What Role Do Atypical Antipsychotic Drugs Have in Treatment-Resistant Depression?

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Despite significant advances in the treatment of depression, many patients fail to respond to treatment with adequate dose and duration. Multiple therapeutic approaches are available for the treatment of patients not responding to standard antidepressant medication. These include switching medication or combination and augmentation strategies. A substantial number of patients do not respond to multiple treatment trials. These patients suffer from treatment-resistant depression (TRD) and represent a challenge to the treating physician. There have been a growing number of reports on the use of atypical antipsychotics as augmenting agents in nonpsychotic TRD. Second-generation antipsychotics are less likely to provoke parkinsonian side effects. It has also been reported that these agents produce lower rates of tardive movement disorders than traditional neuroleptics. Furthermore, second-generation antipsychotics are serotonin-2A/2C antagonists, possibly allowing them to improve the efficacy and some aspects of the side effect profile of selective serotonin reuptake inhibitors (SSRIs). Weight gain and sedation are likely to be the most common adverse events of such combined therapy. In a recent controlled clinical trial, the atypical antipsychotic olanzapine was combined with fluoxetine therapy in an 8-week, double-blind clinical trial in patients with TRD. This combination drug therapy demonstrated clinical efficacy on several rating scales and showed rapid onset of action. Although more studies will be required to confirm and extend these findings, the results suggest that there may be a clinical benefit to combining atypical antipsychotics with SSRIs in nonpsychotic TRD.

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Depressive disorders are common but potentially chronic, and relapsing conditions can have devastating psychosocial consequences.[1] Unfortunately, a significant minority of those affected by depression fail to respond to standard antidepressant treatments.[2] Indeed, it is hard to imagine a practicing general psychiatrist who does not regularly encounter patients with depression who have failed to respond to multiple medication trials. There is thus great interest in each new therapeutic development that may, or may not, benefit patients with treatment-resistant depression (TRD). Recently, there have been a number of reports describing the use of atypical antipsychotic medications in the management of depression, depressive symptoms, and TRD.[3–7] In this article, current strategies for dealing with TRD will be reviewed briefly, and clinical and preclinical studies that suggest that atypical antipsychotics may offer a viable option as an augmenting agent in TRD will be examined.

DEFINITION OF TREATMENT-RESISTANT DEPRESSION

Nonresponse to a trial of an antidepressant is often defined as a failure to respond to 6 weeks of therapy administered at adequate doses.[8] It can then be said that the patient's depression is resistant to drug A, analogous to the way that a bacterial infection is classified in relation to different antibiotics. A more generic use of the term *treatment-resistant depression* has been proposed, for example, nonresponse to at least 2 trials of antidepressants (adequate dose and duration) from at least 2 different classes.[9] Thase and Rush[10] have proposed a staging system for TRD (Table 1) ranging from failure of a single agent (stage 1) to failure of multiple agents and electroconvulsive therapy (stage 5). In the contemporary practice, stage 2 resistance (e.g., failure to respond to at least 2 adequate trials with medication from different pharmacologic classes) represents a minimal definition of TRD. Likewise, Thase and Rush recommended reserving the term *refractory depression* to describe patients in stage 5 TRD.[10]

CLINICAL MANAGEMENT OF TREATMENT-RESISTANT DEPRESSION

In the decade following the introduction of fluoxetine, selective serotonin reuptake inhibitors (SSRIs) largely

Table 1. Proposed Staging Criteria for Treatment-Resistant Depression[a]

Stage	Description
1	Failure of at least one adequate trial of a major class of antidepressant
2	Stage 1 resistance plus failure of an adequate trial of an antidepressant from a distinctly different class
3	Stage 2 resistance plus failure of an adequate trial of a tricyclic antidepressant
4	Stage 3 resistance plus failure of an adequate trial of a monoamine oxidase inhibitor
5	Stage 4 resistance plus failure of a course of bilateral electroconvulsive therapy

[a]Adapted from Thase and Rush.[10]

Table 2. Effectiveness of Switching Strategies in Treatment-Resistant Depression[a]

