Partial Response and Nonresponse to Antidepressant Therapy: Current Approaches and Treatment Options

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Background: Response to antidepressant drug therapy is less than optimal for a considerable proportion of depressed patients; at present, however, few data exist to guide their rational therapeutic management. This review describes general principles for the management of such patients. This review is the result of an expert roundtable meeting convened to review published clinical data and clinical experience and provide clinicians with evidence-based principles on the management of patients who fail to respond optimally to initial antidepressant therapy.

Roundtable Findings: Failure to respond may be defined as a < 25% decrease on an accepted symptom rating scale such as the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D) in a patient who has received an adequate dosage for 4 weeks. In these patients, a neuropharmacologic rationale exists to switch to an agent with a different mode of action or a dual action. Partial response may be defined as 6 to 8 weeks at an adequate dosage and 25% to 50% decrease in MADRS or HAM-D score. In these patients, dose escalation should be considered, followed by augmentation and switching strategies. For augmentation, knowledge of neuropharmacology may allow prediction of which second agent will potentiate or complement the action of the first agent; it may also permit the prediction of potential safety concerns.

Conclusions of the Panel: On the basis of a review of the medical literature and clinical experience regarding patients with partial response or nonresponse to antidepressant drug therapy, it appears that simultaneous targeting of both the noradrenergic and serotonergic systems is one of the most effective augmentation strategies. Switching to an agent of a different class is probably optimal for those patients who fail to respond to first-line therapy.

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This review is the result of the expert roundtable "Reboxetine–Meeting the Long-Term Challenge," which was held July 8, 2000, in Brussels, Belgium. The meeting was convened to review published clinical data and clinical experience and provide clinicians with evidence-based principles on the management of patients who fail to respond optimally to initial antidepressant therapy.

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Depression is a highly prevalent and debilitating disorder, with significant socioeconomic and quality-of-life implications, yet frequently remains undiagnosed and undertreated in the community.[1,2] For the majority of patients, depression represents a chronic or recurrent condition that is often characterized by the persistence of symptoms between episodes. For example, around 30% of patients will experience further episodes of depression within 2 years of diagnosis and treatment,[3] with a cumulative probability of recurrence of 13% after the first 6 months, and 87% after 15 years.[4]

Changes in our understanding of the course of depressive illness have been paralleled by improvements in the number and type of agents available for its therapeutic management. For example, the selective serotonin reuptake inhibitors (SSRIs), which allow selective targeting of the serotonergic system, have largely replaced older tricyclic antidepressants (TCAs) as first-line therapy in many countries. A number of agents with a dual mechanism of action on both the serotonergic and noradrenergic systems are also emerging, such as venlafaxine,[5] mirtazapine,[6] and possibly paroxetine.[7] More recently, the first selective norepinephrine reuptake inhibitor (selective NRI), reboxetine, has become available in several countries.[8] However, while we now have a greater number of treatment options for the individual patient, many of which show improved safety and tolerability, one major caveat exists: overall efficacy for improving symptoms of the acute phase of depression has not greatly increased. For example, the intent-to-treat response rate in 102 controlled trials of TCAs was 51% compared with a response rate of 47% in a meta-analysis of 39 studies with SSRIs.[9] The overall conclusion, therefore, is that up to half of all patients with depressive illness will require some change in treatment, including switching to another antidepressant and addition of a second antidepressant agent ("combination") or a non-antidepressant agent ("augmentation"). The need to modify treatment may be necessary because of failure of first-line monotherapy (partial response/nonresponse) or the failure to achieve remission (still exhibit residual symptoms) even though they achieve a response (improvement). Prognostically, these patients are more vulnerable to relapse, work impairment, and suicide,[10] underscoring the need for a vigorous approach to treatment. The aim of this review is to present general principles for the management of such patients based on an expert roundtable meeting convened July 8, 2000, to discuss published clinical data and clinical experience on switching and augmentation therapy in patients with depressive illness.

CURRENT MANAGEMENT OF PATIENTS WITH AN INADEQUATE RESPONSE TO TREATMENT

As previously stated, up to half of all patients treated for depression do not respond adequately to first-line monotherapy. Before discussing current management approaches for such patients, it is important to define what is meant by partial response as this allows cross-study comparisons. Lack of treatment response is generally defined as less than 50% improvement from baseline on a recognized depression rating scale, the mostly widely used of which are the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Rating Scale for Depression (HAM-D). Criteria for defining response to antidepressant therapy using these scales are shown in Table 1.

