Novel Antipsychotics: Schizophrenia, Psychosis and Beyond CME

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Introduction

The introduction of the first antipsychotic agents in the 1950s marked a dramatic improvement in the care for individuals with schizophrenia and other forms of severe and persistent mental illness. The discovery of antipsychotic medications encouraged medical science's more systematic investigation of the biological underpinnings of schizophrenia and the development of additional agents that were effective in decreasing the psychotic features of schizophrenia and related disorders. Unfortunately, the emergence of extrapyramidal side effects (EPS) and tardive dyskinesia (TD) rendered the conventional neuroleptics intolerable for a number of patients, particularly in the long-term management of these disorders.

The advent of the novel antipsychotics (eg, clozapine, risperidone, olanzapine, quetiapine, and ziprasidone) during the past 15 years represents a significant improvement over the effectiveness of conventional antipsychotics (eg, chlorprormazine, thioridazine, haloperidol, fluphenazine). Because the novel antipsychotics are associated with fewer motor disturbances and a broader spectrum of efficacy, their use has expanded beyond schizophrenia to include applications in dementia, mood disorders, anxiety disorders, and developmental disorders. However, these agents are not a "magic bullet" and are associated with their own attendant treatment complications, such as weight gain, diabetes mellitus, hyperprolactenemia, and QTc prolongation. Understanding how these agents exert their effects, familiarity with their side effect profiles, and knowing which agents tend to be most helpful for different subgroups of patients is helpful in making informed clinical decisions in the treatment of individuals with schizophrenia and other chronic mental illnesses.

At a recent symposium in Syracuse, New York, entitled, "Novel Antipsychotics: Psychosis and Beyond," experts on novel antipsychotics presented research and clinical guidelines on the use of these agents in patients with schizophrenia and other disorders.

Novel Antipsychotics in Treatment of Schizophrenia

Rajiv Tandon, MD, from the University of Michigan, Ann Arbor, provided an overview of novel antipsychotics in the treatment of schizophrenia. The conventional neuroleptics and the novel antipsychotic agents clozapine, risperidone, olanzapine, quetiapine, and ziprasidone are all effective in treating the symptoms associated with schizophrenia. The newer medications are considered "novel," however, because they are efficacious in attenuating psychotic symptoms without the same degree of EPS observed with the conventional agents. This more benign effect on the extrapyramidal system is also associated with lower rates of TD and greater compliance, as well as a broader spectrum of efficacy with respect to fewer negative symptoms, less dysphoria, and improved cognition relative to the older medications.[1-5]

How Novel Antipsychotics Work

Shitij Kapur, MD, PhD, from the Center for Addiction and Mental Health, Toronto, Canada, expanded the discussion by detailing the mechanism of action novel antipsychotics.

Critical Interval of Antagonism. Research suggests that blockade of more than 65% of dompamine-2 receptors (D2 receptors) is key to the antipsychotic efficacy of both the conventional neuroleptics and the novel antipsychotics.[6,7] However, one of the most significant clinical challenges posed by the use of antipsychotic medications is the difficulty of antagonizing enough D2 receptors to promote a reduction in positive symptoms without blocking so many D2 receptors that unwanted side effects are induced. For example, occupation of 72% or more D2 receptors is associated with elevations in prolactin, and occupation of 78% or more D2 receptors is associated with EPS and akathisia.[6,7] Thus, the task facing clinicians who employ antipsychotic medications is to find the optimal therapeutic window so that symptoms are ameliorated but the agents are still tolerable to the patient. Recent work by Dr. Kapur and colleagues suggests that knowledge of the relative blockade of D2 receptors by different novel agents may allow clinicians to predict side effects and to match agents with patients accordingly.

