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Review Article

Augmentation in treatment-resistant depression

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Abstract

Almost one-third of patients with major depressive disorder do not respond to a series of treatments and are considered treatment-resistant. Many pharmacological strategies have been evaluated for the management of treatment-resistant depression, but none have been formally approved for the disorder. There is evidence to support the efficacy of both lithium and thyroid hormone as augmentation agents, although this is mostly based on studies with tricyclic antidepressants. The current review assesses strategies for augmentation with nonantidepressant drugs and evidence based on published studies. Preclinical studies that provide evidence for proposed mechanisms of action have also been included. Strategies with evidence including at least one randomized, controlled trial include augmentation of the primary antidepressant with olanzapine, buspirone, lamotrigine, pindolol or methylphenidate. However, it appears that the choice of augmentation strategy is based largely on clinical preference and therapeutic need in individual patients, rather than on evidence of efficacy from randomized, controlled studies.

Introduction

Major depressive disorder is a significant public health problem. The yearly incidence of the disorder is estimated to be almost 6% for men and 10% for women. Depression is generally a chronic and frequently recurring condition. Thus, the cycle of relapse and remission presents a challenge for its effective management. There are many treatment options available, broadly based on the use of three major classes of drugs: tricyclic antidepressants, monoamine oxidase (MAO) inhibitors and selective serotonin reuptake inhibitors (SSRIs). There are also new-generation antidepressants with novel mechanisms of action. However, between 30% and 50% of patients do not respond to the first antidepressant that is prescribed, and as many as 30% do not respond to a series of treatments, although studies investigating predictors of resistance are lacking (1-3).

A number of definitions of treatment resistance and a variety of options for its management have been proposed. These include combining antidepressants of different classes, switching from one antidepressant to another and augmenting an antidepressant with a drug of another class. Treatment augmentation is the addition of an antidepressant or nonantidepressant drug to enhance the effect of a currently prescribed antidepressant. Although several pharmacological strategies have been proposed in the augmentation of antidepressant therapy, no specific therapy has been approved for the management of treatment-resistant depression and very few strategies have met criteria to support level A or B evidence for their use in this disorder. A large multicenter study funded by the National Institute of Mental Health (NIMH), Sequenced Treatment Alternatives to Relieve Depression (STAR*D), is currently ongoing and is expected to provide supportive evidence for treatment alternatives. In the meantime, sufficient evidence based on randomized, controlled trials is only available for lithium and thyroid hormone (3-6).

The current review focuses on augmentation strategies with nonantidepressant drugs. Augmentation strategies can be selected to complement the presumed mechanism of action of the primary antidepressant and proposed mechanisms of action are therefore discussed. Evidence supporting the various strategies is also reviewed.

Lithium and triiodothyronine

The evidence supporting the use of lithium as an augmentation strategy in treatment-resistant depression is strong. A systematic review of lithium augmentation studies was conducted based on published data from 1966 to February 2003, and identified 27 prospective clinical stud-

ies published since 1981. Of these, 10 were double-blind, placebo-controlled trials and 4 were randomized, comparative trials. Five of 9 acute-phase trials demonstrated significant efficacy for lithium augmentation compared with placebo, with an overall response rate of 45% compared with 18% for placebo ($p < 0.001$). Evaluation of the open and controlled studies indicated that approximately 50% of patients responded to lithium augmentation within 2-6 weeks (7).

Although the efficacy of lithium as an augmentation strategy is well documented, the evidence for its use is largely based on trials with tricyclic antidepressants (TCAs) and there are relatively few studies with SSRIs. Indeed, two more recent studies have not shown an advantage for lithium-treated patients either *versus* placebo (8) or compared to desipramine or high-dose fluoxetine in partial responders and nonresponders to fluoxetine (9). The use of lithium as an augmentation agent has declined in popularity more recently, probably due to the availability of newer, better tolerated alternatives. Lithium treatment may be associated with significant adverse effects; it also has a low therapeutic index and serum lithium levels must be monitored. However, despite these limitations, the body of evidence supporting the use of lithium as an augmentation strategy in treatment-resistant depression is superior to that of any more novel strategy (3, 5).

Animal studies have provided robust evidence that lithium augmentation increases 5-HT neurotransmission, although molecular studies have identified novel cellular targets for the action of lithium, and indicate that enhanced 5-HT neurotransmission may not be the only mechanism by which lithium potentiates the effects of antidepressants. There is also evidence that lithium may stimulate the hypothalamo-pituitary-adrenocortical (HPA) system (7, 10).

