21. Thase ME, Kupfer DJ, Jarret DB. Treatment of imipramine-resistant recurrent depression: I. An open clinical trial of adjunctive L triiodothyronine. *J Clin Psychiatry* 1989;50(10):385–8.
22. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. *Arch Gen Psychiatry* 1996;53:842–8.
23. Joffe R. Triiodothyronine potentiation of fluoxetine in depressed patients. *Can J Psychiatry* 1992;37:48–50.
24. Keck PE Jr. Bipolar depression: A new role for atypical antipsychotics? *Bipolar Dis* 2005;7 Suppl 4:34–40.
25. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001;158(1):131–4.
26. Hirose S, Ashby CR Jr. An open pilot study combining risperidone and a selective serotonin reuptake inhibitor as initial antidepressant therapy. *J Clin Psychiatry* 2002;63(8):733–6.
27. Papakostas G, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J Clin Psychiatry* 2004;65(2):217–21.
28. Marangell LB, Johnson CR, Kertz B, et al. Olanzapine in the treatment of apathy in previously depressed participants maintained with selective serotonin reuptake inhibitors: An open-label, flexible dose study. *J Clin Psychiatry* 2002;63(5):391–5.
29. Barbee J, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J Clin Psychiatry* 2004;65(7):975–81.
30. Viner M, Chen Y, Bakshi I, Kamper P. Low-dose risperidone augmentation of antidepressants in nonpsychotic depressive disorders with suicidal ideation. *J Clin Psychopharmacol* 2003;23(1):104–6.
31. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *J Clin Psychiatry* 1999;60(4):256–9.
32. Stahl S. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications, Second Edition.* Cambridge:

Interestingly, the large literature base briefly reviewed [in this article] often demonstrates that, "the most common augmentation strategies in depression are those with the least controlled evidence."

Cambridge University Press, 2000.
33. Pope HG Jr., Cohane GH, Kanayama G, et al. Testosterone gel supplementation for men with refractory depression. A randomized, placebo-controlled trial. *Am J Psychiatry* 2003;160(1):105–11.
34. Soares CN, Poitras JR, Prouty J, et al. Efficacy of citalopram as a monotherapy or as an adjunctive treatment to estrogen therapy for perimenopausal and postmenopausal women with depression and vasomotor symptoms. *J Clin Psychiatry* 2003;64(4):473–9.
35. Bouwer C, Claassen J, Dinan TG, Nemeroff CB. Prednisone augmentation in treatment-resistant depression with fatigue and hypocortisolaemia: A case series. Depression and anxiety. 2000;12(1):44–50.
36. Schneider LS. Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. *Am J Geriatr Psychiatry* 2001;9(4):393–9.
37. Mattes J. Pergolide to augment the effectiveness of antidepressants: Clinical experience and a small double-blind study. Ann Clin Psychiatry 1997;9(2):87–8.
38. Izumi T, Inoue T, Kitagawa N, et al. Open pergolide treatment of tricyclic and heterocyclic antidepressant-resistant depression. *J Affect Dis* 2000;61:127–32.
39. Bouckoms A, Mangini L. Pergolide: An antidepressant for mood disorders? Psychopharmacol Bull 1993;29(2):207–11.
40. Isaac MT, Isaac MB, Gallo F, Tournoux A. Milnacipran and pindolol: A randomized trial of reduction of antidepressant latency. *Human Psychopharmacol Clin Exp* 2003;18:595–601.
41. Perez V, Puiigdemont D, Gilaberte I, et al. Grup de Recerca en Trastorns Afectius. Augmentation of fluoxetine's antidepressant action by pindolol: Analysis of clinical, pharmacokinetic, and methodologic factors. *J Clin Psychopharmacol* 2001;21(1):36–45.
42. Perez V, Soler J, Puigdemont D, et al. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Arch Gen Psychiatry* 1999;56:375–79.