Relationship Between Receptor Blockade and Side Effects. Both in vitro and in vivo studies over the last decade have demonstrated that a common characteristic of the novel antipsychotic agents is a higher ratio of serotonin 5-HT2 receptor blockade to D2 receptor blockade compared with that for the conventional neuroleptics.[8,9] This property is also consistent with the lower rate of treatment-emergent EPS, TD, and elevated prolactin levels associated with the novel agents relative to conventional neuroleptics. However, the novel antipsychotic agents begin to resemble the conventional antipsychotic agents with respect to emergence of these side effects when doses are raised such that a blockade of more than 70% of D2 receptors occurs. This has been demonstrated with risperidone and olanzapine.[10] Clozapine and quetiapine, on the other hand, do not give rise to EPS or prolactin elevation because they are unable to block more than 70% of D2 receptors.[10] However, when haloperidol, a potent D2 antagonist, is added to clozapine, an increase in D2 blockade and concomitantly abnormal elevations of prolactin are observed.[11]

Specificity of D2 Receptor Affinity. Are the lower rates of EPS, TD, and prolactin elevation observed with the novel antipsychotics due to their greater affinity for the 5-HT2 receptor? The answer appears to be “no,” because the conventional antipsychotics and the novel agents demonstrate comparable affinity for the 5-HT2 receptor.[8] Instead, the differential rates of EPS, TD, and prolactin elevation appear to be accounted for by the novel agents’ lower affinity for the D2 receptor. Specifically, the relatively lower affinity for the D2 receptor by the novel antipsychotics appears to be determined by their faster rate of dissociation (ie, unbinding) from the D2 receptor, a property known as “Koff”.[6,7,12] Clozapine and quetiapine dissociate fastest from the D2 receptor, followed by decreasing rates of dissociation for olanzapine, risperidone, haloperidol, and chlorpromazine, respectively.

Furthermore, variability in affinity for the D2 receptor appears to account for the differential rates of EPS, TD, and prolactin elevation observed among the novel agents themselves. The relative rates of dissociation from the D2 receptor are inversely related to the rates of EPS, TD, and prolactin elevation—that is, the faster the rate of drug dissociation, the lower the rates of these treatment-emergent side effects. Thus clozapine and quetiapine have the lowest rates of EPS, TS, and prolactin elevation, and these side-effect rates increase with the use of olanzapine, risperidone, haloperidol, and chlorpromazine, respectively.

Thus, the mechanism of efficacy for all antipsychotics is the antagonism of D2 receptors. Differential percentage of blockade and rate of dissociation may also account for observed side effects.

Effectiveness of Novel Antipsychotics in Schizophrenia

Dr. Tandon continued by discussing the effectiveness of novel antipsychotics in the treatment of schizophrenia. According to Dr. Tandon, antipsychotic agents are generally effective in the treatment of psychotic symptoms, but questions have been raised as to whether one agent is "better" than another in the treatment of schizophrenia. It has been suggested that the most informed means of answering this question is to address it empirically using an evidence-based approach.

With respect to efficacy, Dr. Tandon presented data suggesting that it does not appear that any one of the novel antipsychotic agents (ie, risperidone, olanzapine, quetiapine, or ziprasidone) is better than another in treating schizophrenia. A careful review of randomized controlled trials suggests that, on average, these medications are each associated with a 20% improvement in symptoms. The exception to comparable antipsychotic efficacy appears to be clozapine, as it is the only second-generation antipsychotic that is more effective than haloperidol in managing treatment-resistant schizophrenia.[13,14] However, because of its potential for treatment-emergent agranulocytosis, seizures, and anticholinergic effects, clozapine is not recommended for use as a first-line agent for schizophrenia.[15]

Differences Among The Novel Antipsychotics. What, then, are the differences among the novel antipsychotics? The differences among the novel agents appear to be in their side effect profiles, which may have implications for effectiveness (ie, how well the agent performs in "the real world with real patients"). The emergence of side effects and how well a given patient tolerates them over time are important clinical features to consider when selecting a novel agent for a given patient.

