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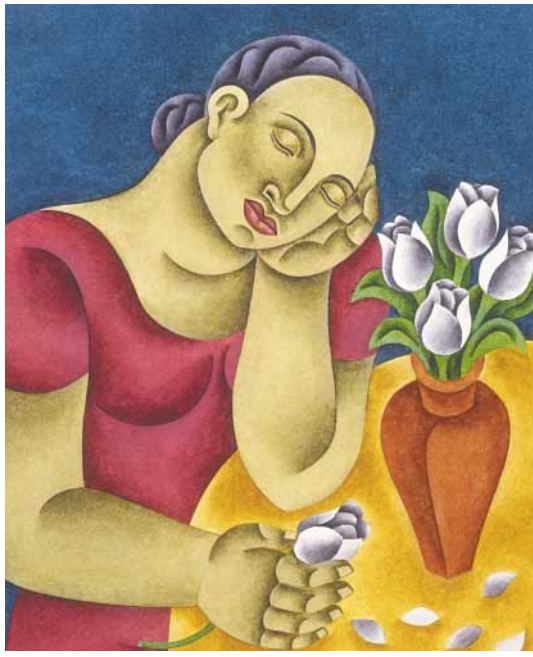
Atypical Antipsychotics in Treatment-Resistant Depression



Atypical Antipsychotic Drug Augmentation in Resistant Major Depressive Disorder

Depression – Treatment and Unmet Medical Needs

Atypical Antipsychotics in Nonpsychotic Disorders

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Treatment-Resistant Depression

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Target Audience

This activity has been developed for psychiatrists and other health care professionals who treat patients diagnosed with major depressive disorder.

Educational Needs

Inadequate treatment of clinical depression remains a challenging problem. Resistance to antidepressants, including selective serotonin reuptake inhibitors, is common. Atypical antipsychotic agents are emerging as beneficial adjunctive therapy for treatment-resistant, nonpsychotic depression. Receptor-binding profiles prognostic of antidepressant activity have been supported by controlled clinical studies. Clinicians should understand the rationale behind augmentation therapy, its molecular basis, and the major role played by dose.

Learning Objectives

By reading and studying this supplement, participants should be able to:

- Describe the treatment challenges encountered in major depressive disorder.
- Discuss atypical antipsychotic agents in terms of mechanisms of action, efficacy, and side effects.
- Identify therapeutic areas other than schizophrenia for which atypical antipsychotic agents are helpful.
- Appreciate the clinical impact of dopamine and serotonin receptor activity and dose of antipsychotic agent.
- Understand the rationale supporting augmentation with antipsychotic agents in treatment-resistant depression.

Faculty and Unapproved Use Disclosures

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

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Introduction

—Maurizio Fava, MD, Chair

Successful treatment of major depressive disorder (MDD) remains challenging. No, or only partial, therapeutic response to selective serotonin reuptake inhibitor (SSRI) monotherapy has been reported in 29% to 46% of depressed patients.[1] Moreover, treatment resistance is common, with nearly 30% of patients not responding and, of the remaining 70%, only 30% to 40% achieving remission.[2] A number of augmentation strategies have been used for treatment-resistant depression, including lithium, thyroid hormone, buspirone, anticonvulsants, stimulants, modafinil, and dopaminergic agents. Conventional antipsychotic agents have long been used to treat psychotic and delusional depression, but atypical antipsychotics, with their milder side-effect profiles, are emerging as beneficial adjunctive therapy for treatment-resistant, nonpsychotic depression.[3]

A growing number of reports suggests that using atypical antipsychotics as augmenting agents can be effective in refractory MDD. Since these second-generation antipsychotic drugs antagonize serotonin-2A/2C (5-hydroxytryptamine $[HT]_{2A/2C}$) as well as dopamine-2 receptors, they may improve the efficacy and some of the side effects associated with SSRIs, the predominant antidepressant drug class. Nevertheless, atypical antipsychotics are a heterogeneous group, each with a distinct and complex set of receptor affinities involving dopamine and 5-HT receptors as well as noradrenergic, histaminergic, and cholinergic systems.

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Atypical Antipsychotic Drug Augmentation in Resistant Major Depressive Disorder

Maurizio Fava, MD and
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Why Would Atypical Antipsychotic Agents Work in Depression?

