New Developments in Antipsychotic Therapy

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference "New Developments in Antipsychotic Therapy," held September 25, 2003.*

The teleconference was chaired by ***Peter J. Weiden****, M.D., Department of Psychiatry, State University of New York Downstate, Brooklyn, N.Y. The faculty were* ***W. Wolfgang Fleischhacker****, M.D., Department of Psychiatry, Innsbruck University Clinics, Austria;* ***John M. Kane****, M.D., Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, N.Y.;* ***Stephen R. Marder****, M.D., Department of Psychiatry, West Los Angeles Veterans Affairs Medical Center, Calif.;* ***J. Michael Ryan****, M.D., Monroe Community Hospital, Rochester, N.Y.; and* ***Stephen M. Strakowski****, M.D., Department of Psychiatry, University of Cincinnati, Ohio.*

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Evolution of Antipsychotic Therapy: A Mechanism-Based Evaluation

W. Wolfgang Fleischhacker, M.D., began the meeting by reviewing the history of the mechanism-based development of antipsychotic drugs. Mechanism-based studies commenced with Paul Janssen's clinical observation in Belgian cyclists that the dopamine agonist amphetamine led to psychosis and abnormal movements similar to those seen in schizophrenia patients. Expanded knowledge about the pathophysiology of schizophrenia, especially the development and acceptance of the dopamine hypothesis, has also motivated more mechanism-based research. After the success of clozapine, which has a number of pharmacologic actions beyond blocking dopamine receptors, the focus shifted to other transmitter systems. According to Dr. Fleischhacker, all of this research, along with advances in psychosocial therapies, has led to several new treatment approaches to schizophrenia (Table 1).

More recent research in schizophrenia has focused on the various subsystems of dopamine neurotransmission,[1] reported Dr. Fleischhacker. However, except for the successful development of specific dopamine D_2 antagonists such as the benzamide amisulpride, research into other specific dopamine receptor subsystems has been largely unsuccessful. Specific D_4 or D_1 antagonists, for example, have not been clinically effective. The most recent addition to the attempts to modulate dopaminergic transmission is the development of aripiprazole, a partial D_2 agonist, which has been shown to be an effective treatment in schizophrenia patients.[2,3]

Other research, Dr. Fleischhacker pointed out, has examined agents that have no direct effect on the dopamine system, although most of them have indirect effects on dopaminergic pathways. The putative antipsychotic action of these drugs has been studied as both monotherapy and add-on treatment. Dr. Fleischhacker presented a list of these agents categorized by mechanism of action (Table 2), and discussed some of the more promising agents—serotonin antagonists, *N*-methyl-D-aspartate (NMDA) glutamate receptor agonists, omega-3 fatty acids, and hormones—in more detail.

Serotonin Antagonists

Dr. Fleischhacker noted that a number of serotonin (5-HT) antagonists have been tried as add-on therapy in patients suffering from schizophrenia, although largely without success against the full spectrum of symptoms. Whereas some results show that these 5-HT antagonists, especially 5-HT_2 antagonists, were effective treatments for negative symptoms,[4] other studies show the opposite.[5]

Glutamate Receptor Agonists

Another system that has been explored in schizophrenia, Dr. Fleischhacker explained, is the glutamate neurotransmitter system. Since

Table 1. New Treatment Approaches in Schizophrenia

Antipsychotics that are chemically similar to existing treatments
New administration routes for second-generation antipsychotics
Newly discovered pharmacologic mechanisms
Pharmacologic add-on strategies
New psychosocial interventions
Combination of pharmacologic and psychosocial interventions
Availability of all of the above to all patients

Table 2. Putative Antipsychotics With No Direct Effect on Dopamine Receptors

Serotonin antagonists
Ritanserin
MDL 100,907
N-methyl-D-aspartate (NMDA) agonists
Glycine
D-Serine
D-Cycloserine
Omega-3 fatty acids
DHA (docosahexaenoic acid)
EPA (eicosapentaenoic acid)
Hormones
Estrogen
Neuropeptide agonists
γ-Endorphin
γ-Aminobutyric acid (GABA) agonists
Diazepam
Bretazenil
Norepinephrine antagonists
Idazoxan
σ Receptor Antagonists
Rimcazole
Panamesine

postmortem glutamate levels are low in patients who had schizophrenia and since receptor antagonists of NMDA (a subtype of the glutamate receptor) induce schizophrenia-like symptoms, it is thought that glutamate dysfunction is part of the pathophysiology of schizophrenia.[6] In fact, the addition of agents such as glycine,[7] D-serine,[8] and D-cycloserine[9] to ongoing antipsychotic treatment has been shown to decrease the severity of negative symptoms and possibly cognitive impairment.