Triiodothyronine (T_3), a thyroid hormone, has been used as an augmentation agent in treatment-resistant depression for more than 20 years. A meta-analysis of 8 controlled trials, 4 of which were randomized, double-blind studies, showed that patients receiving TCA augmentation with triiodothyronine were twice as likely to respond as those in control groups (5, 11, 12). As is the case with lithium, most of the evidence for the efficacy of T_3 is based on studies with TCAs and there is little evidence for its use with newer classes of antidepressants. However, 3 open-label studies in small numbers of patients have indicated that T_3 augmentation of SSRI-resistant depression may also be an effective strategy (13-15). Lithium and T_3 augmentation were compared following two failed treatments for depression as a third-step treatment in the STAR*D study. In 142 outpatients with nonpsychotic major depressive disorder, remission rates were 16% with lithium augmentation and 25% with T_3 augmentation after a mean of 9.6 weeks of treatment. Although the difference between the treatments was not statistically significant, lithium was more frequently associated with side effects and more patients in the lithium group discontinued therapy due to side effects. These differences suggested a modest advantage for T_3 compared with lithium augmentation in patients who had failed two previous medications. It is interesting to note that despite the increased incidence of side effects in the lithium group, mean daily doses at discontinuation were low (860 mg; median lithium blood level, 0.6 mEq/l), which may have accounted for the modest remission rates (16).

In vivo microdialysis studies investigated the effect of combined treatment with an SSRI (fluoxetine) and T_3 on 5-HT_{1A} and 5-HT_{1B} autoreceptor activity. Fluoxetine alone increased serotonergic transmission by inducing desensitization of autoreceptors in the frontal cortex. The combination of fluoxetine and T_3 induced desensitization of 5-HT_{1B} autoreceptors in the hypothalamus, indicating that T_3 augmentation may exert its therapeutic effect via this route (17).

For a summary of recent clinical studies on lithium and T_3 augmentation see Table I.

Antipsychotics: olanzapine, aripiprazole, risperidone and ziprasidone

Novel antipsychotic agents are often considered as augmenting agents in treatment-resistant depression as the risk of patients developing extrapyramidal symptoms or tardive dyskinesia is much lower than with conventional antipsychotic agents. In an initial randomized, double-blind study in 28 patients with recurrent, treatment-resistant depression without psychotic features, augmentation of fluoxetine treatment with olanzapine demonstrated superior efficacy to either agent alone (18). However, the results of this preliminary study were not replicated in a larger confirmatory study conducted in 500 patients with treatment-resistant major depressive disorder (19). In this latter study, the olanzapine/fluoxetine combination did not differ significantly from monotherapy with olanzapine, fluoxetine or nortriptyline at the 8-week study endpoint, although it demonstrated a more rapid response, which was maintained until the end of treatment. There were a number of methodological issues highlighted in this study which may have influenced the outcome.

In a subsequent randomized, double-blind study, 605 patients who had failed to respond to an 8-week fluoxetine lead-in phase were randomized to treatment with an olanzapine/fluoxetine combination or monotherapy with olanzapine or fluoxetine. Patients treated with the combination demonstrated significantly greater improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) after 8 weeks. Response rates were 40% for the combination, 30% for fluoxetine and 26% for olanzapine. However, adverse events in the combination treatment group included weight gain, increased appetite, dry mouth, fatigue and headache. Mean increases in cholesterol levels were also approximately 5-15-fold higher in the combination group than in either of the monotherapy groups (20). Indeed, all atypical antipsychotics, particularly olanzapine, are associated with a long-term risk of hyperglycemia, dyslipidemia and the “metabolic syndrome” (5). A double-blind, placebo-controlled trial of

Table I: Recent clinical studies on lithium and triiodothyronine as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Lithium	Randomized Double-blind	Lithium + Nortriptyline, 25-100 mg/d x 6 wks Placebo + Nortriptyline, 25-100 mg/d x 6 wks	35	Lithium was not more effective than placebo in patients with depression	8
	Randomized Double-blind	Lithium, 300-600 mg/d p.o. [titrated from 300 mg/d over 1 wk] + Fluoxetine, 20 mg/d p.o. x 4 wks Desipramine, 25-50 mg/d p.o. [titrated from 25 mg/d over 1 wk] + Fluoxetine, 20 mg/d p.o. x 4 wks Placebo + Fluoxetine, 40-60 mg/d [titrated from 20 mg/d over 1 wk according to response and tolerability] p.o. x 4 wks	101	No differences were found regarding the efficacy of high-dose fluoxetine compared to lithium or desipramine augmentation in patients with major depression previously failing fluoxetine 20 mg/d. High-dose fluoxetine was associated with non-significantly higher response rates	9
	Open	Lithium x 8 wks Lamotrigine x 8 wks	40	Lamotrigine and lithium were equieffective in improving depressive symptoms, but in patients with treatment-resistant depression better tolerability was observed with lamotrigine despite an earlier response with lithium	49
Triiodothyronine	Open	Triiodothyronine, 25 µg/d p.o. + Prior therapy x ≥2 wks Triiodothyronine, 50 µg/d p.o. [titrated from 25 µg/d over 1 wk] + Prior therapy x ≥2 wks	15	Triiodothyronine augmentation may be useful for the treatment of depression resistant to selective serotonin reuptake inhibitors (SSRIs), although it may be less effective in male patients. The effect of triiodothyronine may be related to thyroid function, even within the normal range	13
	Open	Triiodothyronine, 50 µg/d p.o. + Prior therapy x 4 wks	20	Triiodothyronine augmentation of SSRI treatment could be beneficial for patients with major depression resistant to therapy, especially in patients with the atypical subtype	14
	Open Multicenter	Triiodothyronine, 50 µg/d p.o. [titrated from 25 µg/d over 1 wk] + Prior therapy x ≥3 wks	12	Triiodothyronine was a viable, safe, inexpensive and effective augmentation treatment for patients with depression resistant to SSRI therapy	15
Lithium/ triiodothyronine	Multicenter Randomized Dose-finding	Lithium, 450 mg/d x 2 wks → 900 mg/d Triiodothyronine, 25 µg/d x 1 wk → 50 µg/d ± Citalopram ± Sertraline ± Bupropion SR ± Venlafaxine ER	142	Remission rates with lithium and triiodothyronine augmentation were modest and not statistically significant in patients with treatment-resistant depression. Lithium was more frequently associated with side effects	16

olanzapine augmentation therapy in up to 60 patients with treatment-resistant depression without psychotic features is ongoing in Germany (21).