Failed Agent	Second Agent	Response Rate (%)
Selective serotonin reuptake inhibitor	Other selective serotonin reuptake inhibitors	50–60
	Tricyclic antidepressant	46–73
	Venlafaxine	33–70
	Bupropion	56
	Mirtazapine	67

[a]Adapted from Howland and Thase.[16]

supplanted tricyclic antidepressants (TCAs) as the first-line treatment of depression. Consequently, most patients with TRD have likely failed 1 or 2 SSRI trials. Although other types of antidepressants also can be considered first-line strategies, this review will focus on the management of patients initially treated with SSRIs. Regardless of the selection of first medication, however, it is important that the clinician makes several distinctions in evaluating such a case. In turn I will consider adherence, inadequate dosing (optimization), and diagnostic issues. Lastly, I will discuss the distinction between nonresponse and partial response and how to appropriately manage each of these common clinical situations.

Adherence

The first consideration is whether the patient has adhered to the prescribed medication regimen. Nonadherence has been estimated to account for as many as 20% of cases considered to be treatment resistant.[11] In some cases, side effects may account for the patient's decision not to take the antidepressant as prescribed. Careful assessment of side effects and appropriate revisions of the treatment plan (e.g., dose adjustment, switching, or use of adjuvant agents) can improve adherence and increase the likelihood of treatment response. The psychiatrist's ability to generate and sustain a therapeutic alliance is important and may facilitate frank discussion about the "downside" of taking antidepressants, including more sensitive matters (e.g., talking about the patient's sexual function, critical or demeaning comments, or ambivalence about the prospects of having a stigmatic mental illness).

Optimization

Full adherence does not ensure response if the antidepressant trial is too short or at too low a dose. Optimizing an ongoing antidepressant trial may mean increasing the dose of the current medication or extending the length of the trial. Clinical experience and published studies have found that patients experiencing an insufficient response to the usual dose of a standard therapy have a 20% to 30% chance of responding to higher doses.[12–15] Some studies have found that a lack of improvement in the first 4 weeks of an antidepressant trial predicts poor response in subsequent weeks unless a change is implemented.[16–18] Combining these recommendations, Thase and Rush[10] suggested a 4-week trial of an antidepressant at usual clinical doses, followed by 1 to 2 more weeks at maximally tolerated doses before switching. We would endorse this recommendation with the caveat that in some cases patient factors may warrant a dosage increase sooner than 4 weeks.

Diagnostic Review

Nonresponse may be attributable to misdiagnosis or failure to detect a complicating medical condition. Relatively common comorbidities that can reduce the probability of antidepressant response include hypothyroidism, substance abuse, and anxiety disorders. On occasion, the comorbidity may not be treatable (e.g., advanced cancer of the head or pancreas). Nevertheless, this possibility should not deter the search for treatable medical causes of treatment resistance.

Nonresponse

In the case of nonresponse despite adherence to optimized antidepressant therapy, the ineffective medication may be tapered and a different antidepressant started (e.g., "switching strategy"). The question of which antidepressant medication to try next is often dictated by clinical factors (the class of agent that failed in the first trial, comorbid medical conditions, interactions with other medications, side effects, etc.). Studies have shown that the response rate, when switching from one antidepressant to another, typically ranges from 40% to 60% across many different classes of antidepressants. The outcomes from such studies are summarized in Table 2.[16] The values in Table 2 are a range of values taken from various studies and represent a rough guideline of what can be expected from a switching strategy. Augmentation strategies described below have not been studied in the cases of nonresponse. The decision whether to switch or augment remains a question of clinician preference.

Unfortunately, a 50% response rate to the second antidepressant means that a significant number of patients who began therapy (about 25% of the group) have developed stage 2 resistance.