Omega-3 Fatty Acids

Dr. Fleischhacker explained that phospholipids are vital compounds of cell membranes. These phospholipids can break down due to oxidative stress, resulting in cell membrane damage, which in neurons can lead to impaired neuronal function. Neuronal damage may in turn explain the psychosis of schizophrenia. A diet low in calories and supplemented by antioxidants and unsaturated fatty acids may correct phospholipid damage; this correction in patients with schizophrenia should theoretically improve illness outcomes.[10] However, according to Dr. Fleischhacker, large clinical trials with the omega-3 fatty acids docosahexaenoic acid (DHA)[11] and eicosapentaenoic acid (EPA)[11–13] have provided inconsistent results.

Hormones

Dr. Fleischhacker noted that women with schizophrenia are older than men at onset of the illness, and symptoms seem to be tied to the menstrual cycle among women who have not yet reached menopause. In addition, women have a lower risk of relapse during pregnancy.[14,15] The epidemiology and course of schizophrenia in women, then, would imply that estrogen has an effect on the illness. Pilot studies of estrogen as a treatment for schizophrenia have produced inconsistent yet encouraging results.[16–18]

Dopamine-2 Partial Agonists

According to Dr. Fleischhacker, the only new mechanism-based agent that has been proven clinically efficacious is one developed as a partial agonist of the dopamine D_2 receptor, the new atypical antipsychotic aripiprazole. Aripiprazole is a high-affinity partial agonist at D_2 receptors. Under conditions of dopamine hyperactivity, it functions as a dopamine antagonist, and under conditions of dopamine hypoactivity, it functions as a dopamine agonist.[19] This antipsychotic has demonstrated efficacy and safety in treating both the positive and negative symptoms of schizophrenia when compared with placebo, haloperidol, and risperidone.[2,3]

Conclusion

A number of mechanisms of action have been explored during the past 30 years. The most successful target in schizophrenia pharmacotherapy is still blockade of D_2 receptors. However, the advent of partial agonists at the dopamine D_2 receptor have greatly enhanced the possibility of treating psychosis. In addition, agents with other mechanisms of action that have been mainly tried as add-on therapies thus far seem to be effective against some of the specific subsyndromes of schizophrenia such as negative and affective symptoms as well as cognitive impairment.

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Acute Treatment of Schizophrenia

Peter J. Weiden, M.D., discussed new developments in the treatment of acute psychosis. Treatment of this phase includes controlling agitation and psychosis immediately, ensuring rapid and sustained response to treatment, and treating all types of symptoms.

One area of interest in acute treatment is the examination of why some physicians rely on conventional antipsychotics early in treatment and whether short-acting intramuscular (i.m.) formulations of atypical antipsychotics will meet those needs. Another area of research in acute treatment of schizophrenia is the possibility of rapid response, by either rapid dose escalation or concomitant treatment with a different type of agent. An effective treatment should not only address acute psychosis and agitation, but it should also alleviate negative and mood symptoms. Lastly, atypical antipsychotic doses should be optimized to ensure the best possible response.

Short-Acting Intramuscular Formulations of Atypical Antipsychotics

Dr. Weiden noted that the first short-acting i.m. atypical antipsychotic available in the United States is ziprasidone. In one study,[1] symptom reduction was significantly greater in the group treated with ziprasidone i.m. than in the group treated with haloperidol i.m. In addition, the ziprasidone-treated group had lower rates of extrapyramidal symptoms (EPS); fewer movement disorders and lower rates of use of anticholinergic medications were noted in the ziprasidone-treated group. Although moderate QTc increases have been reported with ziprasidone treatment, this study of the i.m. formulation found similarly low increases in QTc in both ziprasidone- and haloperidol-treated patients.