Table 1. Definitions of Response and Remission According to the Improvement in the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D) Score During Treatment

Improvement in total score, %	
Response	≥ 50
Partial response	25–49
Nonresponse	< 25
Absolute total score	
Remission	
MADRS	≤ 8–12
HAM-D	≤ 7–12

Table 2. Epidemiology of Partial Response and Nonresponse to Antidepressant Therapy[a]

Study	Partial Response Plus Nonresponse, %	Nonresponse, %
Double-blind studies		
Completer analysis	34	19
Intent-to-treat analysis	46	38
Open studies	29	…
All studies	36	…

[a]Data from Fava and Davidson.[11]

Using these criteria and the HAM-D scale, Fava and Davidson[11] conducted a systematic review of 36 clinical trials in order to determine the epidemiology of partial response and nonresponse (Table 2). Across all studies, both open and double-blind, the combined rate of partial response and nonresponse was 36%. However, it remains unclear as to whether a definition of response of ≥ 50% improvement from baseline is sufficient for all severity levels of depression.

In those patients with more severe depression, for example, a 50% improvement in HAM-D score often leaves considerable residual symptoms, which are known to be associated with a poor long-term prognosis.[12] Moreover, many patients meeting criteria for full remission may still have residual symptoms,[13] most commonly generalized and somatic anxiety and irritability[14] with persistence of social dysfunction. Trials in which strict remission criteria were imposed for entry into the maintenance phase of treatment show that response is still suboptimal for a significant proportion of patients. In studies that used a remission criteria of HAM-D score ≤ 7[15] or ≤ 8,[16] for example, over one third of patients remained symptomatic.

Taken together, these findings indicate that achieving "remission" as currently defined is not necessarily synonymous with a fully asymptomatic state. When selecting antidepressants and assessing treatment outcomes, therefore, it is important to consider other aspects such as quality of life and psychosocial functioning, historically areas that have been overlooked in clinical studies of antidepressant agents.

Table 3. Possible Causes of Apparent Treatment Resistance[a]

True resistance
Misdiagnosis of depressive subtype
Comorbid psychiatric disorder
Comorbid medical disorder
Inadequate dosage
Insufficient treatment duration
Poor compliance

[a]Based on Souery et al.[17]

Table 4. Summary of Serotonin and Norepinephrine Depletion Studies in Patients With Depression[a]

Responded to	Serotonin Depletion	Norepinephrine Depletion
Selective serotonin reuptake inhibitor	++++	+
Norepinephrine reuptake inhibitor	+	++++
Norepinephrine and specific serotonergic antidepressant	++++	++++

[a]Data from Delgado and Moreno.[24] Symbols: + = 20% to 25% of patients relapsed, ++++ = 50% to 80% of patients relapsed.

Treatment Resistance: Definition and Key Factors

Traditionally, those patients who do not respond adequately to antidepressant monotherapy are defined as "treatment resistant," although the reasons for such a response are varied and often do not reflect true resistance to treatment.[17] Consequently, a variety of definitions of treatment resistance exist in the literature. Recently, Ananth[18(pp61–62)] defined treatment resistance as "failure to respond adequately to 2 successive courses of monotherapy with pharmacologically different antidepressants given in adequate dose for a sufficient length of time." This definition includes a number of the major key parameters important in defining treatment resistance, notably the correct diagnosis, adequacy of treatment (in terms of dosage, duration, and compliance), and previous therapy,[19] although it lacks a clear definition of an adequate dosing regimen.

Linden et al.,[20] Thase and Rush,[21] and Souery et al.[17] favor a staged approach to conceptualizing treatment resistance based on past treatment history. The authors consider stages ranging from failure of at least 1 adequate trial of a major class of antidepressants to failure of adequate trials of antidepressants from at least 2 distinct pharmacologic classes (e.g., a TCA, a monoamine oxidase inhibitor [MAOI]) and a course of bilateral electroconvulsive therapy (ECT). The staging approach also provides a useful guide to future therapeutic approaches.

A number of factors may give rise to apparent treatment resistance (Table 3) and should be addressed before a definitive diagnosis of true treatment resistance is applied.[17] Psychiatric comorbidity can also result in apparent treatment resistance. As many as three quarters of patients with treatment-resistant depression have comorbid psychiatric disorders, including personality and panic disorders and alcohol/substance abuse.[22,23] In these cases, the outcome of treatment depends on the efficacy of therapy for the depression as well as for the comorbid disorder. A range of medical conditions and drugs is also known to cause depression, while certain drugs may interfere with the antidepressant response. Finally, Sharan and Saxena[23] have identified several factors predictive of poor response, including a family history of affective disorders, severe depression and suicide attempts, number of previous episodes and long duration of depression prior to treatment, negative life events, and poor social support.