Extensive evidence implicates dysregulation of noradrenergic, serotonergic, and dopaminergic neurotransmission in the pathophysiology of mood disorders. Receptor-binding profiles of atypical antipsychotics are consistent with putative antidepressant activity.

5-HT_{2A} Antagonism: The reduced liability for movement disorders characteristic of atypical antipsychotic agents is attributable to 5-hydroxytryptamine $(HT)_{2A}$-receptor blockade, which may also address symptoms such as insomnia, agitation, and weight loss and may indirectly enhance 5-HT_{1A}-mediated neurotransmission. The cortical dopamine release triggered by this 5-HT_{2A} blockade may be critical for improvement of cognitive function.

5-HT_{2C} Antagonism: Blockade of 5-HT_{2C} receptors may enhance dopaminergic and noradrenergic neurotransmission,[1,2] thus improving cognitive[3,4] and affective[5,6] symptoms. Theoretically, antipsychotic drugs with high 5-HT_{2C}/D_2 ratios could affect 5-HT_{2C}-receptor antagonism without substantial dopamine-2 (D_2) receptor antagonism at low doses. Clinically, then, low doses of these agents could trigger antidepressant activity without substantial antipsychotic activity.

5-HT_{1A} Agonism: Not only has cognitive improvement following treatment with atypical antipsychotics in schizophrenia been attributed by some researchers to 5-HT_{1A} activity,[7,8] but 5-HT_{1A} agonism also is thought to moderate other nonpsychotic features of schizophrenia, such as anxiety, depression, and hostility.[9] Moreover, selective 5-HT_{1A}-receptor partial agonists, such as buspirone, gepirone, and ipsapirone, have demonstrated antidepressant effects.[10] Distinguishing it from other atypical antipsychotics, ziprasidone and aripiprazole are strong 5-HT_{1A} receptor agonists[11,12] that induce dopamine release in rat prefrontal cortex.[13]

5-HT_{1D} Antagonism: Antagonism of 5-HT_{1D}, a presynaptic autoreceptor inhibiting serotonin release, indicates potential efficacy in major depression.[14] Ziprasidone is the only atypical antipsychotic that potently blocks this receptor, thus disinhibiting 5-HT release.[15]

5-HT and Monoamine Antagonism: Antidepressant efficacy superior to that of selective serotonin reuptake inhibitors (SSRIs) has been reported with

inhibitors of both norepinephrine and 5-HT uptake, such as clomipramine, venlafaxine, and duloxetine, when compared with SSRIs.[10] Ziprasidone was several orders of magnitude more potent than olanzapine, quetiapine, and risperidone at human serotonin, norepinephrine, and dopamine transporters, with a binding profile similar to that of antidepressants that block monoamine transport.[14]

Clinical Studies of Atypical Antipsychotics in Resistant Depression

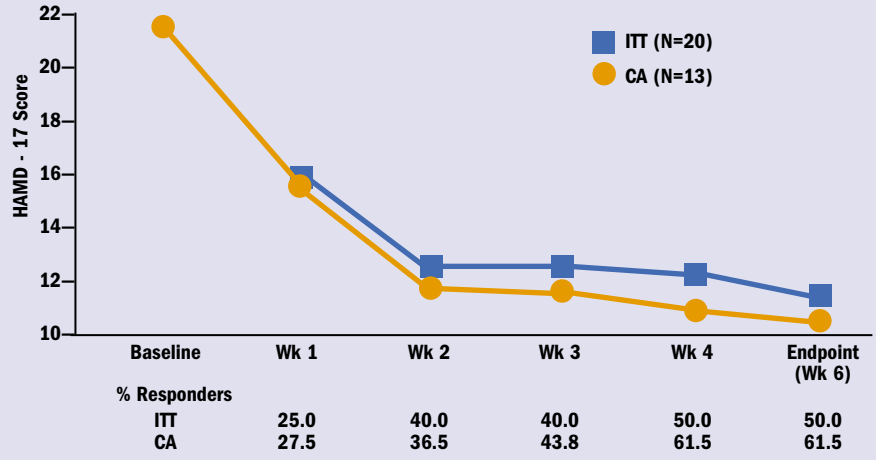
Consequences of incomplete recovery from major depressive disorder (MDD) include not only far-reaching psychological difficulties but also physical comorbidity and probable relapse. In patients with treatment-resistant depression, augmenting therapy with atypical antipsychotic agents can improve the likelihood of full remission. This augmentation strategy has been studied in a number of small, often controlled, studies assessing utility in this unapproved, off-label use.