Although as a class, the these agents are associated with relatively low rates of EPS, and certain novel antipsychotics are associated with a dose-dependent increase in EPS when dosages are raised to the point that D2 receptor occupancy is greater than 78%. For example, at doses of 2-6 mg/day, risperidone is associated with a lower rate of EPS during long-term treatment than is haloperidol. However, at doses above 6 mg/day, risperidone's side effect profile appears comparable to that of the conventional neuroleptics. Differences in rates of EPS are also relative to the agents being compared within the class of novel antipsychotics. For example, when compared to olanzapine, rates of EPS associated with risperidone are comparable,[16] but when compared to quetiapine, rates of moderate to severe EPS are higher.[17]

Because risperidone at doses higher than 4 mg/day and olanzapine at doses higher than 20 mg/day are associated with an increased risk of treatment-emergent EPS, these agents may be rendered less effective for particular patients due to noncompliance. Thus, according to Dr. Tandon, to achieve the optimal balance between efficacy and tolerability, it is recommended that the following daily doses of novel agents be used in the treatment of nonelderly adults (< 65 years) with schizophrenia:

Risperidone 2-4 mg/day

Olanzapine 10-20 mg/day

Quetiapine 600-900 mg/day

Ziprasidone 100-120 mg/day

Side effects, however, are not always to be avoided. Instead, clinicians may actively exploit the different side effect profiles of the novel antipsychotics to help target specific symptoms of individual patients. For example, among agitated patients, quetiapine administered in the evening may have a calming effect due to its tendency to induce sedation.

Next-Step Strategies for Schizophrenia: Switching and Combining. According to Dr. Tandon, variations in the pharmacologic profiles of the different novel medications may also help clinicians select next-step strategies when electing to switch antipsychotics in patients who are not responsive to an adequate trial of monotherapy (ie, 8-12 weeks at an appropriate dose) or who are unable to tolerate the side effects of a particular agent after its dose has been decreased. Following the decision to switch antipsychotic medications, cross-titration in which the old agent is continued until the new agent is titrated to its therapeutic dose may be most helpful. Over the next 6-12 weeks, the patient may be slowly tapered off the old agent. In the event that a patient has not responded after 6 months of continuous treatment with 2 different agents, switching to clozapine may be helpful.[18]

Although there is sparse data to support the practice of combination antipsychotic treatment,[19] this approach may be reasonable in patients who fail to respond adequately to a single agent. When electing to use more than 1 antipsychotic agent, it may be helpful to select agents with different pharmacologic profiles. For instance, rather than combining risperidone and olanzapine, both of which are potent D2 blockers whose combination could induce or exacerbate EPS, it may be advisable to combine clozapine with risperidone or with a depot antipsychotic such as haloperidol or fluphenazine. Other reasonable combinations are a depot antipsychotic with a novel antipsychotic other than risperidone or the combination of risperidone and quetiapine. Because there are few, if any, long-term studies of the efficacy and safety of combination antipsychotic pharmacotherapy, Dr. Tandon recommends that combined antipsychotic treatment be used only for 3 months or less.

Novel Antipsychotics in Bipolar Disorder

Naveed Iqbal, MD, of Albert Einstein College of Medicine, Bronx, NY, contributed to the discussion by focusing on the use of novel antipsychotics in the treatment of bipolar disorder. Approximately 40% of patients who present with a major depressive episode may actually be experiencing a depressive episode in the context of bipolar disorder, and failure to properly diagnose bipolar patients has important clinical implications.[20] Research has shown that certain antidepressants may induce or exacerbate mania or rapid cycling in bipolar patients if an antidepressant is given without concurrent administration of a mood stabilizer.[21-23]

One feature that may help clinicians differentiate between individuals experiencing a major depressive episode in the context of bipolar disorder from those experiencing a major depressive episode in the context of major depressive disorder is that bipolar patients will display a decreased need for sleep but are not tired the next day. Once patients have been diagnosed with and treated for bipolar disorder, it is recommended that clinicians use a mood stabilizer to treat acute mania or depression and to prevent subsequent manic episodes.