Scientific and Clinical Rationale of Combination, Augmentation, and Switching Therapy

It is well established that both noradrenergic and serotonergic systems are involved in depression,[24] although the specific impairments have not yet been defined and are likely to differ between patients. Neurotransmitter depletion studies in depressed patients have shown that depletion transiently reverses antidepressant response in the majority, yet the observed response depends on the pharmacologic profile of the antidepressant (Table 4). While the efficacy of different antidepressants is well established, it remains difficult to predict which agent will be effective for which individual patient despite extensive attempts to identify clinical and biological markers. However, knowledge of the neuropharmacology of antidepressants may provide assistance in the selection of a second agent to potentiate or complement the action of the first agent if monotherapy proves unsuccessful. This is the concept underlying combination and augmentation therapies, whereby either the pharmacologic effect of the first drug is enhanced or the second agent provides a new pharmacologic effect to complement the action of the first drug. Combination therapy or augmentation may be most appropriate for patients who have experienced a partial response to their initial therapy for whom there may be a risk of losing the partial response if the initial therapy is removed.

Switching involves withdrawal of the first agent followed by initiation of an alternative treatment with an agent that generally has different pharmacology or a "dual" mechanism of action. Switching to an agent of a different class is probably more appropriate for those patients who fail to respond to first-line therapy. The following sections describe the findings of clinical trials of combination, augmentation, and switching therapies, the respective advantages and disadvantages of which are summarized in Table 5. The overall conclusion of such studies is that simultaneous targeting of both the noradrenergic and serotonergic systems is likely the most effective strategy.

Augmentation

Lithium. Augmentation with lithium is the most extensively studied augmentation therapy to date and was first

Table 5. The Advantages and Disadvantages of Augmentation and Switching Strategies in Patients Who Fail to Respond to Antidepressant Monotherapy

Strategy	Advantages	Disadvantages
Augmentation	Effective in ≈ 50% of treatment-resistant patients	Paucity of data for newer agents
	May have rapid onset	Little information on dosages
	No need to taper first agent	Potential for causing disturbing or dangerous side effects
		May require laboratory monitoring
		Additional cost
		Compliance may decrease
Switching	Minimizes polypharmacy	May need to taper first agent or use a washout period
	Second agent may be better tolerated	Loss of partial efficacy of first agent
	Less costly	Delayed onset of action

described by de Montigny and colleagues[25] 20 years ago. Of 9 double-blind, placebo-controlled studies, 7 showed a benefit for lithium augmentation, with response rates of up to 50%.[26–31] However, the utility of lithium augmentation is limited by annoying side effects (e.g., nausea, diarrhea, abdominal pain, muscle weakness, tremor). A practical limitation is that some patients are not able to tolerate lithium at levels at the bottom of the dose-response range.[32] There may also be patient objections to the use of lithium, given the general perception that the drug is used to treat serious mental illness.[33]

Thyroid hormone. Thyroid hormone, a term that encompasses both triiodothyronine (T_3) and thyroxine (T_4), has a long history of use as an augmentation agent in the treatment of depression.[34] Open studies have suggested efficacy for triiodothyronine in the augmentation of TCAs, with several randomized, double-blind, placebo-controlled studies supporting these findings.[35–37] The study by Joffe and Singer[36] indicated that the augmentation effect of triiodothyronine was superior to T_4 but comparable to that of lithium, although the mechanism of action is unclear. Various mechanisms have been proposed including correction of underlying (subclinical) hypothyroidism and enhancement of noradrenergic neurotransmission.[38,39] However, there is a paucity of data on the efficacy of thyroid augmentation of SSRIs,[40] as well as the long-term effect of such augmentation on endogenous thyroid function.

Pindolol. Pindolol is a β-adrenoceptor antagonist that also blocks 5-HT_{1A} and 5-$HT_{1B/1D}$ autoreceptors and therefore prevents the negative feedback effect of increased somatodendritic serotonin.[41] These predictions were supported by positive findings that pindolol augmentation was able to enhance an early response in a primary care setting in a small number of recurrent depression patients,[42,43] but not in a psychiatric setting with more chronic or recurrent depression patients.[43–46]

Two open studies[47,48] have suggested a possible use for pindolol augmentation in treatment-refractory patients. However, controlled trials[49,50] have failed to show an advantage over placebo in this group of patients. A recent study[51] suggests that the doses of pindolol used actually provided sufficient occupancy of the 5-HT_{1A} receptor and, as such, the hypothesis may not, as yet, have been adequately tested. The utility of this approach, therefore, remains in question.

Trazodone and nefazodone. Trazodone and nefazodone share similar pharmacologic properties. Both are 5-HT_{2A} receptor antagonists and show moderate inhibition of serotonin reuptake. Nefazodone moderately and transiently inhibits norepinephrine reuptake and blocks 5-HT_{1A} receptors.[6] Several studies have evaluated the efficacy of these agents as augmentation therapy. Maes et al.,[52] for example, studied 26 treatment-resistant patients treated with trazodone, 100 mg/day, in a double-blind, placebo-controlled trial. In combination with placebo, the response rate for trazodone-treated patients was 12.5%, increasing to 62.5% and 70%, respectively, in combination with pindolol and fluoxetine. More recently, Sajatovic et al.[53] performed a retrospective analysis of 20 patients with treatment-refractory or treatment-intolerant depression (treatment-refractory depression was defined as lack of response to 6 weeks' treatment with a TCA, fluoxetine, or sertraline). Overall, 55% of patients showed a response when treatment was augmented with or switched to nefazodone.