Olanzapine: In a small, double-blind study, olanzapine plus fluoxetine produced significantly greater improvements than either monotherapy in persons diagnosed with unipolar depression, who had failed to respond to previous antidepressants.[16] In an open-label study, this combination produced rapid and sustained improvement of depressive symptoms in patients with treatment-resistant MDD,[17] and, based on medical claims, this combination reduced outpatient, office, and inpatient utilization, as well as medical costs.[18]

Quetiapine: In a small study evaluating quetiapine as adjunctive SSRI therapy for patients with anxiety symptoms complicating depressive or anxiety disorders, significant reductions in the Hamilton Rating Scale for Depression score were evident by the second week of treatment.[19]

Risperidone: In SSRI-resistant depression, risperidone augmentation produced full remission of symptoms within 1 week and improved sleep disturbances and sexual dysfunction.[20]

Figure. Ziprasidone Augmentation Improves HAMD-17 Scores



% Responders	Baseline	Wk 1	Wk 2	Wk 3	Wk 4	Endpoint (Wk 6)
ITT		25.0	40.0	40.0	50.0	50.0
CA		27.5	36.5	43.8	61.5	61.5

CA = completer analysis; HAMD-17 = 17-item Hamilton Rating Scale for Depression; ITT = intent-to-treat analysis.

Adapted with permission from: Papakostas GI, Petersen TJ, Nierenberg AA, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *J Clin Psychiatry.* 2004;65:217-221.[10]

Also in patients with treatment-resistant depression, risperidone decreased rapid eye movement sleep, an action characteristic of conventional antidepressant medications.[21]

Ziprasidone: In an open study, one of every two subjects with depression who were resistant to adequate SSRI trials responded when ziprasidone was added to their antidepressant regimen; one of every four subjects experienced complete remission.[10] Therapeutic response was strong and swift, with considerable improvement within the first week (**Figure**), and ziprasidone augmentation induced neither severe adverse events nor clinically significant QTc prolongations.

Aripiprazole: In a small series of patients with mood or anxiety disorders unresponsive to SSRI treatment, augmentation with aripiprazole produced signficant clinical improvement.[22]

Conclusions

Considering the serious consequences of incomplete remission, successful treatment of MDD is crucial, yet resistance to SSRI treatment is common. Consistent with their characteristic 5-HT antagonism, atypical antipsychotics have proved beneficial as adjunctive therapy for treatment-resistant, nonpsychotic depression. Ziprasidone, with its unique monoamine antagonism, 5-HT_{1A} agonism, and extremely potent affinity for 5-HT receptors, may be particularly advantageous in therapeutic areas beyond schizophrenia.

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Depression – Treatment and Unmet Medical Needs

Prakash S. Masand, MD

Major depressive disorder (MDD) is common, affecting 320 million people worldwide,[1] and requires long-term management. It follows only respiratory infections, perinatal conditions, and HIV/AIDS in contributing to global disease burden.[2] By 2020, it is estimated that MDD will surpass all but cardiovascular disease in causing disability worldwide,[2] and it is already the second-leading cause among individuals 15 to 44 years of age[3] and among women.[4] In the United States, more than 30 million adults suffer from MDD,[5] which annually afflicts 10% of the population older than 18 years of age.[6] Depression may lead to suicide, which annually accounts for more than one million deaths worldwide,[3] including more than 30,000 in the United States.[7]

Treatments

Historically, tricyclic antidepressants and, to a lesser degree, monoamine oxidase inhibitors were the predominant pharmacologic interventions approved for MDD. In contrast, newer antidepressants exhibit greater receptor selectivity and, consequently, more benign side-effect profiles.