Disadvantages of Conventional Antipsychotics in Bipolar Disorder

A number of patients present with psychotic symptoms in the context of a manic episode. Conventional antipsychotics have long been used to in the acute treatment of mania, but there is

limited evidence that they are effective during the maintenance phase of treatment for bipolar disorder. Moreover, the long-term use of typical antipsychotics is complicated by the increased risk of, TD, EPS, cardiac problems, and neuroleptic malignant syndrome.[25]

Using Novel Antipsychotics in Bipolar Disorder

The efficacy and more benign side effect profile of the novel antipsychotics in schizophrenia have also been observed in patients with bipolar disorder, and they have been reviewed extensively by Ghaemi.[26] Thus far, currently available data suggest that many of the currently available novel antipsychotics are effective in the acute management of mania.

Clozapine appears to be useful in the treatment of bipolar disorder and other severe mood disorders.[27] However, as with its use in the treatment of schizophrenia, clozapine is not recommended as a first-line treatment for bipolar disorder because of the associated risks of agranulocytosis and seizures.

As monotherapy, risperidone 6 mg/day was as efficacious in the acute treatment of mania as haloperidol 10 mg/day and lithium 800-1200 mg/day for 1 month in a non-placebo-controlled study.[28] Two double-blind trials have also demonstrated that risperidone as an add-on to mood stabilizers was superior to a mood stabilizer plus placebo.[29] Adjunctive risperidone also appears helpful, particularly during maintenance therapy for bipolar disorder. A small study of patients treated with adjunctive risperidone following breakthrough symptoms while on maintenance mood stabilizing medication found improvement in several patients and no manic relapse in any patients.[30]

Data from several studies suggest that olanzapine is effective in the acute and longer-term treatment of mania. In recent double-blind, controlled trials, patients acutely treated with olanzapine as monotherapy demonstrated significantly greater reductions in mania than did patients treated with placebo.[31,32] A small, open study of olanzapine as an adjunct to mood-stabilizing medications also found significant improvements among patients following the addition of olanzapine in the acute stages of treatment.[33] Data from a recent double-blind study suggests that intramuscular olanzapine is similarly safe and effective in reducing acute agitation in patients with bipolar mania.[34] In this study, patients treated with olanzapine were significantly calmer 2 hours after the injection than were patients treated with lorazepam or placebo. With respect to long-term use, olanzapine appears to be effective and safe for bipolar disorder as an adjunct to mood stabilizers.[35,36]

Emerging data suggest that quetiapine is helpful as an add-on therapy for patients who do not respond fully to mood stabilizing medication. A small study of patients with bipolar disorder or schizoaffective disorder who demonstrated a suboptimal response to mood stabilizers found that quetiapine added in an open fashion was associated with significant reductions in mania and depression.[37]

The novel antipsychotics are not without their side effects, however. Weight gain is particularly salient among patients treated with olanzapine and may be compounded by mood-stabilizing agents, which are themselves associated with substantial weight gain (eg, divalproex). In a recent study published by Guille and colleagues,[38] bipolar patients treated with olanzapine demonstrated significantly greater weight gain (mean weight of 16.1 lbs) compared with those treated with risperidone (mean weight gain of 7.8 lbs).

Algorithm for Acute Treatment of Bipolar Disorder. Ghaemi has recommended that the treatment of acute mania should follow these steps[26]:

Begin with lithium or valproate as monotherapy.

If patients do not respond fully within 1 week, then novel antipsychotics such as risperidone, quetiapine, or olanzapine may be added. These agents have the advantage of stabilizing mania without worsening depressive symptoms. Clinicians may also consider adding clonazepam.

If patients still do not respond adequately within 4-6 weeks, clinicians may consider adding anticonvulsants such as valproate or carbamazapine to lithium, or lithium to valproate.

As a next step, clinicians may consider adding novel anticonvulsants such as lamotrigine, topiramate, or gabapentin.

If patients present with persistent depression, bupropion or paroxetine may be added but should be tapered after 1 month of euthymia.