SSRIs plus noradrenergic TCAs. Studies in animal models support augmentation therapy with a noradrenergic TCA in patients who fail to respond to an SSRI alone, in that the combination of desipramine and fluoxetine achieves a more rapid down-regulation of β-adrenoceptors than does desipramine alone. Indeed, desipramine alone caused slower down-regulation, while fluoxetine alone had no effect on receptor density.[54] Evidence from one report suggests that patients treated with the combination of desipramine and fluoxetine may experience a more rapid response than those treated with desipramine alone.[55] Fava et al.[14] subsequently evaluated the efficacy of desipramine augmentation in 41 patients who partially responded or failed to respond to 8 weeks' treatment with fluoxetine, 20 mg/day. Overall, 25% of those treated with fluoxetine plus desipramine achieved a response similar to that observed for lithium augmentation (29%). However, neither strategy was as effective as increasing the dosage of fluoxetine alone (53% response rate). More recently, a 3-arm study[56] showed that remis-

sion rates were higher for desipramine plus fluoxetine therapy (50%) than for either agent alone (desipramine, 0%; fluoxetine, 7%).

Nortriptyline is another noradrenergic TCA that has been evaluated in the augmentation setting. In a small study of patients who failed to respond to a standard antidepressant and/or a full course of ECT, Seth et al.[57] reported concomitant administration of nortriptyline and an SSRI was successful in all cases.

However, caution should be exercised when combining SSRIs and TCAs given the effects of the SSRIs on the cytochrome P450 (CYP) system and the likelihood of increased plasma TCA levels.

SSRI plus buspirone. Buspirone is a partial 5-HT_{1A} agonist that is believed to activate postsynaptic 5-HT_{1A} receptors. A major metabolite of buspirone [1-(2-pyrimidinyl)-piperazine], however, enhances norepinephrine release. Buspirone, therefore, may exert a dual mechanism of action.

Several open-label studies have assessed the efficacy of augmentation therapy with buspirone, 20 to 30 mg/day, reporting response rates of 43% to 100%.[30,58–60] However, a randomized, double-blind, placebo-controlled trial of buspirone augmentation in 119 patients who failed to respond to 4 weeks' monotherapy with either citalopram or fluoxetine found no difference in response rate compared to that observed in the placebo group (51% and 47%, respectively).[61] The authors speculated that several factors may have contributed to this observed lack of efficacy, including an unusually high placebo response (possibly related to improved clinical management of patients during the trial, and hence increased compliance) and the fact that the 4-week treatment period with SSRIs before augmentation may have been too short to attain full therapeutic potential. Indeed, a poststudy, open-label phase in which patients continued to receive buspirone augmentation led to a 69% response rate. A more recent study also failed to demonstrate a benefit over placebo for buspirone augmentation of SSRI therapy (fluoxetine or citalopram).[62] A subanalysis revealed a potential benefit among patients with higher baseline MADRS scores (> 30 points), although a more detailed analysis is required.

SSRI plus reboxetine. The potential use of reboxetine as an augmentation agent in treatment-resistant depression has been examined in animal studies as well as in controlled clinical investigations. The antidepressant activity of reboxetine, either with or without concomitant treatment with an SSRI (sertraline), was first investigated in a rat model of depression.[63] Overall, the onset of the antidepressant effect (as measured by the "open field" test) was comparable for both reboxetine and sertraline alone and when the drugs were administered in combination. Interestingly, however, adaptive changes in 5-HT_{1A} receptors and changes in central α_2-adrenoceptor sensitivity (as measured by 8-OH-DPAT– and clonidine-induced hypothermia, respectively) occurred more rapidly when reboxetine was used in combination with the SSRI than with either agent alone. Subsequently, a double-blind, randomized pharmacodynamic and pharmacokinetic interaction study was performed in 30 healthy volunteers treated with either reboxetine (8 mg/day) or fluoxetine (20 mg/day) alone, or the 2 drugs in combination, for 8 days.[64] In terms of tolerability, characteristic adverse events were not increased by concomitant administration and, as expected, no instances of serotonin syndrome were observed. No statistically significant treatment effects on cognitive function were apparent, and there were no relevant effects of either agent on the pharmacokinetics of the concomitant antidepressant. Overall, such findings suggest that reboxetine could be used in combination with fluoxetine without risk of tolerability concerns.