Since the first selective serotonin reuptake inhibitor (SSRI), fluoxetine, entered the US market in 1988, its unquestionable efficacy and superior tolerability encouraged development and introduction of other SSRIs (citalopram, escitalopram, fluvoxamine, paroxetine, sertraline) as well as other agents (bupropion, duloxetine, mirtazapine, nefazodone, venlafaxine).

With their specific and sustained antidepressant and anxiolytic effects, SSRIs eventually became an alluring treatment option for psychiatric disorders beyond depression, such as panic disorder, anxiety disorders, posttraumatic stress disorder, obsessive compulsive disorder, eating disorders, and premenstrual dysphoric disorder.[8]

Treatment Objectives

The treatment objective for depression is full remission (resolution of all symptoms for at least 4 to 6 months) and prevention of recurrence. Adequate treatment of depression requires long-term therapy. American Psychiatric Association (APA) guidelines recommend 6 to 8 weeks of acute treatment followed by 4 to 9 months of maintenance treatment once symptoms have resolved.[9] Persons who achieve full remission not only enjoy the benefits of decreased disability and improved functioning in work, family, and social situations, but also have a lower risk of disease progression and relapse.

"The treatment objective for depression is full remission (resolution of all symptoms for at least 4 to 6 months) and prevention of recurrence."

Despite these benefits, however, MDD frequently remains undiagnosed or inadequately treated. Unfortunately, because few individuals attain full remission, residual symptoms and likely recurrence of depression are typical. Strategies for overcoming obstacles to remission include careful diagnosis, patient education and support, and mindfulness of residual symptoms or partial response by adjusting or augmenting treatment.

Consequences of Incomplete Remission

Most depressions are recurrent conditions, complicated by comorbid psychiatric and medical disorders. Compared with patients in full remission, partial responders exhibit poorer physical and social function, more substance abuse, increased hospital admissions, more use of disability benefits, and increased risk of stroke and coronary events; moreover, they are four times more likely to die.[10,11] Suicide accounts for more than one million deaths annually,[3] and almost 60% of suicides stem from MDD.[11] Of those admitted to psychiatric hospitals for depression, nearly 15% eventually kill themselves.[11]

MDD relapse rates are three to six times higher among individuals with residual symptoms than among those fully remitted.[10] Unless adequately treated, persons experiencing one MDD episode carry a 50% risk of experiencing a second episode, and this likelihood increases to 80% or 90% following two MDD episodes.[12] Furthermore, time to recurrence or relapse is four times shorter for individuals with residual symptoms.[13]

Insufficient Treatment

Too often depression remains untreated. It is estimated that only half of depressed individuals receive any form of therapy,[14] and, among those administered antidepressants, less than 30% receive adequate therapy.[5,11] The most common cause of initial treatment failure is inadequate treatment due to insufficient duration, subtherapeutic dosage, poor adherence, or some combination of these three factors.

Despite very low rates of remission (27% to 39%), clinicians often fail to prescribe adequate treatment that is consistent with APA guidelines, and patients receiving insufficient therapy are more likely to discontinue treatment prematurely. Furthermore, because clinical studies of antidepressants typically last 6 to 8 weeks—an insufficient treatment duration—it is not surprising that approximately one third of study subjects experience only partial remission, characterized by the presence of poorly defined residual symptoms.[10]

Whereas continuing antidepressant therapy long after remission of acute symptoms may protect against MDD relapse or recurrence, individuals inadvertently or intentionally may skip doses or discontinue antidepressant therapy when symptoms improve or side effects appear.[15] Among individuals prescribed antidepressants, 28% and 44% discontinued treatment within 1 and 3 months, respectively.[16] Among

nearly 700 outpatients for whom SSRIs were prescribed, 43% prematurely discontinued or switched medications within the first 3 months because of an unwanted side effect.[17]

Time-consuming dose titration or delayed onset of therapeutic action may interfere; if adverse events precede relief from depression, a patient may discontinue treatment before an adequate dosage can be attained.[18] Also, it should be remembered that depressed individuals may not be highly motivated to care for themselves and they may feel hopeless about recovery.[9] They may discontinue therapy because they dislike taking medication, feel stigmatized, or lack a support network.