Table 3. Various Augmentation Strategies in Treatment-Resistant Depression[a]

Augmenting Agent	Controlled Studies With SSRIs	Efficacy	Comments
Lithium	Yes	++	Targets serotonin transmission
Thyroid hormone	No	+	Safe in combination with SSRI
Additional antidepressant	None yet published	+	Possible drug-drug interactions in SSRI-TCA combinations
Stimulants	No	+/–	Popular, but few studies in combination with SSRIs
Dopamine agonists	Yes	+/–	Pramipexole, bromocriptine
Buspirone	Yes	+/–	May treat persistent anxiety and SSRI-induced sexual dysfunction

[a]Adapted from text of Thase and Rush[10] and Howland and Thase.[16] Abbreviations: SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant. Symbols: + = some evidence, ++ = much evidence, +/– = inconsistent findings.

Partial Response and Augmentation

At some point in the treatment algorithm, a patient may exhibit a partial but insufficient response to an antidepressant trial (e.g., only a 40% reduction in symptom severity). Assuming that the current treatment has already been optimized, partial response to an antidepressant presents the clinician with the dilemma of whether to switch to another agent or to attempt to augment the agent that yielded the partial response. Switching the antidepressant often has the disadvantage that time is lost as the first agent is tapered and the second agent is gradually titrated. The alternative strategy to switching is to augment the current antidepressant medication—that is, maintaining the current antidepressant and adding another agent to improve symptomatic response.

CONVENTIONAL AUGMENTATION STRATEGIES

The literature documenting open trials and anecdotal case series is plentiful, but there is a lack of double-blind trials that test many of the common augmentation strategies currently in practice. The discrepancy between what is done in everyday practice and what has been learned from well-controlled trials points out the inadequacies of the current system of funding research. Clearly, there is a great need for more controlled clinical trials of augmentation strategies in TRD in order to give more guidance to practitioners. Consequently, the choice among different augmentation strategies is often dictated by clinician preference and multiple patient factors (such as comorbid anxiety, mood instability, etc.).

Most of the controlled studies of augmentation strategies have dealt with augmenting TCAs. Because TCAs are primarily noradrenergic, it cannot be assumed that these augmentation strategies will be applicable to SSRIs. Thus, controlled studies with SSRIs and different augmenting agents are urgently needed to anchor contemporary practice with empirical evidence. Common augmentation strategies are described below and summarized in Table 3.

Lithium

Lithium salts have modest antidepressant effects for nonbipolar depression and, of course, broaden the "coverage" of pharmacotherapy for patients with as yet unrecognized bipolar disorders. Lithium augmentation (typically at lower plasma levels, e.g., 0.5 to 0.8 mEq/L) is the best-studied augmentation strategy for TCA nonresponders. Only 3 controlled studies have evaluated the combination of lithium and SSRIs.[13,19,20] Although this combination is generally well tolerated, given that lithium is thought to potentiate serotonergic transmission there is a theoretical risk of serotonin syndrome.[16] Also, it is possible that certain serotonergically mediated side effects, including diarrhea and other gastrointestinal disturbances, may be exaggerated when lithium and SSRIs are used concurrently.

Thyroid Hormone

Thyroid augmentation (generally liothyronine [T_3], 25 to 50 μg/day) has not been validated in combination with SSRIs by controlled clinical trials. However, there are anecdotal reports of benefit, and the combination is certainly safe and well tolerated.[16] Unlike lithium, thyroid hormone is thought to potentiate the noradrenergic system, which may suggest that thyroid supplementation may be more useful when combined with TCAs than with SSRIs. In any event, thyroid augmentation is a valuable strategy for the minority of antidepressant nonresponders who have subtle or subclinical thyroid dysfunction.

Tricyclic Augmentation

Adding TCAs to SSRIs has been suggested to be effective in several uncontrolled studies.[21,22] However, the addition of low-dose desipramine to fluoxetine was relatively ineffective in the one small, double-blind trial evaluating this strategy.[13] Clinicians sometimes pick more antihistaminically active tertiary amine tricyclics to provide extra benefits to patients with insomnia. Ultimately, however, it may be the more noradrenergic secondary amine TCAs and metabolites that result in the true augmentation of therapeutic effects by adding a second mechanism of action to the mix. The addition of a TCA to an SSRI must be done with attention to potential metabolic interactions between the 2 agents (e.g., cytochrome P450 1A2 or 2D6 inhibition by SSRIs) that can inhibit metabolism of the TCA. For this reason, TCA additions to an

SSRI should start with low doses and be accompanied by careful monitoring of plasma TCA levels and serial electrocardiograms.