Dr. Weiden noted that short-acting i.m. formulations of other atypical antipsychotics are currently being studied. For example, i.m. olanzapine is in the final stage of development and study of i.m. aripiprazole has started. He argued that with the better EPS profile of the atypicals compared with conventional drugs as well as the new black box warning on the older agent droperidol, i.m. formulations of atypical antipsychotics may be the new standard of care when treating acute psychosis.

Rapid Response

Another area of interest, according to Dr. Weiden, is the attempt for a more rapid response to oral atypical antipsychotic treatment in the first week or so of treatment. For many agents, the rapidity of response may be related to a rapid titration schedule. For example, a recent study[2] examined olanzapine as an acute treatment for agitated patients with psychosis or mania. Patients received either rapid initial dose escalation of olanzapine (up to 40 mg/day on days 1 and 2, up to 30 mg/day on days 3 and 4, and up to 20 mg/day thereafter) or usual clinical practice. Agitation in both groups of patients had decreased significantly after 24 hours, but patients on the rapid dose escalation treatment saw a greater benefit than did those on treatment as usual.

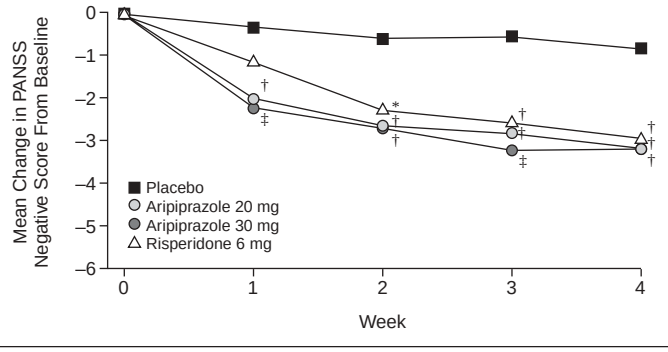
Dr. Weiden pointed out that adding a different type of medication to antipsychotic treatment may be another way to boost response. A combination study[3] showed that adding divalproex to acute treatment with either risperidone or olanzapine led to more rapid acute psychotic symptom resolution than either antipsychotic alone. Several strategies, then, are available that can hasten response and bring about earlier reduction of symptoms than we see in usual clinical practice.

Broad-Spectrum Efficacy of Atypical Antipsychotics

Dr. Weiden then discussed the newest antipsychotic, aripiprazole, which has been shown to be as effective as the older comparator haloperidol.[4] A recent study[5] also found that aripiprazole, 20 or 30 mg/day, was as efficacious as 6 mg/day of risperidone. Patients treated with either agent experienced a significant decrease in Positive and Negative Syndrome Scale (PANSS) total scores, positive scores, and negative scores compared with placebo. In the aripiprazole groups, the separation from placebo in PANSS negative subscale scores occurred at week 1; in the risperidone-treated group, this separation occurred at week 2 (Figure 1). In addition, patients treated with aripiprazole experienced few EPS and little-to-no weight gain or serum prolactin level increases.

Dr. Weiden argued that these efficacy results support the notion that results from short-term, atypical antipsychotic trials look more similar than different in the acute phase of the illness. Although the atypicals have more broad-spectrum efficacy, they do not match clozapine for efficacy against the most severe persistent posi-

Figure 1. Mean Change in PANSS Negative Scores From Baseline During 4 Weeks of Treatment with Aripiprazole, Risperidone, or Placebo[a]



[a]Reprinted with permission from Potkin et al.[5]
*p < .05 vs. placebo. †p < .01 vs. placebo. ‡p < .001 vs. placebo.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

tive symptoms. For example, Kane and coworkers[6] found that clozapine was significantly more effective in treating positive and negative symptoms of schizophrenia than the conventional agent chlorpromazine. Although many studies of atypical agents have used that basic design—comparing the atypical to the conventional after a prospective lead-in with another antipsychotic to establish nonresponse—they have not shown the kind of effects that were shown with clozapine. Dr. Weiden offered that psychiatry is still looking for another clozapine without its dangerous side effects, and that the newer medicines available now have not achieved that goal.