Unwanted Side Effects

Patients often discontinue antidepressant treatment prematurely, especially during the first month of therapy, because of unwanted side effects. Although patient education as well as a sound patient-physician relationship are critical, some extended-release formulations may improve adherence by simplifying dosing or reducing peak plasma drug concentrations, thus improving tolerability.[18]

Although SSRIs are generally well tolerated, their discontinuation within the first month of treatment frequently is associated with nausea, which typically emerges during the first week.[18] Although SSRI-related nausea and headache usually resolve within 2 to 4 weeks,[8] treatment discontinuation is likely to precede their resolution.[17]

Significant weight gain puts individuals at increased risk of coronary heart disease, hypertension, type 2 diabetes, dyslipidemia, and cancer.[19] To maximize quality of life and adherence to treatment, it is essential for clinicians to manage weight gain or loss. Although weight gain has been reported with long-term SSRI use, in some cases, it may be due to recovery from depression.[19] Nevertheless, antidepressant treatment, especially with mirtazapine, may require aggressive nutrition and exercise counseling. For patients at particular risk for weight gain, antidepressants occasionally associated with weight loss (venlafaxine, bupropion) offer treatment alternatives.[20]

In addition to being a common symptom of MDD, sexual dysfunction is a common side effect associated with antidepressant therapy, particularly with SSRIs.[19] As many as 60% of SSRI-treated individuals experience sexual dysfunction in the form of reduced libido, delayed ejaculation, or diminished orgasm,[8] and as many as 25% switch to another class of therapy because of these issues.[21]

"Treatment objectives for MDD include remission of all symptoms and prevention of recurrence or relapse, yet most depressed individuals do not reach these treatment objectives because MDD remains underdiagnosed and inadequately treated."

Treatment Resistance

Therapeutic response following SSRI initiation typically occurs within the first 8 weeks. More than half of eventual responders start to respond by week 2 and more than 75% start to respond by week 4. Conversely, lack of response by week 6 is associated with about a 10% chance that patients will respond by 8 weeks.[22] Therefore, if a patient fails to respond by 6 weeks, it may be time to change treatment plans.

Treatment resistance is common, with nearly 30% of patients not responding to antidepressant therapy and, of the remaining 70%, less than 35% achieve full remission.[23] Switching from one antidepressant to another can be effective and is especially appropriate for patients not responding or responding inadequately to the initial treatment or for those whose response was limited by side effects. Augmentation strategies may be prudent for partial responders whose treatment has not been limited by side effects. Treatment augmentation with other psychoactive agents enables several neurotransmitter systems to be influenced simultaneously, potentially improving therapeutic effects.

Treatment Augmentation

Augmentation with lithium or lamotrigine may be appropriate when a patient displays symptoms suggestive of bipolarity. Low-dose thyroid hormone (triiodothyronine) may be the adjuvant of choice, especially if the patient is an elderly female. Low-dose psychostimulants, such as methylphenidate, dextroamphetamine, or modafinil, which might be particularly useful in patients displaying apathy or sleepiness, are another approach to treatment-resistant depression. Bupropion or tricyclic antidepressants also can be added to SSRIs.

Atypical antipsychotics have long been effective in treating patients with psychotic or delusional depression. Not only do they ameliorate symptoms of depression in patients with schizophrenia, but they also are effective in augmenting treatment for nonpsychotic, treatment-resistant depression.[24] Dopaminergic and adrenergic effects may improve symptoms relating to pleasure, motivation, psychomotor activity, insomnia, appetite, and agitation, and adrenergic effects may contribute to pharmacologic activation; serotonergic effects may resolve some SSRI-induced side effects, such as agitation, insomnia, and sexual dysfunction.[25] Augmentation with low-dose olanzapine,[25,26] risperidone,[27,28] quetiapine,[29] ziprasidone,[30] or aripiprazole[31] shows rapid, robust, and sustained improvement in treatment-resistant depression.

Conclusions

Treatment objectives for MDD include remission of all symptoms and prevention of recurrence or relapse, yet most depressed individuals do not reach these treatment objectives because MDD remains underdiagnosed and inadequately treated. Compared with individuals fully remitted, MDD relapse rates are three to six times higher, and time to recurrence or relapse is four times shorter among those with residual symptoms.