The synergistic action of olanzapine and fluoxetine in treatment-resistant depression has been attributed to large, sustained increases in extracellular levels of dopamine and norepinephrine, as demonstrated in the rat prefrontal cortex using microdialysis (22). This effect might be consistent with 5-$HT_{2A/2C}$ receptor blockade, which would be expected to enhance the effect of SSRIs in potentiating monoamine neurotransmission. An increase in slow-wave sleep observed in 12 patients with SSRI-resistant depression following 3 weeks of olanzapine treatment might also be attributable to 5-$HT_{2A/2C}$ receptor blockade (23). Long-term adaptive changes in postsynaptic monoaminergic receptors have also been proposed in the synergistic action of olanzapine and fluoxetine (24), as well as an increase in fibroblast growth factor-2 (FGF-2) expression (25).

Augmentation with aripiprazole has been evaluated in 3 small open-label studies in patients with treatment-resistant depression and the results indicated a possible therapeutic benefit (26-28). A retrospective chart review conducted in 30 patients with unipolar depression who had failed multiple previous antidepressants also supported the efficacy of aripiprazole in this indication (29). A number of studies of aripiprazole as augmentation in treatment-resistant depression are ongoing, including an open-label safety study and a 14-week randomized, double-blind, placebo-controlled study, each in over 1,000 patients (30-33). Aripiprazole has potent partial agonist activity at dopamine D2 receptors but also binds with high

affinity to recombinant human 5-HT_{1A} receptors in Chinese hamster ovary (CHO) cell membranes. This study indicated that aripiprazole was the first dopamine/5-HT system stabilizer (34).

A 9-month international study conducted in the U.S.A., Canada, France and the U.K. evaluated the effect of long-term augmentation treatment with risperidone in patients with confirmed treatment-resistant depression. In this 3-phase study, 489 patients entered an open-label citalopram monotherapy phase (20-60 mg/day). Nonresponders entered an open-label risperidone augmentation phase of 4-6 weeks' duration. Patients achieving symptom resolution entered a 24-week double-blind continuation phase and were randomized to receive risperidone plus citalopram or placebo plus citalopram. A total of 386 nonresponders entered the augmentation phase, 241 of whom entered the double-blind phase. Mean MADRS and Hamilton Depression Rating Scale (HAM-D-17) total scores were significantly reduced during the open-label risperidone augmentation phase; however, approximately 50% of patients in both treatment groups relapsed during the double-blind phase. The study showed a significant benefit for initial augmentation with risperidone in patients with treatment-resistant depression, but the longer term benefits of this strategy were not demonstrated (35). Two further studies of risperidone augmentation in patients with treatment-resistant depression were recently completed (36, 37).

In preclinical studies, risperidone potentiated SSRI-induced increases in dopamine and norepinephrine in rat medial prefrontal cortex (38). Electrophysiological studies in rat brain showed that risperidone reversed escitalopram-induced inhibition of norepinephrine neuronal activity by a mechanism involving 5-HT_{2A} receptors (39). These findings were consistent with studies with olanzapine.

Ziprasidone is a novel antipsychotic with a good safety profile and a unique receptor affinity profile. In an open-label study in 20 patients with major depressive disorder who had not experienced significant clinical improvement following treatment with SSRIs of adequate dose and duration, a 50% response rate was observed as measured by the HAM-D (40).

For a summary of clinical trials with antipsychotics as an augmentation strategy in treatment-resistant depression, see Table II.

Anxiolytics: buspirone

Buspirone is a 5-HT_{1A} partial agonist that lacks the sedative and adverse cognitive effects associated with other anxiolytics. Initial studies (Table III) demonstrated a 50-60% response rate as measured by the Clinical Global Impression (CGI) scale in patients who had failed to respond to initial treatment with an SSRI (41, 42). In the latter study, however, there was no significant difference in response between buspirone and placebo, as the placebo group demonstrated a 47% response rate. A further randomized, double-blind study in 102 patients who had failed to respond to a minimum of 6 weeks' treatment with either fluoxetine or citalopram also failed to demonstrate superiority over placebo as determined by CGI-Severity of Illness and MADRS scores (43).