Combination treatment with reboxetine (dose titrated up to 6–8 mg/day) and citalopram (dose titrated up to 60 mg/day) has been evaluated in an open-label study in 10 patients, who had not previously responded to at least 2 SSRIs, venlafaxine, and antidepressant augmentation (with lithium, liothyronine, or psychotherapy).[65] Mean HAM-D scores declined from 30.4 at baseline to 13.1 at week 8 and to 6.1 at week 16, with the combination being well tolerated and the most frequently reported adverse events being mild-to-moderate sweating, nausea, and headache.

SSRI plus bupropion. Bupropion, which is structurally related to amphetamine, may act selectively on the noradrenergic and dopaminergic systems, although the evidence is quite weak. While bupropion may, therefore, be of use in augmentation therapy, no controlled studies have been reported. To date, in fact, beneficial effects of bupropion come from case reports and case series. In their study, for example, Boyer and Feighner[66] reported that 35% of patients achieved a moderate or marked response when treated with fluoxetine in combination with bupropion, all patients having previously failed on either treatment alone. More recently, a study in a similar group of patients reported a 70% response rate for combination therapy.[67] One disadvantage of the combination, however, was that over one third of patients experienced notable side effects.[68] Concerns have also been raised over an increased risk of seizures during combination therapy with bupropion and SSRIs.[68]

Mirtazapine. Mirtazapine is an antidepressant with multiple mechanisms of action, which include antagonism at α_2-adrenoceptors. To date, little information exists on the efficacy of mirtazapine in augmentation strategies. In one recently published study of 20 patients with major depression or dysthymic disorder who had not responded to standard antidepressants, Carpenter et al.[69] administered open-label mirtazapine, 15 to 30 mg/day, for 4 weeks in addition to existing therapy. A total of 55% of patients responded to the combination therapy, although side

Table 6. Efficacy of Switching From One Selective Serotonin Reuptake Inhibitor (SSRI) to Another

Reason for Switching	First Drug	Switched To	Sample Size	Response Rate N/N	Response Rate (%)
SSRI-intolerant					
Brown and Harrison (1995)[110]	Fluoxetine	Sertraline	100	69/91	(75.8)
Thase et al (1997)[111]	Sertraline	Fluoxetine	34	24/34	(70.6)
Overall efficacy in SSRI-intolerant patients			134	93/125	(74.4)
Nonresponsive					
Joffe et al (1996)[112]	SSRI	Different SSRI	55	28/55	(50.9)
Zarate et al (1996)[113]	Fluoxetine	Sertraline	42	13/31	(41.9)
Thase et al (1997)[111]	Sertraline	Fluoxetine			
	Low dose (50 mg/d)		30	21/30	(70.0)
	Medium dose (75–100 mg/d)		20	8/20	(40.0)
	High dose (≥ 150 mg/d)		22	13/22	(59.1)
Overall efficacy in nonresponders			169	83/158	(52.5)

effects such as weight gain and sedation were common. The role of augmentation therapy with mirtazapine therefore awaits confirmation from studies performed under randomized, placebo-controlled conditions as well as a detailed examination of potential drug interactions.

Switching Therapy

SSRI switch to another SSRI. On first impression, it would seem highly logical that a patient who fails to respond to inhibition of serotonin reuptake with one SSRI would not respond to a second SSRI. However, SSRIs share the property of serotonin reuptake blockade but have other distinct neurochemical effects. Moreover, if treatment resistance was explained by poor compliance as a result of side effects, then a second SSRI with improved tolerability may achieve greater compliance and therefore treatment response.

Several studies have evaluated the efficacy of switching patients from one SSRI to another, focusing on patients either intolerant to or unresponsive to the first agent (Table 6). Although response rates of up to 75.8% were observed in some studies, all were of an open-label design, and none included a randomly assigned comparator group. Moreover, the higher response rates were observed for patients switched to a second agent that led to improved tolerability; response rates were poorer for those patients who showed no response to the first agent. Such findings suggest that one major determinant of success with SSRIs relates to tolerability.

SSRI switch to TCA. Few studies have been published on switching patients from an SSRI to a TCA, mainly because of the improved safety of newer agents. In one double-blind study, however, 11 (73%) of 15 patients who failed to respond to paroxetine did respond when switched to imipramine.[70]

SSRI switch to reboxetine. As previously discussed, switching to a non-SSRI antidepressant is a popular choice for patients who fail to respond to an adequate trial of SSRI monotherapy. Although the choice of switching therapy is wide, there is a clear neuropharmacologic and clinical rationale to switch to an agent that has noradrenergic properties. Several studies have demonstrated the efficacy and favorable tolerability of reboxetine in the short- and long-term treatment of major depression as monotherapy compared with placebo, imipramine, desipramine, and fluoxetine.[71–74] Reboxetine may also provide benefits in terms of improved social functioning, leading to better compliance with treatment, improved quality of life, and pharmacoeconomic implications (e.g., reduced costs to employers and individuals as a result of days lost to work and decreased productivity).[75] Importantly, reboxetine has been shown to have a low potential for drug-drug interactions[76] and may, therefore, offer a safer alternative to noradrenergic TCAs for augmentation or switching therapy.