Optimal Dosing

Dr. Weiden said that the understanding of how to best dose these newer medications—in particular, quetiapine, ziprasidone, and aripiprazole—continues to evolve. Quetiapine[7] and ziprasidone[8,9] seem to have a linear dose response curve within the therapeutic range, such that higher doses will move a patient toward higher levels of response. In contrast, a meta-analysis of aripiprazole[10] shows that equivalent efficacy occurs across the therapeutic range, from 15 to 30 mg/day. These controlled trials are helpful to establish reasonable dosing parameters. The antipsychotic treatment should then be adjusted to optimize individual patient response.

Conclusion

The study of schizophrenia and the measurement of its symptoms have not changed at the same pace, Dr. Weiden stated. Although clinicians and researchers are more and more concerned with finding ways to treat the negative symptoms, mood symptoms, and cognitive dysfunction associated with schizophrenia, the standard outcome scales have not changed. In addition, clinicians and researchers are more aware of side effects and their effects on a patient's health and quality of life. While more research is clearly needed in antipsychotic medications, cognitive-behavioral therapies may be able to improve symptoms over and above what medication can do alone. When moving beyond the acute phase, then, promising approaches exist that combine medicines with certain kinds of psychosocial treatments, and it may be that the best outcomes will be the result of these combinations.

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Diagnostic Boundaries Between Bipolar Disorder and Schizophrenia

Stephen M. Strakowski, M.D., addressed the challenges of distinguishing between bipolar disorder and schizophrenia. The conditions share many symptoms, which makes diagnosis difficult, especially in patients experiencing their first episode of psychosis. Fortunately, second-generation antipsychotics appear to be effective for both disorders, although Dr. Strakowski emphasized that effective treatments are not a replacement for accurate diagnosis.

A Historical Perspective

Dr. Strakowski began by pointing out that almost a hundred years ago, Emil Kraepelin[1] attempted to distinguish between bipolar disorder and

schizophrenia when he differentiated manic-depressive insanity from what he called dementia praecox, which has more or less evolved into the current diagnosis of schizophrenia. Kraepelin primarily based this distinction on the differences in the course of illness that the conditions exhibited; that is, patients with manic-depressive insanity showed a recovery between acute exacerbations, whereas patients with dementia praecox showed a more deteriorating, chronic course.

Although Kraepelin's distinction was an advance in psychiatry, practically and clinically it was not particularly helpful. Clinicians could not wait the many years necessary to determine a course of illness before diagnosing, treating, and prognosticating the illness. Therefore, throughout much of the rest of the century, a significant effort was made to identify ways to separate what are now known as bipolar disorder and schizophrenia from each other through different symptoms and symptom constructs, which evolved into the *International Classification of Disease* and *Diagnostic and Statistical Manual of Mental Disorders* criteria.

For most of the 20th century, reported Dr. Strakowski, distinguishing between bipolar disorder and schizophrenia was an academic exercise because the treatments for the disorders were not particularly different. It was not until the development of lithium as a treatment that making the distinction became important; people with bipolar disorder responded quite well to lithium, whereas those with schizophrenia did not.

Shared Symptoms of Bipolar Disorder and Schizophrenia

Dr. Strakowski explained that bipolar disorder and schizophrenia share many symptoms (Table 3), thereby making it difficult to decide in an acute, cross-sectional evaluation with which illness the patient is presenting. Both conditions present with psychosis, particularly in the manic phase of bipolar disorder. Attempts to identify types of psychotic symptoms that are specific for each condition have typically failed, especially in multicultural samples.

Table 3. Bipolar Disorder and Schizophrenia: Common Symptoms

Psychotic
Depressive
Manic[a]
Neurovegetative
Cognitive
Negative[b]

[a]Manic syndrome is relatively specific for bipolar disorder.
[b]Negative syndrome is relatively specific for schizophrenia.

Depressive symptoms are also common to both disorders. Almost all patients with schizophrenia will develop depressive episodes at some point in their course of illness. Mania, one of the most specific syndromes in psychiatry and a relatively good predictor of a bipolar course, may unfortunately resemble an acute agitated psychotic exacerbation of schizophrenia. Both conditions share neurovegetative symptoms and signs as well as cognitive disabilities. Finally, schizophrenia has a relatively specific negative syndrome, but in clinical practice, this negative syndrome can be difficult to distinguish from bipolar depression.