Buspirone augmentation was evaluated as a second-step treatment (level 2) in comparison to augmentation with the antidepressant bupropion in the STAR*D trial (Table III). These treatments were compared in 565 patients who did not achieve remission on or who were intolerant of the SSRI citalopram. Remission of symptoms, defined as a score of 7 or less on the HAM-D-17, was the primary outcome parameter and similar rates of remission of 30% were observed in both groups. In this study, designed to mirror clinical practice, bupropion demonstrated certain advantages over buspirone, including a greater reduction in the number and severity of symptoms as measured by the Quick Inventory of Depressive Symptomatology (Self-Report), and it was also associated with fewer adverse events (44).

Studies in rat brain demonstrated region-specific changes in 5-HT_{1A} and $GABA_B$ receptor-activated G-proteins following chronic buspirone treatment, which may contribute to its clinical effects (45).

Antiepileptics: lamotrigine and phenytoin

Lamotrigine is an antiepileptic that is also approved for the maintenance treatment of bipolar II disorder and is in phase III development for schizophrenia. Its use as augmentation therapy in treatment-resistant depression has recently been reviewed (46). Most of the evidence relating to the efficacy of lamotrigine is based on retrospective chart reviews and small open-label studies (see details in Table IV) (47-51). Although these provided initial supportive evidence for its use in treatment-resistant depression, only 1 randomized, double-blind, placebo-controlled study has been conducted. In 23 patients concomitantly treated with fluoxetine for resistant major depressive episodes, no statistically significant difference was observed between the two groups in the HAM-D score at endpoint, the primary outcome measure. However, lamotrigine was statistically significantly superior to placebo when response was assessed by the CGI scale, both in absolute terms and using a responder analysis. As the study sample included patients with bipolar II disorder and major depressive disorder, it provided early evidence of efficacy for lamotrigine as augmentation therapy in this heterogeneous population (52).

Studies in rats demonstrated that one mode of action of lamotrigine may be the downregulation of cortical 5-HT_{1A} receptor-mediated adenylyl cyclase (AC) response (53). Findings from more recent studies also indicated the involvement of postsynaptic 5-HT_{1A} receptors (54) and an inhibitory effect of lamotrigine on presynaptic glutamate release in rat prefrontal cortical slices (55).

The classical antiepileptic phenytoin is currently being investigated as augmentation therapy in up to 40 patients with major depression without psychotic features who have responded inadequately to at least 3 weeks of treatment with an SSRI (56).

Table II: Clinical studies of antipsychotic drugs as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Olanzapine	Randomized Double-blind	Fluoxetine, 20 mg [→ 60 mg] o.d. x 14 wks → [if response] Fluoxetine + Olanzapine x 8 wks Fluoxetine, 20 mg [→ 60 mg] o.d. x 6 wks → Olanzapine, 5 mg [→ 20 mg] o.d. x 8 wks → [if response] Fluoxetine + Olanzapine x 8 wks Fluoxetine, 20 mg [→ 60 mg] o.d. x 6 wks → Fluoxetine, 52 mg + Olanzapine, 13.5 mg o.d. x 8 wks → [if response] Fluoxetine + Olanzapine x 8 wks	34	Combination therapy with olanzapine plus fluoxetine was more effective than monotherapy in patients with major depression without psychotic features	18
	Multicenter Randomized Double-blind	Olanzapine, 6-12 mg/d p.o. x 8 wks Fluoxetine, 25-50 mg/d p.o. x 8 wks Olanzapine, 6-12 mg/d p.o. + Fluoxetine, 25-50 mg/d p.o. x 8 wks Nortriptyline, 25-175 mg/d p.o. x 8 wks	500	The olanzapine plus fluoxetine combination showed a more rapid response, which was sustained until the end of the study, although therapies did not differ significantly at endpoint	19
	Randomized Double-blind	Olanzapine x 8 wks Fluoxetine x 8 wks Olanzapine + Fluoxetine x 8 wks	605	The combination of olanzapine plus fluoxetine showed significantly greater improvement in depressive symptoms compared with either drug alone in patients with treatment-resistant major depression	20
	Randomized Double-blind	Olanzapine, 10 mg x 2 wks Placebo	60	This phase III study will evaluate the efficacy of olanzapine in improving the Hamilton Rating Scale for Depression (HAM-D) scores in patients with treatment-resistant major depression	21
Aripiprazole	Open	Aripiprazole 30 mg/d p.o. [titrated from 10 mg/d over 2-3 wks] + Prior therapy x 8 wks	12	Aripiprazole augmentation therapy could be useful for patients with major depression refractory to SSRI therapy	26
	Open	Aripiprazole, 2.5 mg/d [increased by 2.5 mg weekly as tolerated] x 4 wks → Aripiprazole [fixed dose] x 4 wks Aripiprazole, 10 mg/d [increased by 2.5 mg weekly as tolerated] x 4 wks → Aripiprazole [fixed dose] x 4 wks	15	The addition of aripiprazole to an anti-depressant regimen was well tolerated and effective in patients with treatment-resistant depression	27
	Open	Aripiprazole, 5-30 mg/d + Prior therapy x 8 wks	13	Aripiprazole augmentation showed clinical benefit in patients with major depression not responding to antidepressant therapy	28
	Retrospective	Aripiprazole + Prior antidepressant therapy x 16 wks	30	Aripiprazole augmentation could be effective for the treatment of highly treatment-resistant depression previously failing another atypical neuroleptic	29
	Open	Aripiprazole + Prior SSRI therapy x 12 wks	15	A study has been initiated to evaluate the effect of aripiprazole as adjunctive treatment for refractory major depression	30
	Open	Aripiprazole, 10 mg/d p.o. x 3 wks	20	A study is ongoing to assess the efficacy of aripiprazole augmentation in patients with refractory major depression	31
	Open Multicenter	Aripiprazole x 52 wks	1120	An ongoing phase III study is investigating the safety of aripiprazole as adjunctive treatment in patients with major depression and incomplete response to antidepressant therapy	32