Recently published recommendations for the treatment of bipolar disorder advocate for the use of lifelong pharmacologic maintenance treatment for the majority of patients suffering from this illness.[39] Although emerging findings support the efficacy of the novel antipsychotics in the acute treatment of mania and in the management of breakthrough symptoms while patients are sustained on mood stabilizing medication, more data are needed before the novel antipsychotics are recommended specifically for the prophylaxis of mania. Thus, current recommendations suggest that first-line acute and maintenance treatment for bipolar disorder should be accomplished with a mood stabilizer and that novel antipsychotics should be used adjunctively among patients who fail to achieve or maintain response with mood stabilizing medication.[26,39]

Broad Spectrum of Efficacy of the Novel Antipsychotics: Focus on Dementia and Related Disorders

Warren Taylor, MD, of Duke University, Durham, North Carolina, and Peter Buckley, MD of the Medical College of Georgia, Augusta, discussed expanding the use of novel antipsychotics beyond the treatment of adult schizophrenia to the treatment of dementia and related disorders. Emerging data suggest that the novel antipsychotics are helpful in disorders other than schizophrenia. In addition to their applications in dementia and bipolar disorder, the novel antipsychotics appear to be helpful in the treatment of conduct disorder, personality disorders, autism, and childhood and adolescent psychosis, as based on preliminary findings. A small study of psychotic patients with borderline personality disorder demonstrated that clozapine was helpful in decreasing self-mutilation and injuries to self and peers,[40] and a small open study of patients with comorbid borderline personality disorder and dysthymia showed that olanzapine was significantly associated with decreases in psychoticism, depression, interpersonal sensitivity, and anger.[41] With respect to autism, Findling and colleagues[42] reported that a small open trial of risperidone monotherapy was useful in improving symptoms in autistic children.

A small recent study of psychotic adolescents demonstrated that quetiapine was associated with significant decreases in positive and negative symptoms,[43] and a small open study of treatment-resistant schizophrenic children and adolescents found that olanzapine was efficacious in improving symptoms.[44] Large, double-blind, controlled studies are needed to further investigate the efficacy and safety of the different novel antipsychotics in these populations.

Dementia

As the population ages, the number of elderly individuals with mental illness also rises. It has been estimated that the number of psychiatrically ill older adults will rise to 15 million by 2030 and that the number of elderly adults with dementia will also rise.[45]

Among older adults, dementia is commonly accompanied by symptoms of psychosis and agitation, which may present in the form of delusions, hallucinations, aggression, and disinhibition. These behavioral disturbances may be particularly challenging for relatives, hospital staff, and other individuals who care for older adults with dementia, and are the most salient reason caregivers elect to hospitalize elderly demented patients.[46] Thus, appropriate differential diagnosis of dementia subtypes and the availability of efficacious and safe medications to treat them are important clinical priorities in gerontology.

Differential Diagnosis of Dementia. Because older adults with dementia may suffer from a variety of physical disorders and may concurrently receive multiple medications, careful assessment of dementia and its subtypes is imperative for proper differential diagnosis and appropriate treatment. Dementia of Alzheimer's type (DAT) is the most common form of dementia observed among older adults. Other forms of dementia include vascular dementia, which may result from strokes; dementia with Lewy bodies (DLB); and dementia associated with excessive alcohol intake, Pick's disease, Parkinson's disease, Huntington's disease, and Cruetzfeldt-Jakob disease.

Dr. Taylor stressed that the differential diagnosis among the dementia subtypes, as well as other medical disorders that may present with similar features, has important implications for treatment. For instance, although patients who suffer from DLB may present with psychotic and agitated features, the disease is a contraindication for the use of conventional antipsychotic agents due to extreme neuroleptic sensitivity, which manifests in the form of parkinsonism and other motor disturbances. Similarly, delirium—which may be the result of an undiagnosed medical illness or iatrogenically caused by medications or withdrawal from substances—is generally reversible and will require treatment with antipsychotic agents in addition to correcting the underlying etiology.[47-51] Lastly, elderly patients who display agitation may not be suffering from dementia; instead, they may be experiencing vision or hearing problems or may be in physical discomfort, considerations which would also suggest against the use of antipsychotic medication.