43. Berman RM, Darnell AM, Miller HL, et al. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: A double-blind, placebo-controlled trial. *Am J Psychiatry* 1997;154:37–43.
44. Moreno FA, Gelenberg AJ, Bachar K, Delgado PL. Pindolol augmentation of treatment-resistant depressed patients. J Clin Psychiatry 1997;58(10):437–9.
45. Lavretsky H, Kim MD, Kumar RA. Combined treatment with methylphenidate and citalopram for accelerated response in the elderly: An open trial. *J Clin Psychiatry* 2003;64(12):1410–14.
46. Lavretksy H, Kumar A. Methylphenidate augmentation of citalopram in elderly depressed patients. *Am J Geriatr Psychiatry* 2001;9:298–303.
47. Gwirtsman H, Szuba MP, Toren L, Feist M. The antidepressant response to tricyclics in major depressives is accelerated with adjunctive use of methylphenidate. *Psychopharmacol Bull* 1994;30(2):157–64.
48. Fawcett J, Kravitz HM, Zajecka JM, Schaff MR. CNS stimulant potentiation of monoamine oxidase inhibitors in treatment refractory depression. J Clin Psychopharmacol 1991;11(2):127–32.
49. Levitt AJ, Joffe RT, Kamil R, McIntyre R. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J Clin Psychiatry* 1999;60(9):613–6.
50. Dimitriou EC, Dimitriou CE. Buspirone Augmentation of Antidepressant Therapy. *J Clin Psychopharmacol* 1998;18(6):465–9.
51. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. *J Clin Psychiatry* 1993;54(7):269–71.
52. Bouwer, C. Stein, DJ. Buspirone is an effective augmenting agent of serotonin selective reuptake inhibitors in severe treatment-refractory depression. *S Afr Med J* 1997;87(4):534–40.
53. Appelberg BG, Syvalahti EK, Koskinen TE. et al. 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(6):448–52.
54. Landen M, Bjorling G, 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(12):664–8.
55. DeBattista C, Doghramji K, Menza MA, et al. Modafinil in Depression Study Group. 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(9):1057–64.
56. DeBattista C, Lembke A, Solvason HB, et al. A prospective trial of modafinil as an adjunctive treatment of major depression. *J Clin Psychopharmacol* 2004;24(1):87–90.
57. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 2000;61(5):378–81.
58. Asakura W, Matsumoto K, Ohta H, Watanabe H. REM sleep deprivation potentiates the effects of imipramine and desipramine but not that of clomipramine in the forced swimming test. *Japan J Pharmacol* 1993;63(4):455–60.
59. Sanacora G, Berman RM, Cappiello A, et al. Addition of the α2-antagonist yohimbine to fluoxetine: Effects on rate of antidepressant response. *Neuropsychopharmacology* 2004;29:1166–71.
60. Cappiello A, McDougle CJ, Malison RT, et al. Yohimbine augmentation of fluvoxamine in refractory depression: A single-blind study. *Biologic Psychiatry* 1995;38:765–67.
61. Smith WT, Londborg PD, Glaudin V, Painter JR. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: A double-blind study. *Am J Psychiatry* 1998;155(10):1339–45.
62. Furukawa TA, Streiner DL, Trevor Y. Is antidepressant-benzodiazepine combination therepy clinically more useful? A meta-analytic study. *J Affect Disord* 2001;65(2):173–7.
63. Nemets B, Stahl Z, Belmaker RH. Addition of Omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry* 2002;159(3):477–9.
64. Levitan RD, Shen JH, Jindal R, et al.Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: Antidepressant and hypnotic effects. *J Psychiatry Neurosci* 2000;25(4):337–46.
65. Delle Chiaie R, Pancheri P, Scapicchio P. Efficacy and tolerability of oral and intramuscular S-adenosyl-L-methionine 1,4-butanedisulfonate (SAMe) in the treatment of major depression: Comparison with imipramine in 2 multicenter studies. *Am J Clin Nutr* 2002;76(5):1172S–6s.