Continuation

Table II (Cont.): Clinical studies of antipsychotic drugs as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Aripiprazole	Multicenter Randomized Double-blind	Aripiprazole + Prior therapy x 14 wks Placebo + Prior therapy x 14 wks	1200	A phase III study has been initiated to evaluate the safety and efficacy of aripiprazole as adjunctive therapy in patients with major depression	33
Risperidone	Pooled meta-analysis	Citalopram, 20-60 mg/d x 4-6 wks → + Risperidone, 0.5 mg/d up to 1 mg/d [if < 55 y] or 0.25 mg/d up to 0.5 mg/d [if > 55 y] x 4-6 wks → Citalopram, 20-60 mg/d + Risperidone 0.5-1 mg/d x 24 wks Citalopram, 20-60 mg/d x 4-6 wks → + Risperidone, 0.5 mg/d up to 1 mg/d [if < 55 y] or 0.25 mg/d up to 0.5 mg/d [if > 55 y] x 4-6 wks → Citalopram, 20-60 mg/d + Placebo x 24 wks	489	Long-term benefits of citalopram augmentation with risperidone were not achieved, although short-term treatment with risperidone significantly improved depression rating scale scores in patients with treatment-resistant depression	35
	Randomized Double-blind	Risperidone, 1-3 mg p.o. ± Prior antidepressant treatment x 4 wks Placebo ± Prior antidepressant treatment x 4 wks	84	This phase III trial will study the safety and efficacy of risperidone augmentation in patients with unipolar depression who failed to respond or only partially responded to an adequate trial of an antidepressant	36
	Open Randomized	Risperidone x 6 wks Bupropion-ER x 6 wks	30	This phase II trial will compare the efficacy of combining risperidone or extended-release bupropion with SSRI medication in patients with treatment-resistant major depression	37
Ziprasidone	Open	Ziprasidone, 80 mg p.o. b.i.d. [titrated from 20 mg b.i.d.] + Prior SSRIs x 6 wks Placebo + Prior SSRIs x 6 wks	20	Ziprasidone augmentation therapy could be beneficial in addition to SSRIs in patients with previously resistant major depression	40

Table IV presents a summary of the clinical trials with antiepileptic drugs as augmentation in treatment-resistant depression.

Antihypertensives: pindolol and mecamylamine

Preclinical studies provided early evidence to support the hypothesis that pindolol could enhance the efficacy of SSRIs due to functional antagonism of 5-HT_{1A} autoreceptors (57, 58). However, the body of evidence from double-blind, placebo-controlled trials published prior to 2000 was not conclusive, with only half of these studies demonstrating a beneficial effect of pindolol in decreasing the latency of onset for SSRI antidepressant treatment (58). Studies using positron emission tomography (PET) suggested that the doses used in these early clinical studies may have been insufficient to fully occupy presynaptic 5-HT_{1A} autoreceptors in man. A subsequent study evaluated the preferential occupancy of 5-HT_{1A} autoreceptors following three different dose regimens of pindolol in depressed patients and healthy volunteers. Autoreceptor occupancy was attenuated in depressed patients compared with healthy volunteers receiving the same dose of pindolol, and there was also a significant negative correlation between the degree of preferential occupancy and the severity of depression measured by HAM-D (59).

A randomized, double-blind, placebo-controlled study of pindolol augmentation (2.5 mg t.i.d.) in 42 patients with SSRI-resistant depression failed to demonstrate any benefit of pindolol treatment in these patients (60).

Mecamylamine is a nicotinic receptor antagonist launched for the treatment of hypertension over 50 years ago, and currently in phase II clinical trials for the treatment of depression. In the tail-suspension test in mice, mecamylamine potentiated the antidepressant-like effects of imipramine and citalopram and the interaction was synergistic (61). A randomized, controlled trial of mecamylamine is ongoing in up to 60 patients with SSRI-refractory major depressive disorder (62).

Clinical studies of antihypertensive drugs as augmentation strategy in treatment-resistant depression are illustrated in Table V.