The efficacy and safety of switching treatment-resistant patients from fluoxetine to reboxetine was recently reported by Faya et al.[77] In a multicenter open-label study, 128 patients not adequately responsive to 6 to 12 weeks' fluoxetine therapy (HAM-D score ≥ 18) were immediately switched to reboxetine, 8 mg/day, for 8 weeks (dosage increment to 10 mg/day was possible after 4 weeks, if necessary). No washout period was used to offset the risk of withdrawal symptoms. Overall, a significant reduction in mean HAM-D score was apparent from week 1 of switching onward. The study also evaluated tolerability, with special reference to weeks 1 to 4 to allow for the possibility of the continued presence of fluoxetine and its metabolite. The most common adverse events during this period were headache, insomnia, dry mouth, diaphoresis, and constipation, all of which decreased in frequency from week 4 onward. This profile of a reduction of adverse events over time probably reflects gradual elimination of fluoxetine during the earlier period of switching to reboxetine. Taken together, these findings suggest that immediate switching to reboxetine is a safe and effective approach for depressed patients who do not respond to fluoxetine and support the neuropharmacologic rationale

that switching to an antidepressant with a different mode of action is a successful switching strategy.

SSRI switch to mirtazapine. Mirtazapine has a dual mechanism of action, in that it enhances both noradrenergic and serotonergic transmission. Switching to open-label treatment with mirtazapine, 15 to 45 mg/day, was recently investigated in 102 patients who failed to respond to treatment with an SSRI.[78] The overall response rate was 47%. Interestingly, the authors showed that abrupt switching did not lead to tolerability concerns and therefore use of a washout period (which can place the patient at risk of withdrawal symptoms) may not be necessary.

Switching to venlafaxine or milnacipran. Venlafaxine and milnacipran exhibit dual mechanisms of action, inhibiting both serotonin and norepinephrine reuptake without the anticholinergic and cardiovascular effects of the TCAs.[5,79] At present, no information exists on the use of milnacipran in partial responders or nonresponders. However, 3 studies have investigated the efficacy of switching to venlafaxine from various antidepressant therapies. Nierenberg et al.[80] studied 84 patients with severe, treatment-resistant depression treated with open-label venlafaxine. After 12 weeks of treatment, 17% had achieved a partial response and 16% met criteria for full response. Of these patients, however, only 46% maintained response to week 24. Saiz-Ruiz and colleagues[81] investigated the efficacy of venlafaxine (75–375 mg/day) in 59 depressed patients who had no therapeutic response to at least 4 weeks of treatment with an SSRI. After 6 months of treatment with venlafaxine, 81.4% of patients were classed as responders (mean decrease in HAM-D total score ≥ 50%). The mean HAM-D total score at study endpoint was 7.4 points. In a later study, de Montigny et al.[82] recruited 159 patients with treatment-resistant depression who were switched to open-label treatment with venlafaxine. After 8 weeks' treatment at an average dosage of 260 mg/day, 58% of patients had responded and 28% had remitted. Venlafaxine is associated with side effects such as headache, insomnia, nausea, constipation, diaphoresis, and xerostomia.

AUGMENTATION AND SWITCHING THERAPY IN CLINICAL PRACTICE

Faced with the wealth of generally insufficient data on augmentation and switching in the medical literature, it is not difficult to see why there is such a diversity of "next step" approaches adopted when physicians encounter a patient who either fails on or achieves a partial response to antidepressant therapy. In the absence of consensus-derived algorithms, many physicians have resorted to developing their own protocols for managing such patients. A recent survey of attendees at a psychopharmacology review course, for example, showed that most would switch a hypothetical patient showing no response to a 4-week course of adequate SSRI treatment to a non-SSRI drug, while others would consider augmentation, raising the dosage, or switching to a different SSRI.[83] The profile of survey responses differed for a patient achieving partial response, for whom an increase in dosage was the preferred strategy followed by augmentation and switching to a non-SSRI. In terms of strategies for augmentation of SSRI therapy, studies show a wide divergence in perceived efficacy of augmenting agents and hence their usage.[84]

Clearly, a need exists for physicians to be provided with evidence-based guidance for treating partial responders or nonresponders to antidepressant therapy. Part of the problem in doing so, however, is that patients in clinical trials of augmentation and switching therapy typically represent a carefully selected cohort in order to ensure comparable baseline populations. In clinical practice, patients often present with more complex affective disorders with comorbid anxiety disorders and are likely to be receiving more complex drug regimens. Furthermore, determination of response is highly individual and does not necessarily correspond to that performed under controlled, clinical trial conditions.