66. Berlanga C, Ortega-Soto H, Ontiveros M, Senties H. Efficacy of S adenosyl-L-methionine in speeding the onset of action of imipramine. Psychiatry Res 1992;44:257–62.
67. Nowak G, Siwek M, Dudek D, et al. Effect of zinc supplementation on antidepressant therapy in unipolar depression: A preliminary placebo-controlled study. Pol J Pharmacol 2003;55(6):1143–7.
68. Taylor MJ, Carney S, Geddes J, Goodwin G. Folate for depressive disorders. *Cochrane Database Syst Rev* 2003;4.
69. Passeri M, Cucinotta D, Abate G, et al. Oral 5'-methyltetrahydrofolic acid in senile organic mental disorders with depression: results of a double-blind multicenter study. *Aging Clin Exp Res* 1993;5(1):63–71.
70. Stryjer R, Strous RD, Shaked G, et al. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol* 2003;18(2):93–6.
71. Dalton J, Rotondi D, Levitan RD, et al. Use of slow-release melatonin in treatment-resistant depression. J Psychiatry Neurosci 2000;25(1):48–52.
72. Barbee J, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. *J Clin Psychiatry* 2002;63(8):737–41.
73. Dursun SM, Devarajan S. Reboxetine plus citalopram for refractory depression not responding to venlafaxine: Possible mechanisms. *Psychopharmacology* 2001;153:497–8.
74. Levine J, Mishori A, Susnosky M, et al. Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. *Biologic Psychiatry* 1999;45:270–3.
75. Fava M, Alpert J, Nierenberg A, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and non-responders to fluoxetine. *J Clin Psychopharmacol* 2002;22(4):379–87.
76. Fava M, Rosenbaum JF, McGrath PJ, et al. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: A double-blind, controlled study. *Am J Psychiatry* 1994;151(9):1372–4.
77. Levitt AJ, Joffe RT, Kamil R, McIntyre R. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J Clin Psychiatry* 1999;60(9):613–6.
78. Nelson JC, Mazure CM, Bowers MB Jr., Jatlow PI. A preliminary, open study of the combination of fluoxetine and desipramine for rapid treatment of major depression. *Arch Gen Psychiatry* 1991;48:303–7.
79. Seth R, Jennings AL, Bindman J, et al. Combination treatment with noradrenalin and serotonin reuptake inhibitors in resistant depression. *Br J Psychiatry* 1992;161:562–5.
80. Lam R, Hossie H, Solomons K, Yatham LN. Citalopram and bupropion-SR: Combining versus switching in patients with treatment-resistant depression. *J Clin Psychiatry* 2004;65(3):337–40.
81. DeBattista C, Solvason HB, Poirier J, et al.

A prospective trial of bupropion SR augmentation of partial and non responders to serotonergic antidepressants. *J Clin Psychopharmacol* 2003;23(1):27–30.
82. Spier S. Use of bupropion with SRIs and venlafaxine. *Depression Anxiety* 1998;7:73–5.
83. Bodkin JA, Lasser RA, Wines JD Jr., et al. Combining serotonin reuptake inhibitors and bupropion in partial responders to antidepressant monotherapy. *J Clin Psychiatry* 1997;58(4):137–45.
84. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *J Affective Disorder* 1996;41:201–10.
85. Zajecka J, Jeffries H, Fawcett J. The efficacy of fluoxetine combined with a heterocyclic antidepressant in treatment-resistant depression: A retrospective analysis. *J Clin Psychiatry* 1995;56(8):338–43.
86. Gómez JMG, Perramón CT. Combined treatment with venlafaxine and tricyclic antidepressants in depressed patients who had partial response to clomipramine or imipramine: Initial findings. *J Clin Psychiatry* 2000;61(4):285-289.
87. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Soc Biologic Psychiatry* 2002;51:183–8.
88. Carpenter LL, Jocic Z, Hall JM, et al. Mirtazapine augmentation in the treatment of refractory depression. *J Clin Psychiatry* 1999;60(1):45–9.
89. Stabl M, Kasas A, Blajev B, et al. A double-blind comparison of moclobemide and thioridazine versus moclobemide and placebo in the treatment of refractory, severe depression. *J Clin Psychopharmacol* 1995;15(4):41S–45S.
90. Taylor FB, Prather MR. The efficacy of nefazodone augmentation for treatment resistant depression with anxiety symptoms or anxiety disorder. *Depression Anxiety* 2003;18(2):83–8.
91. Fava M, Alpert J. 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(4):379–87.
92. Peet M, Horrobin D. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry* 2002;59(10):913–19.
93. 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* 2005;66(1):85–93.
94. O'Reardon J, Brunswick D, Amsterdam J. Treatment-resistant depression in the age of serotononin: Evolving strategies. *Curr Opin Psychiatry* 2000;13:93–8.
95. DeBattista C. Augmentation and combination strategies for depression. *J Psychopharmacol* 2006;20(3):11–8.
96. Dodd S, Horgan D, Malhi G, Berk M. To combine or not to combine? A literature review of antidepressant combination therapy. *J Affect Disorder* 2005;85:1–11.
97. Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. *J Clin Psychiatry* 2005;66(Suppl 8:13–21.
98. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. *J Clin Psychiatry* 2005;66(10):1216–20.
99. Barbee JG, Conrad EJ, Jamhour NJ. Aripiprazole augmentation in treatment-resistant depression. *Ann Clin Psychiatry* 2004;16(4):189–94.
100. Thase ME. Therapeutic alternative to difficult-to-treat depression: A narrative review of the state of the evidence. *CNS Spectr* 2004;9:808–21.
101. Joffe RT. The use of thyroid supplements to augment antidepressant medication. *J Clin Psychiatry* 1998;59(Suppl 5):26–9.
102. Scweitzer I, Tuckwell V. Risk of adverse events with the use of augmentation therapy for the treatment of resistant depression. *Drug Exp* 1998;19(6):455–64.
103. Trivedi MH. Treatment-resistant depression: New therapies on the horizon. *Ann Clin Psychiatry* 2003;15(1):59–70.
103. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *NEJM* 2006;354(12):1243–52.
104. Papakostas GI, Worthington JJ, Iosifescu D, et al. The combination of duloxetine and bupropion for treatment-resistant major depressive disorder. *Depression Anxiety* 2006;23(3):178–81.
105. 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(4):403–7.
106. Gutierrez RL, McKercher RM, Galea J. Jamison KL. Lamotrigine augmentation strategy for patients with treatment-resistant depression. *CNS Spectr* 2005;10(10):800–5.
107. Rocha FL, Hara C. Lamotrigine augmentation in unipolar depression. *Int Clin Psychopharmacol* 2003;18(2):97–9.
108. Seidman SN, Mivazaki M, Roose SP. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: Randomized, placebo-controlled clinical trial. *J Clin Psychopharmacol* 2005;25(6):584–8.
109. 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(1):20–4.
110. Corya SA, Anderson SW, Detke HC. Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: A 76-week open-label study. Lilly Research Laboratories, Eli Lilly and Company, 2002.
111. Worthington JJ, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmenter of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Boston, MA: Center for Anxiety and Traumatic Stress Disorders, Massachusetts General Hospital
112. Breslau N, Roth, T. Rosenthal, L. Andreski, P. Sleep Disturbance and Psychiatric Disorders: A longitudinal epidemiological study of young adults. *Biologic Psychiatry* 1996;39:411–18.
113. Rashid A, Schwartz TL. *Augmentation/combination pharmacotherapy trends in major depressive disorder.* In Press P&T, 2006.