Other therapies for treatment-resistant depression

Parkinson's disease therapy: pramipexole and ropinirole

The dopamine agonists pramipexole and ropinirole have been identified as potential augmentation therapies in treatment-resistant depression. A 16-week naturalistic study and the 1-year follow-up extension study indicated

Table III: Clinical studies of buspirone as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Buspirone	Open	Buspirone, 10 mg p.o. t.i.d. [titrated from 5 mg t.i.d. as tolerated] + Prior therapy x 4-5 wks	33	Buspirone augmentation provided marked clinical improvement in patients with depression initially failing standard antidepressant therapy	41
	Multicenter Randomized Double-blind	Buspirone, 60 [max.] mg/d p.o. [titrated from 10 mg/d according to tolerability] + SSRI x 4 wks Placebo + SSRI x 4 wks	119	Buspirone augmentation of SSRI therapy was safe and well tolerated but did not show efficacy in the management of treatment-refractory depression	42
	Multicenter Randomized Double-blind	Buspirone, 60 [max.] mg/d p.o. [titrated from 10 mg b.i.d.] + Prior therapy x 6 wks Placebo + Prior therapy x 6 wks	102	Buspirone augmentation of SSRI therapy was beneficial in patients with severe depression and could accelerate the onset of action of the antidepressants	43
	Open Multicenter	Bupropion-SR, 400 [max.] mg/d + Citalopram, 55 [mean] mg/d x 12 wks Buspirone, 60 [max.] mg/d + Citalopram, 55 [mean] mg/d x 12 wks	565	Augmentation of citalopram with bupropion or bupirone led to remission in approximately one-third of patients with major depressive disorder not responding to citalopram alone	44

that pramipexole augmentation of antidepressants might be an effective strategy in these patients (63, 64). A randomized, double-blind, placebo-controlled study of adjunctive pramipexole in up to 80 patients with treatment-resistant major depressive episodes is under way (65). Some evidence supporting the efficacy of ropinirole in treatment-resistant depression was obtained in a small pilot study (66), and an open-label study is evaluating ropinirole as adjunctive therapy in up to 60 patients with major depression (67).

Attention deficit hyperactivity disorder therapy: methylphenidate

Methylphenidate is a dopamine transporter (DAT) inhibitor marketed worldwide for the treatment of attention deficit hyperactivity disorder (ADHD). A randomized, double-blind, placebo-controlled trial in 60 patients with treatment-resistant depression failed to show a benefit for methylphenidate as measured by HAM-D scores (68). However, a double-blind, placebo-controlled pilot trial in elderly patients receiving citalopram and methylphenidate showed a significant improvement in depressive symptoms compared with those on citalopram and placebo (69). A randomized, controlled trial is ongoing to evaluate methylphenidate as add-on therapy to antidepressants (SSRIs or selective norepinephrine reuptake inhibitors [SNRIs]) in up to 130 patients with treatment-resistant major depression without psychotic features (70).

Wake-promoting agent: modafinil

Modafinil is approved for use in patients with excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea and shift work sleep disorder. It has also been evaluated as an adjunctive therapy in patients with a partial response to previous antidepressants and a prevalence of fatigue and sleepiness (5). In a randomized, double-blind, placebo-controlled study in 136 patients, modafinil significantly improved fatigue and sleepiness during the first 2 weeks of treatment, although differences between modafinil and placebo were not statistically significant at 6 weeks (71). In a multicenter, placebo-controlled study in 311 patients with major depressive disorder and partial response to SSRI monotherapy, modafinil significantly improved patients' overall clinical condition compared with placebo, as assessed by the CGI-Improvement scale at 8 weeks. However, there were no significant differences between modafinil and placebo in specific scores for fatigue (72). In an open-label extension study, modafinil augmentation relieved excessive sleepiness and reduced fatigue (73).

In a dual-probe microdialysis study in rats, low-dose modafinil significantly enhanced the fluoxetine-induced increases in 5-HT levels in the prefrontal cortex and dorsal raphe nucleus. Modafinil also enhanced the acute effect of imipramine (74).

Hormone replacement therapy: testosterone

The androgen receptor agonist testosterone has been proposed as an antidepressant supplement in men with treatment-resistant depression based on the hypothesis that androgen supplementation of a serotonergic antidepressant might increase serotonergic neurotransmission. However, a randomized, placebo-controlled trial in 26 men with a partial or no response in two adequate antidepressant trials failed to show any benefit of intramuscular injections of escalating doses of testosterone compared with placebo (75). Two randomized, controlled trials of testosterone gel (AndroGel®) in men with treatment-resistant depression and low testosterone levels produced equivocal results: one study in men aged 30-65 years demonstrated a significantly greater improvement

Table IV: Clinical studies of antiepileptic drugs as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Lamotrigine	Open	Lamotrigine + Prior therapy x 12 wks	16	Adjunctive lamotrigine may be beneficial for the treatment of major depression resistant to antidepressant therapy	47
	Retrospective	Lamotrigine, 24.6 [mean] mg/d p.o. + Antidepressant therapy x 1 y	34	Treatment augmentation with lamotrigine was a well-tolerated and effective therapy for patients with treatment-resistant depression	48
	Open	Lamotrigine x 8 wks Lithium x 8 wks	40	Lamotrigine and lithium were equieffective in improving depressive symptoms, but in patients with treatment-resistant depression better tolerability was observed with lamotrigine despite an earlier response with lithium	49
	Retrospective	Lamotrigine, 300 [max.] mg/d p.o. [titrated from 50 mg/d]	25	Lamotrigine augmentation was a promising therapeutic approach for treatment-resistant unipolar depression. Double-blind studies are warranted to confirm this finding	50
	Retrospective	Lamotrigine [adjusted from 25 mg/d p.o. according to response/tolerability] + Prior antidepressant therapy @ max. tolerated dose x ≥ 6 wks	37	Lamotrigine augmentation was especially effective in patients with treatment-resistant depression who had been depressed for shorter periods and had failed fewer trials of antidepressants. Patients with co-morbid anxiety disorders and/or chronic pain syndrome also showed a trend towards increased response	51
	Randomized Double-blind	Lamotrigine, 100 mg/d [titrated from 25 mg/d over 4 wks] + Fluoxetine, 20 mg/d p.o. x 6 wks Placebo + Fluoxetine, 20 mg/d p.o. x 6 wks	23	A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes is under way	52
Phenytoin	Randomized Double-blind	Phenytoin + Prior therapy Placebo + Prior therapy	40	A clinical study was initiated to assess the effect of phenytoin augmentation in patients with depression failing SSRI therapy	56