Dopamine Agonists

Although augmenting dopaminergic function has become a common strategy for TRD, it has virtually no empirical basis.[24,25] Most antidepressants have little effect on dopaminergic function, and dysfunctional dopamine neurotransmission is clearly implicated in symptoms such as anhedonia and psychomotor retardation. The psychostimulants are grouped in this category because they indirectly promote dopamine release in relevant terminal fields of the brain. Many of these drugs also have significant noradrenergic effects. Small, open trials and anecdotal case reports generally suggest that stimulants have beneficial effects in TRD.[25–28] Moreover, stimulants are combined with SSRIs either to counteract SSRI-induced fatigue or to remedy sexual dysfunction.[24]

Direct dopamine agonists have also been reported to be useful in antidepressant augmentation strategies. For example, pramipexole, a D_2/D_3 dopamine receptor agonist, was shown to be more effective than placebo in improving symptoms in subjects with nonpsychotic major depression.[29] Bromocriptine, a direct-acting D_2 dopamine receptor agonist, was reported to be useful as an augmenting agent in depression[30,31] and as monotherapy in open trials.[32–34] Use of direct dopamine agonists is limited by side effects such as nausea.[29,35]

USE OF ATYPICAL ANTIPSYCHOTICS IN AFFECTIVE DISORDERS

The use of antipsychotics in depression has a long history. However, until the advent of the newer atypical agents, the use of antipsychotics in affective disorders has been limited to psychotic depression and mania because of the risk of tardive dyskinesia. In this section, the rationale for the use of antipsychotic medications in depression is reviewed and whether the new generation of atypical antipsychotics hold promise as augmenting agents in nonpsychotic TRD is considered.

Antipsychotics and Affective Disorders: A Historical Perspective

The first TCA, imipramine, was discovered as part of the search for alternatives for the neuroleptic chlorpromazine. Although it was recognized that these 2 medications had different clinical effects, early clinical trials nonetheless explored the use of phenothiazine antipsychotics as a treatment for depression. For example, between 1960 and 1976, chlorpromazine and thioridazine were studied for depression in 17 double-blind trials, involving nearly 1700 patients.[36] Looking across studies, phenothiazine antipsychotics were found superior to placebo and comparable to antidepressants.[36] Antipsychotic therapy was, however, consistently associated with a greater incidence of extrapyramidal side effects than TCAs in these studies.[36]

Although the use of phenothiazine antipsychotics in nonpsychotic depression as monotherapy never became widespread, the use of antipsychotic agents in depressive disorders is not a new idea. Further, the combination of a neuroleptic and an antidepressant has been established as a treatment of first choice for the psychotic or delusional forms of major depressive disorder.[37] Likewise, adjunctive therapy with typical, higher-potency neuroleptics such as perphenazine or haloperidol was commonly undertaken (in combination with antidepressants) for patients with more severe, agitated, or "near psychotic" depressions.[38] Given the superiority of the newer antipsychotic medications such as olanzapine, quetiapine, and risperidone in terms of lower rates of extrapyramidal symptoms and (in all likelihood) lifetime risk of tardive dyskinesia, investigators have begun to examine the use of atypical antipsychotics in affective disorders.

Atypical Antipsychotics and Psychotic Depression

Several case reports and small clinical series have reported that the atypical antipsychotics appeared to have beneficial properties in psychotic mood disorders, including use as monotherapy.[4,39–43] Although these findings have not been confirmed by double-blind, controlled clinical trials, it appears that the newer agents will prove to be at least equally efficacious as the traditional neuroleptics in psychotic depression. In addition, there is some promise that atypical antipsychotics may be beneficial as monotherapies. Given equal efficacy, the tolerability of the atypical antipsychotics compared with that of the older agents is an important advantage.