Patients often discontinue antidepressant treatment prematurely, especially during the first month of therapy, because of unwanted side effects, and nearly 30% of patients do not respond to antidepressant therapy. Of the

remaining 70%, fewer than 35% achieve full remission. Strategies to overcome treatment-resistant MDD include switching antidepressants and augmentation with lithium, thyroid hormone, a psychostimulant, or an atypical antipsychotic.

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Atypical Antipsychotic Drug Augmentation

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Atypical Antipsychotics in Nonpsychotic Disorders

Philip D. Harvey, PhD

The atypical antipsychotic drugs (clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole) revolutionized the treatment of psychotic disorders such as schizophrenia. They are more effective in controlling the negative symptoms of schizophrenia than are conventional antipsychotics (chlorpromazine, fluphenazine, thioridazine, and haloperidol), and they are much less liable to generate extrapyramidal symptoms (EPS) or tardive dyskinesia, properties principally derived from their shared antagonism of serotonin (5-hydroxytryptomine [5-HT]) and dopamine (D) neuroreceptors.

All antipsychotic drugs are approved by the US Food and Drug Administration (FDA) for treatment of schizophrenia; risperidone, olanzapine, and quetiapine are also approved for treatment of bipolar mania. Risperidone and quetiapine are approved to treat manifestations of psychotic disorders, whereas olanzapine and ziprasidone are approved to treat acute agitation in psychotic patients.

Because atypical antipsychotics produce fewer motor disturbances and have a broader spectrum of efficacy, their use has expanded beyond schizophrenia to include unapproved applications in a variety of psychiatric disorders. In fact, atypical antipsychotic drugs are prescribed most frequently for therapeutic conditions other than schizophrenia. In 1999, nearly 70% of prescriptions worldwide involved off-label use of antipsychotic medications.[1]

Effect on Cognitive and Affective Dysfunction

Unlike conventional antipsychotic drugs that mainly block D_2 receptors, second-generation drugs also block 5-HT_{2A} receptors. The cortical dopamine release triggered by this 5-HT_{2A} blockade may be critical for improvement of cognitive function.[2] Atypical antipsychotics also increase release of acetylcholine, a neurotransmitter implicated in cognitive dysfunction in illnesses such as Alzheimer's disease.[3] These neurobiologic effects provide a major advantage to second-generation antipsychotic drugs – their ability to enhance cognitive and affective function, which, in turn, improves social, functional, and adaptive outcomes.

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In elderly patients with schizophrenia or schizoaffective disorder, low doses of risperidone and olanzapine improved aspects of cognitive function related to functional outcome.[4] Ziprasidone-treated patients exhibited significant advances in many cognitive domains associated with better functional outcome.[5] Although published data with quetiapine are limited, it did successfully treat delirium, an organic psychiatric syndrome involving impaired cognition.[6]

Nonpsychotic Depression

Whereas no antipsychotic drug is approved for treatment of depression by the FDA, the first medication for depressive episodes associated with bipolar disorder was approved in January 2004. This product combines olanzapine and the selective serotonin reuptake inhibitor (SSRI) fluoxetine in a single tablet.

Because incomplete remission of major depressive disorder (MDD) increases likelihood of chronicity and recurrence, it is disheartening that more than half of depressed patients fail to respond successfully to antidepressant treatment.[7] It has been recognized that atypical antipsychotic agents treat depression in patients with schizophrenia, but, at low doses, they also improve remission rates in nonpsychotic, treatment-resistant depression.[7,8] Dopaminergic effects may improve symptoms relating to pleasure, motivation, psychomotor activity, insomnia, appetite, and agitation; whereas, adrenergic effects may contribute to pharmacologic activation and serotonergic effects may resolve some SSRI-induced side effects, such as agitation, insomnia, and sexual dysfunction.[9,10]

Augmentation with low doses of risperidone (0.5 to 1.0 mg/day) produced full remission of symptoms within 1 week and improved sleep disturbances and sexual dysfunction among patients with SSRI-resistant depression.[11] Furthermore, results of an open-label study indicated that the addition of risperidone (0.5 to 1.0 mg/day) to an SSRI from initiation of antidepressant therapy improved therapeutic outcome since 76% of the study subjects achieved full remission.[12]