Table V: Clinical studies of antihypertensive drugs as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Pindolol	Randomized Double-blind	Pindolol, 2.5 mg p.o. t.i.d. + Prior SSRIs x 6 wks Placebo + Prior SSRIs x 3 wks → Pindolol, 2.5 mg p.o. t.i.d. + Prior SSRIs x 3 wks	42	Pindolol did not show efficacy in augmenting clinical response to treatment with SSRIs in patients with treatment-resistant depression	60
Mecamylamine	Randomized Double-blind	Mecamylamine, 5 mg p.o. b.i.d. [titrated from 5 mg o.d. over 2 wks] + Prior therapy x 8 wks Placebo + Prior therapy x 8 wks	60	A phase II study has been initiated to evaluate the effect of mecamylamine augmentation for the treatment of SSRI-refractory major depression	62

in HAM-D scores in men receiving testosterone (76), while the other study in older men (> 50 years) found no significant difference between the treatments (77). A randomized, controlled trial is ongoing in up to 100 men with treatment-resistant depression and low testosterone levels (78).

Alzheimer's disease therapy: memantine

Memantine is an NMDA receptor antagonist launched originally for the treatment of spasticity, and more recently for Alzheimer's-type dementia. Studies using the forced swimming test in rats indicated that the combination of

Table VI: Clinical studies of several other treatment approaches as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Pramipexole	Open	Pramipexole, 0.375 mg/d [starting dose] + Antidepressant treatment x 6 wks	37	Adjunctive treatment with pramipexole was relatively well tolerated and effective in patients with depression	63
	Open	Pramiprexole, 1.5 mg/d [titrated from 0.375 mg/d over 2 wks] + Prior antidepressant therapy x 48 wks	23	Pramiprexole augmentation was relatively safe and could be effective for the long-term treatment of resistant depression	64
	Randomized Double-blind	Pramipexole x 8 wks Placebo	80	This clinical study was initiated to evaluate the effectiveness of pramipexole for the treatment of resistant major depression	65
Ropinirole	Open	Ropinirole, 0.25 mg p.o. @ bedtime x 3 d → [escalated to 0.75 mg/d by d7] x 4 d → escalated to 1.5 mg/d over 1 wk x 14 wks	10	Ropinirole augmentation of antidepressants was effective and relatively well tolerated in patients with treatment-resistant depression	66
	Open	Ropinirole-CR + Prior antidepressant therapy	60	This phase III study will assess the safety and efficacy of adding controlled-release ropinirole to antidepressant medication in patients with major depression	67
Methylphenidate	Randomized Double-blind	Methylphenidate OROS®, 18-54 mg/d p.o. + Prior therapy x 4 wks Placebo+ Prior therapy x 4 wks	60	Treatment augmentation with methylphenidate OROS® was well tolerated and associated with a higher response rate than placebo in patients with refractory depression, although without achieving statistical significance	68
	Randomized Double-blind	Methylphenidate, 5-20 mg [titrated by 2.5 mg b.i.d. 1x/3 d] x 8 wks [tapered off over 2 wks] + Citalopram, 20-40 mg o.d. x 10 wks + Lorazepam, 1 [max.] mg/d PRN Placebo + Citalopram, 20-40 mg o.d. x 10 wks + Lorazepam, 1 [max.] mg/d PRN	16	The combination of citalopram and methylphenidate was associated with rapid and improved antidepressant response compared with citalopram monotherapy in elderly patients with depression. However, the use of the combination was limited by its safety and tolerability	69
	Multicenter Randomized Double-blind	Methylphenidate, 18-54 [max.] mg p.o. o.d. Placebo	130	This phase III study will evaluate the safety and efficacy of adding methylphenidate to oral antidepressant medication in patients with major depression	70
Modafinil	Multicenter Randomized Double-blind	Modafinil, 100-400 mg/d [titrated from 100 mg/d over 2 wks] + Prior therapy x 6 wks Placebo + Prior therapy x 6 wks	136	Adjunctive therapy with modafinil may be useful for the short-term management of residual fatigue and sleepiness in patients with major depression partially responding to antidepressant therapy	71
	Multicenter Randomized Double-blind	Modafinil, 100 mg p.o. o.d. x 3 d → 200 mg p.o. o.d. x 8 wks Placebo	314	Modafinil was well tolerated and potentially effective in patients with major depression treated with SSRIs showing persistent fatigue and sleepiness	72
	Open Multicenter	Modafinil, 100-400 mg/d p.o. [titrated from 100 mg/d over 2 wks] + Prior therapy x 12 wks	250	Modafinil augmentation therapy reduced excessive sleepiness and fatigue and improved the overall clinical condition of patients with depression, including mood	73
Testosterone	Randomized Double-blind	Testosterone i.m. x 6 wks Placebo	26	Add-on testosterone was ineffective in adult male patients with treatment-resistant major depressive disorder treated with SSRIs	75
	Randomized Double-blind	Testosterone 1% gel, 10 g/d top. x 8 wks Placebo	22	Testosterone gel may have antidepressant effects in men with refractory depression and low testosterone levels	76