Are Atypical Antipsychotics Useful in TRD Without Psychotic Features?

There have been a growing number of reports describing the use of atypical antipsychotics as augmentation strategy in nonpsychotic TRD. For example, Ostroff and Nelson[6] reported on 8 patients with nonpsychotic major depression who had failed to respond to an SSRI alone. They found that the addition of risperidone was shown to have beneficial effects in all cases.[6] In a case report, the addition of risperidone to tranylcypromine also resulted in improvement.[44] In the only published report of a controlled clinical trial to date, olanzapine was combined with fluoxetine therapy in an 8-week, double-blind clinical trial in patients demonstrating stage 2 treatment resistance.[45] The combination drug therapy demonstrated clinical efficacy on several rating scales and was shown to result in more responders than either olanzapine or fluoxetine alone.[45] The combination of olanzapine plus fluoxetine also had a more rapid onset of action than either agent alone. Although more research is required to confirm these findings, these studies suggest that there may be clinical benefit to combining atypical antipsychotics with SSRIs in nonpsychotic TRD. In particular, the increased efficacy and more rapid onset of action suggest that the olanzapine-plus-fluoxetine combination may hold great promise in TRD.

Neuropharmacologic Rationale for Atypical Antipsychotic Efficacy in TRD

Why might atypical antipsychotics be effective in augmenting an antidepressant effect in TRD? Although it may be argued that the addition of an antipsychotic is treating an unrecognized psychotic state, this explanation seems unlikely in accounting for all of the cases that have been reported to date. Another explanation may lie in the neural effects of the atypical antipsychotic medications. The unique properties of atypical antipsychotics on various neurotransmitter systems are discussed in the next section.

PRECLINICAL STUDIES OF ATYPICAL ANTIPSYCHOTICS

Early models of the neuropharmacology of antidepressant response suggested that the medications were effective because they reversed or corrected a deficit state involving one or another of the monoamine neurotransmitters. Thus, the logic of adding stimulants or dopamine receptor agonists to augment the effects of antidepressants makes intuitive sense because the goal (i.e., to enhance dopamine transmission in the brain) is to augment an SSRI or TCA effect. There has long been a hypothesis that dopamine plays an important role in depression, linking the involvement of dopaminergic systems in psychomotor activity, motivation, pleasure, and appetite with the symptoms of depression.[46] Likewise, the rationale for the use of antipsychotics in delusional depression is straightforward because blockade of postsynaptic dopamine receptors can control a functionally hyperdopaminergic state. The paradox of apparently agonist and antagonist effects on dopamine neurotransmission is not unlike what is observed in treatment of schizophrenia with atypical antipsychotics, i.e., relief of both negative and positive symptoms. To better understand how atypical antipsychotics may work, preclinical animal studies will be reviewed to examine the effect of atypical antipsychotics on various relevant brain systems.

Effects of Clozapine on Neuronal Activation

The atypical antipsychotic clozapine has vastly different effects on various neural systems when compared with a typical antipsychotic medication such as haloperidol. For example, clozapine selectively increases the burst firing of dopamine neurons projecting to limbic brain regions, whereas the antipsychotic haloperidol does not.[47] Clozapine produces a different anatomic pattern of neuronal activation in the prefrontal cortex compared with haloperidol. Haloperidol activates neurons in the basal ganglia regions such as the striatum, whereas clozapine has no effect in the striatum but large activation effects in limbic regions such as the nucleus accumbens, as well as the frontal cortex.[48–50] Since clozapine, unlike haloperidol, spares the striatum, this difference is thought to explain the absence of extrapyramidal side effects. Similarly, the effect of clozapine on cell firing in the prefrontal cortex might underlie the greater effects on negative symptoms of schizophrenia as compared with conventional neuroleptics.[48] Prefrontal cortical activation may also have salutary effects on mood. Many of the new atypical agents have effects on the prefrontal cortex comparable to those of clozapine.