Advantages of Novel Antipsychotics. When a thorough assessment has been completed, other causes of psychotic or agitated behavior have been addressed or ruled out, and a differential diagnosis of dementia has been assigned, the clinician is faced with the task of deciding which symptoms to target and which intervention(s) to choose for a given patient. Conventional and novel antipsychotic medications, which are indicated for psychosis, are effective in treating symptoms of dementia, although none are specifically indicated for dementia.

Conventional antipsychotics have demonstrated modest efficacy in the treatment of elderly patients with dementia,[52] but their adverse side effect profile and high risk of TD render them less than desirable in this patient population.[53] The efficacy and more benign side effect profile of the novel antipsychotic agents in schizophrenia and related psychotic disorders[54] has led a number of clinical researchers to test the utility of these agents in elderly patients with dementia.

Overview of Several Novel Antipsychotics for Dementia

Quetiapine appears to be helpful in decreasing psychotic features and hostility, although doses in research samples may have been lower than needed to demonstrate robust antipsychotic efficacy.[55,56] In these studies, quetiapine was not associated with substantial EPS,

anticholinergic effects, or toxicity. Its most salient side effect appears to be somnolence, which may actually be helpful in managing demented patients who demonstrate disturbed sleep-wake cycles or evening agitation.

Olanzapine also appears to be effective in the management older adults with dementia. A recent study[57] in which nursing home patients were assigned to fixed doses of olanzapine (5, 10, and 15 mg/day) found that the lower doses were significantly better in the management of agitation and psychotic features and that somnolence and gait disturbance emerged at a significantly higher rate among patients treated with 15 mg/day. However, the clinician should be mindful of anticholinergic side effects of olanzapine in the elderly.

Risperidone is the most extensively studied novel antipsychotic agent in the elderly. Data from several trials support its efficacy in attenuating psychotic features, agitation, and aggression in elderly patients with dementia.[58,59] Doses of 1-2 mg/day appear to be most effective in reducing symptoms, but 1 mg/day appears to be the optimal dose for balancing efficacy and managing the emergence of EPS and TD.[58] Because of risperidone's tendency to induce EPS at higher doses, it is not recommended for elderly patients suffering from DLB.

Clozapine is particularly effective as an antipsychotic for patients with treatment-resistant schizophrenia, but because of its potential for treatment-emergent adverse events, such as agranulocytosis, anticholinergic effects, and seizures, it is not recommended as a first-line therapy for elderly patients.

Ziprasidone, the newest novel antipsychotic approved by the FDA, has low anticholinergic activity. However, there are currently no published studies on its use in elderly subjects. Dr. Taylor emphasized that caution should be exercised when administering it to older adults with cardiac disease or those who receive other medications that may result in QTc prolongation.

Long-Term Side Effects of Novel Antipsychotics

Dr. Prakash Masand, who chaired the symposium, discussed long-term side effects of novel antipsychotics. The lower rate of movement disorders is one of the most salient advantages of the novel antipsychotic agents over the conventional neuroleptics. However, the novel antipsychotics are not without their unwanted effects. In particular, it is critical that clinicians be mindful of metabolic consequences of novel antipsychotics, such as weight gain and diabetes mellitus, that may result from the use of certain novel agents in order to optimize the benefits without compromising the physical health of patients.

Tardive Dyskinesia

Independent of treatment, certain individuals are at an increased risk for developing TD relative to the general population. These include the elderly, individuals with schizophrenia, those with mood disorders, those with preexisting EPS, and those with current diabetes mellitus.[60-62] Among those at risk, approximately one third may experience a natural remission.[61] Thus, long-term, double-blind studies are useful in understanding the effects that antipsychotic agents may play in exacerbating or attenuating symptoms of TD above and beyond the baseline level of TD in these populations.