Continuation

Table VI (Cont.): Clinical studies of several other treatment approaches as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Testosterone	Randomized Crossover	Testosterone 1% gel, 5 g top. o.d. x 12 wks Placebo	12	Testosterone gel augmentation therapy produced clinically significant improvement in depressive symptoms in patients with depression with a partial response to antidepressant therapy, although no statistical difference compared to placebo was detected	77
	Multicenter Randomized Double-blind	Testosterone 1% gel, x 9 wks Placebo	100	A clinical study will be conducted to evaluate the effect of testosterone gel for the treatment of men with refractory major depression and low or borderline testosterone levels	78
Memantine	Randomized Double-blind	Memantine, 20 mg p.o. o.d. x 8 wks Placebo	50	A clinical study was initiated to evaluate the efficacy of memantine augmentation in patients with depression not responding to antidepressant therapy	81

Table VII: Clinical studies of vagus nerve stimulation (VNS) as augmentation strategy in treatment-resistant depression (from Prous Science Integrity®).

Augmentation treatment	Design	Treatments	n	Conclusions	Ref.
Vagus nerve stimulation	Open Multicenter	Vagus nerve stimulation + Previous therapy x 24 mo	59	Adjunctive vagus nerve stimulation produced long-term benefits in patients with chronic or recurrent major depression	86
	Open	Vagus nerve stimulation x 12 mo Control	329	Addition of vagus nerve stimulation to usual treatment offered superior antidepressant benefits compared to usual treatment alone in individuals with refractory depression	87
	Open	Vagus nerve stimulation + Antidepressant drugs as required x 9 mo	205	One-year continuous exposure to vagus nerve stimulation was well tolerated and produced significant reductions in depression scores in patients with major depression or depressive bipolar disorder	88

traditional antidepressant drugs and memantine may produce enhanced antidepressant effects (79, 80). A randomized, controlled trial is assessing memantine augmentation of antidepressants in up to 50 patients not fully responding to antidepressant medications (81).

Table VI summarizes clinical studies of several treatment approaches as augmentation strategies in treatment-resistant depression.

Vagus nerve stimulation

The Vagus Nerve Stimulation (VNS) Therapy System™ is a device which is implanted adjacent to the collar bone and delivers programmed, intermittent electrical pulses to the vagus nerve. It was initially launched in the United States in 1997 for the treatment of epilepsy, and in 2005 approval was granted by the Food and Drug Administration (FDA) for the adjunctive long-term treatment of chronic or recurrent depression in patients who have not had an adequate response to four or more adequate antidepressant treatments (82). Two studies are ongoing as a requirement of the FDA approval. One of these is a natural history, longitudinal, prospective study resulting in the establishment of a treatment-resistant depression registry of 2,000 patients. At least 1,000 patients receiving VNS therapy will be followed for 5 years (83). The second study is a randomized, double-blind trial comparing different doses of electrical charge in up to 460 patients (84). In addition, three mechanism of action studies have been initiated to identify areas of the brain activated by acute and long-term VNS Therapy™ and to further establish the rationale for the sustained long-term responses that have been reported with the therapy (85). The results of several completed studies of VNS as augmentation therapy in treatment-resistant depression are summarized in Table VII (86-88).

Conclusions

Many strategies have been evaluated for the management of treatment-resistant depression in formal clinical trials or in clinical practice based on hypotheses from proposed mechanisms of action in preclinical studies. Although many different classes of nonantidepressant drugs have been investigated, very few randomized, controlled trials have been performed and evidence of efficacy is limited for the majority of augmenting agents. Both lithium and triiodothyronine appeared to be useful as augmentation therapy, although the majority of studies are based on augmentation of the older classes of tricyclic antidepressants, and few studies have used SSRIs. Despite the evidence supporting the efficacy of lithium augmentation, there may be a reluctance to use it because of tolerability issues and the need to monitor lithium levels to achieve therapeutic levels. Interestingly, lithium and T_3 have been compared in level 3 of the STAR*D study and a modest advantage was shown for T_3. Newer strategies for augmentation that have been evaluated in at least 1 controlled trial include olanzapine, risperidone, buspirone, lamotrigine, pindolol and methylphenidate, although controlled trials with other agents are ongoing. At the present time, it must be concluded that the choice of augmentation strategy is based largely on clinical preference and therapeutic need in individual patients, rather than evidence of efficacy based on randomized, controlled studies.

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