Table 4. Effects of Atypical Antipsychotics on Neurotransmitter Release in the Prefrontal Cortex[a]

Drug	Serotonin	Norepinephrine	Dopamine
Clozapine	0	++	++
Olanzapine	0	++	+
Risperidone	0	+	+
Haloperidol	–	0	+/–

[a]Data from Zhang et al.[52] Symbols: + = modest effect, ++ = large effect, +/– = inconsistent effect, – = small decrease, 0 = no effect.

Effects of Atypical Antipsychotics on Dopamine and Norepinephrine Release

Recently, the effects of different antipsychotic medications on the real-time release of dopamine and norepinephrine in the brain have been studied. Consistent with its effect on dopamine neuronal firing, clozapine selectively increases dopamine release in the prefrontal cortex but not in the striatum.[51] As seen in Table 4, olanzapine and risperidone also increase dopamine release in the prefrontal cortex, whereas haloperidol does not. Moreover, typical neuroleptics increase dopamine release in the striatum but have no effect in the prefrontal cortex.[51] Clozapine and olanzapine also increase norepinephrine release in the prefrontal cortex.[52,53] In contrast, risperidone alone has a more modest effect on norepinephrine and dopamine release in the prefrontal cortex (Table 4).[52] The clinical consequences of these neurochemical differences have not been determined and definitely warrant further study.

Effects of Atypical Antipsychotics Plus SSRIs on Neurotransmitter Release

Recently, the effect on neurotransmitter release of combining an SSRI with different antipsychotic agents was examined.[52] In that study, rats were administered various antipsychotics alone, fluoxetine alone, or the combination. Table 5 summarizes the effects of the anti-

Table 5. Synergistic Effects of Combining Atypical Antipsychotic Agents and Haloperidol With Fluoxetine on Neurotransmitter Release[a]

Drug + Fluoxetine	Serotonin	Norepinephrine	Dopamine
Clozapine	0	++	–
Olanzapine	–	+++	+++
Risperidone	0	0	++
Haloperidol	0	0	0

[a]Data from Zhang et al.[52] Symbols: ++ = moderate effect, +++ = large effect, – = small decrease, 0 = no effect.

Table 6. Defining Characteristics of Atypical Antipsychotics and Haloperidol[a]

Drug	Acute EPS	Risk of TD	Elevated Prolactin Levels
Clozapine	0	0	0
Risperidone	+/0[b]	?	++
Olanzapine	+/0[b]	?	+/–
Quetiapine	+/0[b]	?	0
Haloperidol	+++	+++	+++

[a]Adapted from Leucht et al.[54] Abbreviations: EPS = extrapyramidal side effects, TD = tardive dyskinesia. Symbols: + = small risk, ++ = moderate risk, +++ = highest risk, +/– = inconsistent risk, 0 = no risk, ? = risk not yet established.
[b]Highly dose-dependent incidence of EPS.

psychotics on neurotransmitter release. Haloperidol had no additive effect on transmitter release when combined with fluoxetine. Risperidone plus fluoxetine had a synergistic effect only on dopamine release, but did not affect norepinephrine levels. By contrast, clozapine plus fluoxetine had an additive effect on norepinephrine release. Olanzapine plus fluoxetine increased the release of both norepinephrine and dopamine (Table 5). Furthermore, the combination of olanzapine and sertraline did not elicit the same amount of norepinephrine release as olanzapine plus fluoxetine.[52] It remains to be seen if these differences have clinically significant implications. Nevertheless, the hypothesis that various antipsychotics and SSRIs do not have interchangeable effects is at least credible and provides a rationale for comparing particular treatment combinations with greater and lesser effects on prefrontal cortex monoamine release.

CLINICAL CONSIDERATIONS IN THE USE OF ATYPICAL ANTIPSYCHOTICS IN TREATMENT-RESISTANT DEPRESSION

In this section, some of the practical issues in the use of atypical antipsychotics will be considered. As several of these compounds have been available for only a few years, some clinicians may be unfamiliar with the similarities and the differences of the atypical antipsychotics.