For example, social functioning of the patient is an important aspect of his or her response to treatment, yet no such measures are incorporated into current definitions of response. Other limitations include the lack of double-blind studies and the heterogeneous profile of patients within any one study (e.g., inclusion of patients who responded poorly to one previous medication as well as those who may have tried several previous therapies), ethical considerations over the use of placebo (despite the fact that studies should be controlled because a high placebo response is common), and the fact that patient numbers are often too small to draw definitive conclusions on the advantages of one strategy over another. There is also little concordance between studies in terms of the definition of partial response, and few studies have evaluated the efficacy of continuation and maintenance therapy for the prevention of relapse and recurrence, respectively. The ongoing Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study[85] funded by the National Institute of Mental Health seeks to address such questions, and the results of this 5-year study are eagerly awaited. Finally, a clear need exists to perform a controlled "head-to-head" study of augmentation versus switching therapy.

Safety Issues

Although there are a number of questions to be answered concerning augmentation and switching therapy, it is obvious that such strategies represent viable options for those patients who have an inadequate response to monotherapy. For augmentation therapy in particular, an overriding issue concerns the safety of such regimens as most studies to date have been too small and of limited duration

to draw definitive conclusions.[86] The greatest concern is that combined therapy with 2 agents that exert effects on the serotonergic system could lead to the "serotonin syndrome," consisting of cognitive (confusion, disorientation), autonomic (fever, shivering, diarrhea, diaphoresis), and neuromuscular (restlessness, hyperreflexia, myoclonus, tremor) effects and hypomania.

Indeed, numerous case reports describe incidences of the serotonin syndrome in patients treated with an SSRI in combination with a second antidepressant that acts on the serotonergic system, such as trazodone,[87,88] nefazodone,[89,90] or venlafaxine.[91] Serotonin syndrome has also been reported when lithium was used in combination with fluoxetine.[92] However, this potentially fatal syndrome is not unique to situations where antidepressants are used in combination. Recently, for example, a case report by Lee and Lee[93] described the occurrence of the serotonin syndrome following concomitant use of erythromycin in a 12-year-old boy receiving sertraline for severe obsessive-compulsive disorder and phobia. The onset of syndrome was attributed to a metabolic interaction between the 2 agents, leading to elevated serum levels of sertraline. Indeed, physicians should carefully consider the potential for drug-drug interactions with antidepressants, the majority of which are metabolized by CYP2D6.[94] Interestingly, some SSRIs act as inhibitors of this enzyme, potently in the case of fluoxetine, its active metabolite (norfluoxetine), and paroxetine,[95,96] which can lead to interactions with other drugs metabolized by this enzyme such as antiarrhythmics, several β-adrenoceptor antagonists, and a number of opioids. In contrast, only a few antidepressants, including nefazadone, venlafaxine, and reboxetine (which is devoid of an effect on CYP2D6 activity[97]), are metabolized by the CYP3A4 pathway, with some antidepressants showing potent inhibition of this enzyme (e.g., nefazadone, fluvoxamine). This is an important consideration because the CYP3A4 isoform is involved in the biotransformation of numerous therapeutic agents.[98]

Although a number of studies have investigated the efficacy of augmentation therapy with an SSRI and a TCA, in vivo evidence suggests the potential for a clinically relevant interaction between such agents.[99] Increased plasma concentrations of TCAs are apparent during coadministration with some SSRIs, which might explain the efficacy of these drugs when used in combination for treatment-resistant depression, although this has been associated with an increased risk of adverse events and serious complications (e.g., delirium, grand mal seizures).[100] As such, TCA therapy should be initiated at a low dose when used to augment SSRI treatment, with titration to an effective dose performed in parallel with monitoring of TCA levels.[86] Isolated cases of anticholinergic toxic syndrome have also been reported for other antidepressants used in combination with a TCA, including venlafaxine.[101]

Is There a Recommended Strategy?

A number of review articles have been previously published in an attempt to provide guidance on the management of treatment-resistant depression. Nelson,[102] for example, concluded that response rates were generally similar for augmentation and switching, advising that switching therapy (e.g., from a SSRI to a drug of different class) may be preferable for patients with mild-to-moderate depression. In contrast, augmentation (e.g., lithium, SSRI plus TCA, or addition of buspirone/stimulants) was proposed as the treatment of choice for patients with severe depression or those with a more refractory history. More recently, the Texas Medication Algorithm Project reached similar conclusions for the management of partial responders.[103,104] Thus, switching was advocated for patients with no history of prior treatment failure and those who quickly develop an intolerance to initial therapy, while augmentation was preferable for patients with a history of prior treatment failures.