Several studies have found that over a 1-year period, patients treated with risperidone and olanzapine were at lower risk of experiencing TD than were patients treated with haloperidol.[63] Because TD is generally irreversible, the most effective means of dealing with

TD is to prevent it. This may be accomplished by using the smallest effective dose of antipsychotic agents, employing novel antipsychotic agents rather than conventional neuroleptics, and potentially using prophylactic vitamin E among patients at risk for developing TD. In the event that a patient has already developed TD, the clinician should first rule out any other neurologic disorders. Possible next steps include lowering the dose of the medication, using vitamin E as an antidote, or switching to another agent. With respect to the latter option, Egan and colleagues[64] have suggested that clozapine may be helpful in decreasing rates of TD among patients who developed it while on conventional neuroleptics.

Weight Gain

The relationship between weight gain and the novel antipsychotics may be likened to the association of EPS and the conventional neuroleptics: both are unwanted side effects of antipsychotic medication, emerge rather early in the course of treatment, are associated with noncompliance, and are often reversible. Nonetheless, both may serve as harbingers of later, more serious consequences of long-term antipsychotic usage.[65] Just as EPS may suggest the possibility of later TD, excessive weight is associated with a number of health complications, including diabetes, cardiovascular disease, and certain types of cancer, according to a recent review of studies.[66] It is also one of the most prominent reasons for noncompliance with medication.[67]

According to a recent meta-analysis of antipsychotic-related weight gain,[68] clozapine and olanzapine are the antipsychotics most likely to cause weight gain after 10 weeks of usage, with an average weight gain of approximately 10 lbs. Ziprasidone was among the agents with the lowest weight gain, with an average weight gain of only 1 lb. Risperidone had intermediate levels of weight gain (approximately 5 lbs), and emerging data suggest that weight gain associated with aripiprozole, a new antipsychotic under investigation for schizophrenia, is comparable to that observed with the intermediate level agents.

Diabetes Mellitus

Independent of the iatrogenic effects of medication, individuals with schizophrenia are also at a greater risk of developing diabetes mellitus relative to the general population. This predisposition to diabetes has been exacerbated by the introduction of the novel antipsychotic agents, as seen by the dramatic rise in the number of published cases of diabetes mellitus associated with the use of these medications, particularly olanzapine and clozapine.[69] As suggested by several authors, the risk of antipsychotic-induced weight gain and secondary diabetes with clozapine and olanzapine may result from changes in glucose metabolism and insulin resistance induced by these agents.[70-73]

Prolactin Elevation

As dopamine receptors are antagonized by antipsychotics, prolactin is freed from inhibition, resulting in elevations of prolactin levels. Because of its potent D2 blocking properties, risperidone is the novel antipsychotic most likely to cause an increase in serum prolactin levels; in contrast, clozapine and quetiapine are less potent D2 blockers and are associated with few long-term effects on prolactin serum levels. Elevations in prolactin are not clinically meaningful

unless accompanied by galactorrhea, gynecomastia, and amenorrhea, which may lead to decreased bone mineral density. Emerging evidence suggests that the newest novel antipsychotic, aripiprazole, is less likely to cause increases in prolactin due to its partial D2 antagonism.

QTc Prolongation

Changes in QTc intervals have been observed with ziprasidone and thioridazine. However, there are currently no formally agreed upon limits for what is "normal" QTc, nor has a minimum threshold of risk been defined. Furthermore, QTc is highly variable across individuals, raising the question of whether a change from one assessment to the next is necessarily indicative of cardiac pathology. In the event that persistent changes in QTc are observed for a patient, clinicians may consider switching agents. In patients with other risk factors for QTc prolongation, clinicians may consider alternative antipsychotics. However, Dr. Masand cautioned that they should weigh the relative dangers of maintaining the patient on ziprasidone vs switching the patient to an agent associated with significant risk of weight gain or diabetes.