The Newer Antipsychotics and "Atypicality"

An issue debated in psychiatric literature is whether all of the newer antipsychotics are appropriately termed "atypical," a label originally applied to clozapine. In practical terms, "atypicality" is defined as an antipsychotic effect within the context of a lack of extrapyramidal side effects, no elevation of serum prolactin levels, and a reduction of the negative symptoms associated with schizophrenia. As it turns out, all of the newer antipsychotic agents have beneficial effects on negative symptoms,[53] but how do they compare with clozapine on other parameters of atypicality?

Motor Side Effects

Compared with haloperidol, second-generation antipsychotics are less likely to provoke parkinsonian side effects, although only clozapine can be said to be free of this side effect (Table 6).[54] It has also been reported that these agents will produce lower rates of tardive movement disorders than the traditional neuroleptics.[55,56] However, a reduction of relative risk of tardive dyskinesia remains to be established after long-term use. Clearly, such information will be an important factor in weighing the cost-to-benefit ratio of atypical antipsychotic augmentation in TRD if it is shown that longer-term therapy is needed.

Prolactin Secretion

Hyperprolactinemia is a well-known but often under-recognized side effect of D_2 dopamine receptor blockers. Chronic elevations of this hormone may increase the risk for certain types of cancer and increase bone loss (osteoporosis) and are known to cause menstrual irregularities and amenorrhea.[57–59] Of the new agents, only risperidone has been shown to cause sustained elevation of prolactin levels, with an incidence level of 90% to 100%.[60–63]

Metabolic Effects

There is little debate about whether or not the second-generation antipsychotics are an improvement over first-generation neuroleptics. However, it appears that these agents have an effect on lipid and glucose metabolism. In particular, the newer atypical antipsychotics may increase serum lipids, triglycerides, and glucose.[64–66] Clozapine and olanzapine may be most likely to cause this effect; however, it is too early to say that risperidone and quetiapine have significantly smaller effects on metabolism. Nevertheless, it appears that clozapine and olanzapine cause weight gain.[67,68] The effect of these drugs on metabolism and weight gain are linked to reports of new-onset diabetes mellitus associated with atypical antipsychotic therapy.[69–74] The clinician should monitor changes in body weight and the onset of suggestive somatic symptoms (e.g., fatigue, polydipsia, or polyuria) and treat as required.

Management of Side Effects With Atypical Antipsychotic Therapy

Clinicians have recognized that some of the common side effects of the atypical antipsychotics can be clinically useful in the management of common problems seen in TRD. For example, the sedating properties of quetiapine or olanzapine can be used to help with insomnia associated with TRD. The calming effects of these drugs may also help agitation and extreme anxiety.

Is the Serotonin Receptor Blockade of Atypical Antipsychotics Helpful?

One of the other important characteristics of second-generation antipsychotics is their antagonistic properties at serotonin-2A ($5\text{-}HT_{2A}$) and $5\text{-}HT_{2C}$ receptors. For example, olanzapine exhibits high affinity at both the $5\text{-}HT_{2A}$ (4 nM) and $5\text{-}HT_{2C}$ (11 nM) receptors. Could the inhibition of these serotonin receptors contribute to their efficacy in TRD? The SSRI medications act initially to increase serotonin in the neuronal synapse. Such elevated levels of serotonin nonselectively activate all classes of presynaptic and postsynaptic serotonin receptors. Activation of $5\text{-}HT_{2A/2C}$ receptors is thought to be responsible for some of the side effects of SSRIs, such as agitation/anxiety, insomnia, and sexual dysfunction.[75] The atypical antidepressant nefazodone (a $5\text{-}HT_{2A/2C}$ antagonist and selective norepinephrine reuptake inhibitor) treats anxiety symptoms[76] and induces less agitation than other reuptake blockers.[77] Nefazodone and the $5\text{-}HT_{2A/2C}$ receptor antagonist mirtazapine have lower rates of sexual side effects than the SSRIs.[75,78,79] Thus, $5\text{-}HT_{2A/2C}$ antagonism of atypical antipsychotic medications may improve the efficacy and side effect profile of SSRIs. Whether the blockade of the $5\text{-}HT_{2A/2C}$ receptors effectively treats affective symptoms remains unclear. However, the $5\text{-}HT_{2A/2C}$ antagonist ritanserin has efficacy in the treatment of dysthymia in clinical trials.[80,81] The success of a simple $5\text{-}HT_{2A/2C}$ receptor antagonist in treating dysthymia suggests that blockade of these receptors may indeed play a therapeutic role in the treatment of affective disturbances.