In a double-blind study in refractory, nonpsychotic, unipolar, treatment-resistant depression without psychotic features, olanzapine (5 to 20 mg/day) combined with fluoxetine was significantly more effective than either agent alone, and clinical response was evident by the first week.[13] Furthermore, this rapid and robust clinical response was sustained for 76 weeks.[14]

Addition of quetiapine to an SSRI in patients with anxiety symptoms complicating depressive or anxiety disorders improved Hamilton Rating Scale for Depression scores at least 50% by the second week of treatment.[15]

Among depressed subjects who had failed to respond to adequate SSRI trials, 62% experienced at least a 50% improvement in depressive symptoms and 39% achieved full remission when ziprasidone (82 mg/day) was added to their antidepressant regimen.[16] Therapeutic response was strong and swift, with considerable improvement evident within the first week.

Table. Different Doses* for Different Effects

Drug	Schizophrenia (dopaminergic)	Nonpsychosis (serotonergic)
Risperidone	4 - 6	0.25 - 1.0
Aripiprazole	10 - 15	5
Olanzapine	10 - 20	6
Ziprasidone	40 - 160	20
Quetiapine	300 - 400	25

*Doses are mg/day.

Other Affective Disorders

Atypical antipsychotics can be effective in a variety of disorders involving aggressive behavior among youngsters with subaverage cognitive or intellectual abilities. In addition to conduct disorder, included in this diverse group are disruptive behavior, aggressive behavior, oppositional defiant disorder, irritable aggression in posttraumatic stress disorder, impulsivity, irritability, or aggression in antisocial personality disorder, and tantrums, aggression, or self-injury in autism. Likewise, second-generation antipsychotic drugs are useful for conduct disorders associated with Tourette's syndrome.

Clinical Effects are Dose-Related

The fundamental property of atypical antipsychotics, their ability to produce an antipsychotic effect in the absence of EPS, can be predicted by brain receptor occupancy. Antipsychotic efficacy, produced by psychotropic drugs, occurs within a therapeutic window ranging from 60% to 80% D_2-receptor occupancy, based on positron emission tomography; incidence of EPS increases beyond 70% occupancy. Daily doses of atypical antipsychotics recommended for treatment of schizophrenia range widely, reflecting diverse receptor-binding affinities (**Table**).

Because all atypical antipsychotics block 5-HT_{2A} receptors more potently than D_2 receptors,[17] they affect the serotonin system at dose levels much lower than dose levels needed to affect the dopamine system (**Table**). Therefore, low-dose therapy with atypical antipsychotics effectively generates therapeutic responses governed mainly by serotonergic mechanisms, such as those influencing cognitive dysfunction and affective symptoms.

Metabolic Side Effects

Despite substantially lower rates of movement disorders, atypical antipsychotics are not without unwanted side effects.[18] In particular, adverse metabolic effects, such as weight gain, diabetes mellitus, and dyslipidemia, have increasingly been reported with the use of second-generation antipsychotic drugs.[19-22] Although no large, controlled trial has quantified prevalence of adverse effects on glucose-insulin homeostasis and lipid metabolism in patients receiving atypical antipsychotics, a review of published reports concluded that the relative risk of glucose intolerance or diabetes mellitus, hyperlipidemia, and hyperleptinemia is highest for clozapine and olanzapine, moderately high for quetiapine, low for risperidone, and lowest for ziprasidone.[23]

Conclusions

Because atypical antipsychotics produce fewer motor disturbances and have broader efficacy than conventional antipsychotics, their use has expanded beyond schizophrenia to include a variety of psychiatric disorders, including depression, yet to be approved by the FDA. Atypical antipsychotics block 5-HT_{2A} receptors more potently than D_2 receptors; as a result, they affect the serotonin system at dose levels much lower than dose levels needed to affect the dopamine system. Therefore, low-dose therapy with atypical antipsychotics effectively generates therapeutic responses governed mainly by serotonergic mechanisms, such as those influencing cognitive dysfunction and affective symptoms. Despite substantially lower risk of EPS and tardive dyskinesia, atypical antipsychotics are not without unwanted side effects.

"...low-dose therapy with atypical antipsychotics effectively generates therapeutic responses governed mainly by serotonergic mechanisms, such as those influencing cognitive dysfunction and affective symptoms."

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