Antipsychotics of the Future

Robert Conley, MD, of the University of Maryland Medical Center, Maryland Psychiatric Research Center, Baltimore, reviewed the new novel antipsychotics and their application across multiple domains of impaired functioning associated with schizophrenia. Historically, pharmacologic treatment for schizophrenia has tended to focus on attenuating positive symptoms. The advent of the novel antipsychotics marked an improvement in the treatment of schizophrenia because many of these agents decrease both positive and negative symptoms. However, attention to cognitive and other domains of impairment associated with schizophrenia has tended to lag behind. Thus, an ideal antipsychotic of the future would demonstrate efficacy not only in treating positive and negative symptoms associated with schizophrenia but would also decrease cognitive impairments, stabilize mood, calm patients, minimize the long-term cardiovascular and metabolic disturbances inherited with schizophrenia, and cause few side effects.

New Preparations of Current Novel Antipsychotics

In the meantime, new preparations of currently available novel antipsychotics are currently under investigation. Within the next year, risperidone will be available in a long-acting preparation, and within the next 2-3 years, olanzapine will also be available in a long-acting depot formulation. Because quetiapine's recommended dose may be lower than needed to achieve efficacy, investigations are currently underway to test its safety at higher doses; efforts to test its efficacy and tolerability in a sustained-release preparation are ongoing.

Aripiprazole: The Newest "Novel" on the Horizon

The newest antipsychotic agent under review for the treatment of schizophrenia is aripiprazole. Aripiprazole is considered to be a partial dopamine agonist (ie, it has a high affinity for dopamine receptors, but there is 10% intrinsic dopamine activity). Aripiprazole has demonstrated superior efficacy for positive and negative symptoms relative to placebo and has demonstrated

antipsychotic efficacy comparable to risperidone.[74] More data are needed to determine if 1 of the clinical implications of its partial agonism of dopamine is the emergence of fewer associated unwanted side effects than those seen with some of the other novel antipsychotics (eg, hyperprolactinemia associated with risperidone).

Novels and Cognitive Improvements

Cognitive impairments displayed by schizophrenic patients include deficits in executive functioning; verbal fluency; working memory; verbal and visual learning and memory; and attention, any or all of which may actually serve as prodromes of a psychotic episode. If, indeed, psychotic episodes are "brain toxic," swift recognition and treatment of these prodromes may improve the prognosis of individuals at risk for future psychotic episodes while simultaneously improving the cognitive functioning of schizophrenic patients.

As new antipsychotics are developed, attention to their ability to ameliorate cognitive impairments may become a more meaningful, important criterion for efficacy. In the meantime, the cognitive effects of currently available agents are being examined more closely. Emerging evidence suggests that the novel antipsychotics may help to improve several domains of cognitive functioning in schizophrenic patients. Meltzer and McGurk[75] have reviewed the data on the ability of clozapine, risperidone, and olanzapine to ameliorate the cognitive impairments in schizophrenia and found considerable evidence that clozapine improves attention and verbal fluency, and moderate evidence that clozapine improves difficulties with executive function. Risperidone appears to be helpful in improving working memory, executive functioning, and attention. Olanzapine appears be helpful in improving verbal learning and memory, verbal fluency, and executive function, but not attention, working memory, or visual learning and memory.

Conclusion

The novel antipsychotics have dramatically improved the treatment of individuals suffering from schizophrenia and other forms of severe and persistent mental illness. Their ability to ameliorate both positive and negative symptoms, their improved tolerability, and their broad spectrum of efficacy make them preferable to the conventional neuroleptics in many cases. Nonetheless, they are associated with their own treatment-emergent adverse events, including weight gain, diabetes, elevated prolactin levels, and QTc prolongation. As the understanding of the biological underpinnings of schizophrenia and related disorders evolves and new targets for medications are developed, patients are offered the hope of improved prognosis for these diseases as well as an improved quality of life. Continued research into the mechanism of action of these medications, their associated side effects, and their benefits across different subgroups of patients will help inform the choices of clinicians who treat individuals with schizophrenia and other chronic mental illnesses.

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