Blockade of $5\text{-}HT_{2A/2C}$ receptors may also have beneficial effects on sleep architecture. Sleep disruption is a core symptom of depression, generally marked by early insomnia and repeated awakenings during the night. Most SSRI medications have been shown to decrease rapid eye movement sleep, prolong sleep latency, worsen sleep efficiency, and increase awakenings in patients with depression.[82] Importantly, medications that block $5\text{-}HT_{2A/2C}$ receptors appear to have more beneficial effects on insomnia. Nefazadone improved sleep architecture by increasing slow-wave sleep and decreasing nocturnal awakenings.[83] Mirtazapine, a potent $5\text{-}HT_{2A/2C}$ antagonist, also had a beneficial effect on sleep maintenance,[84] although this compound is a potent antihistamine. Daytime sedation is, of course, a not uncommon side effect for $5\text{-}HT_{2A/2C}$ antagonists.

Thus, the $5\text{-}HT_{2A/2C}$ antagonist properties of the second-generation antipsychotics may provide additional efficacy when these agents are combined with SSRIs by contributing to improved efficacy (treating affective and anxiety symptoms) and side effect profile (sexual side effects and sleep problems) in TRD.

CONCLUSION

TRD remains an important problem that most clinical psychiatrists must face daily. Usually, potentially antidepressant-responsive and -nonresponsive patients cannot be distinguished beforehand. Some studies have attempted to answer this question using single-photon emission computerized tomography imaging of treatment-refractory subjects, but this type of inquiry is merely the beginning.[23] Unfortunately, the various pathways to TRD remain misunderstood and understudied.

It seems likely that evidence from controlled clinical trials of augmentation strategies for TRD will continue to lag behind clinical experience. When treatments are inexpensive, well tolerated, safe, and rapidly effective, it may be less critical to have definitive data from controlled studies; however, none of the options commonly used for TRD meet these criteria.

With respect to augmentation therapy with an atypical antipsychotic, clinical experience and research suggest fairly good tolerability and safety, good coverage of the "hyperarousal" symptom profile of depression (i.e., insomnia, weight loss, anxiety, agitation), and antipsychotic effects. Until better data are available, clinicians should choose atypical antipsychotics for patients manifesting more severe symptoms and use other strategies when the predominant profile is characterized by anergia, psychomotor slowing, and hypersomnolence. Only time will tell if this commonsense strategy actually improves a patient's chances for successful treatment.

A number of other important questions must be answered. For example, are all newer antipsychotics equally efficacious in TRD? Does the combination work better with some SSRIs than others? What about efficacy in combination with nonserotonergic antidepressants? Are there any patient characteristics that would help the clinician predict who will or will not benefit from antipsychotic and antidepressant combinations? How long should one continue the antipsychotic after remission is achieved? What is the long-term risk of tardive dyskinesia? What are the best methods of limiting metabolic effects?

Clearly, much work needs to be done in studying the combination therapy of newer antipsychotics and antidepressants for TRD. This strategy appears most promising for severely depressed patients who have failed to respond to several other approaches.

Drug names: bupropion (Wellbutrin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), liothyronine (Cytomel, Triostat, and others), mirtazapine (Remeron), nefazadone (Serzone), olanzapine (Zyprexa), perphenazine (Trilafon and others), pramipexole (Mirapex), quetiapine (Seroquel), risperidone (Risperdal), tranylcypromine (Parnate), venlafaxine (Effexor).

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