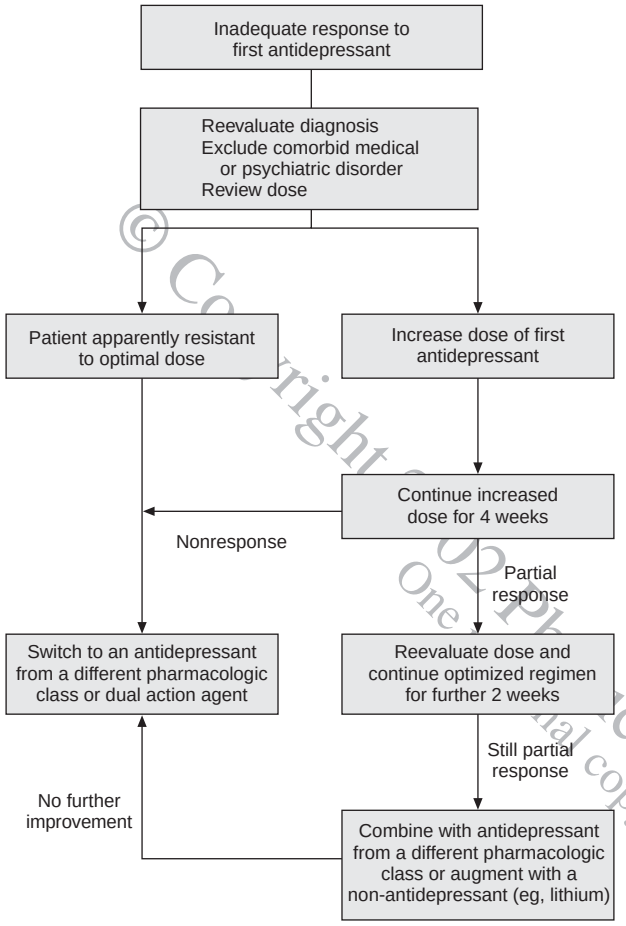
When Should Treatment be Changed?

It is well recognized that a lag in onset of efficacy is apparent for antidepressant therapy, which needs to be taken into account when deciding on a timeline for changing treatment. In their large observation study, for example, Quitkin et al.[105] recommended that treatment should be changed after 4 weeks if there was no apparent improvement within this time frame, with a further 1 to 2 weeks' treatment for those patients showing minimal levels of improvement. However, patients included in this study were treated with TCAs, MAOIs, or mianserin. On the basis of more recent data and clinical experience, particularly with SSRIs, the 4-week timeline for intervention would appear to be appropriate for those patients who fail to respond at an adequate dosage (i.e., < 25% decrease in the MADRS or HAM-D score). For those patients who achieve a partial response on first-line therapy (i.e., 25%–50% decrease in MADRS or HAM-D score), treatment should continue for 6 to 8 weeks at an adequate dosage before considering a change in therapeutic management.

Management of the Patient With Apparent Treatment Resistance

The management of a patient with an inadequate response to antidepressant therapy, whether the response is partial or nonexistent, is best approached in a step-wise manner (Figure 1). Thus, the first step involves a careful reevaluation of the appropriateness of the current diagnosis, followed by the exclusion of contributing factors such as psychiatric or medical comorbidity and concomitant drug therapy. The next step involves reevaluation of the adequacy of current treatment in terms of dosage, duration, and compliance.[17] Patients for whom no confounding factors are identified and yet who still remain symptomatic are candidates for combination, augmentation, or switching therapy.

Figure 1. The Step-Wise Approach to Management of the Patient With an Inadequate Response to Antidepressant Therapy



CONCLUSIONS

Management of the patient who fails to adequately respond to first-line antidepressant monotherapy poses a unique challenge. With the advent of new antidepressants, physicians now have a wide range of treatment choices for such patients, including augmentation and switching strategies.

Looking to the future, vagus nerve stimulation[106,107] and augmentation of SSRIs with atypical neuroleptics may add to the clinical choices available.[105,107–109] The choice of whether to use an augmentation approach or switch to a different agent can be largely driven by the response to the initial course of treatment and by taking into account the neuropharmacologic profile of available agents. Given that depression involves both the noradrenergic and serotonergic systems, a strong rationale exists to simultaneously target both systems as part of an augmentation strategy. This approach seems highly appropriate for those patients achieving a partial response to monotherapy. Similarly, switching to an agent of a different class appears to be a scientifically sound therapeutic approach for those patients who fail to improve on first-line therapy (e.g., an SSRI).

One potential limitation, however, is the lack of controlled clinical trials to aid further decision making in terms of the optimal agent to use in augmentation and switching strategies. Safety issues, such as the risk of serotonin syndrome when drugs that each have serotonergic effects are used in combination, also need to be resolved. One potential means by which such problems can be circumvented is by using a second agent that has a selective neuropharmacologic profile distinct from that of the agent which it either is combined with or replaces.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa), clonidine (Catapres and others), desipramine (Norpramin and others), erythromycin (Ery-Tab, E-Mycin, and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), liothyronine (Cytomel and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil), pindolol (Visken and others), trazodone (Desyrel and others), venlafaxine (Effexor).

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