With so many shared symptoms, the course of illness really is the determining factor differentiating these conditions, but clinicians cannot wait to see what the course is going to be before deciding upon treatment. Complicating diagnosing bipolar disorder and schizophrenia is that a large number of patients do not fit neatly in either group, and those patients, who bridge the 2 groups, are therefore diagnosed as schizoaffective disorder patients. Recently, an alternate approach has suggested that affective illness is a continuum with schizophrenia at the severe end and unipolar depression at the mild end. Dr. Strakowski acknowledged that although this was an interesting conceptual model that may be correct in that there seem to be some shared genes, it still does not help to develop treatment strategies.

Making a Diagnosis in Patients With New-Onset Psychosis

According to Dr. Strakowski, determining a diagnosis of bipolar disorder or schizophrenia in patients with a new-onset psychotic illness is difficult because there is no prior psychiatric history, so no course of illness data exist. Another complicating factor in first-episode psychosis is that patients and their families are confused: the patient does not understand what is happening and the family has never seen this behavior in the patient. Therefore, the psychiatrist has little information with which to make a diagnosis, so preliminary diagnoses are often assigned on the ability to identify the relative prominence of manic or depressive symptoms, which often are upstaged in acute psychosis by the more dramatic psychotic symptoms. Occasionally, family history information is helpful, but unfortunately many patients with bipolar disorder often have schizophrenia in their family and vice versa.

In light of the difficulties associated with differentiating between bipolar disorder and schizophrenia, clinicians must try to make the best diagnosis possible and then identify the most useful treatment, recognizing that approximately 15% of patients who are diagnosed with either affective psychosis or schizophrenia will be assigned another diagnostic category within 1 to 2 years.[2] Further, patients with schizophreniform disorder, a diagnosis frequently given to patients with first-episode psychosis and often thought of as a category for people who will develop schizophrenia, go on to develop conditions other than schizophrenia, primarily affective psychosis, at a rate of about 40%.[3]

Treating Patients With New-Onset Psychosis

Dr. Strakowski reminded clinicians that, when initiating treatment in new-onset psychotic patients, they must realize that diagnosis is tenuous and will have to be reconsidered over time. Historically, an uncertain diagnosis presented the problem of deciding which treatment to use: a mood stabilizer, such as lithium or divalproex, which is effective for mania but not particularly effective for psychosis, or a conventional antipsychotic, which is effective for mania but not particularly effective

for preventing depressive symptoms and may even worsen the depression in bipolar patients. Fortunately, the development of the second-generation antipsychotics has helped to solve the problem of how to treat new-onset psychosis patients who may have bipolar disorder or schizophrenia. In recent years, all second-generation antipsychotics—risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole—have been shown to be effective acute antimanic treatments, thus providing a new class of treatment alternatives for managing new-onset psychosis patients who might have a manic condition.

Second-Generation Antipsychotics as Antidepressant and Maintenance Treatments

Dr. Strakowski reported that a second-generation antipsychotic, olanzapine, has been shown to be an effective acute antidepressant in bipolar disorder[4] as well as an effective maintenance agent in bipolar disorder.[5] These findings are important because they suggest that the newer antipsychotics, unlike the conventional antipsychotics, may treat and not worsen bipolar depression. Dr. Strakowski allowed that this effect could be specific to olanzapine, but he suspected that the effect will be found in several of the new antipsychotics. They seem to share the ability to treat depressive symptoms in patients with schizophrenia, which suggests that they have some antidepressant properties. Quetiapine[6] and aripiprazole[7] demonstrated some ability to prevent recurrence of affective illness in 12-week mania trials, suggesting atypical antipsychotics other than olanzapine may have maintenance capability.

Choosing a Second-Generation Antipsychotic

Because the various second-generation antipsychotic drugs have been shown to be effective for psychosis and mania, Dr. Strakowski suggested that clinicians may find themselves choosing a treatment on the basis of an agent's side effect profile. They should identify in a given patient what side effect is likely to be most problematic and then match the patient with a drug that has a low risk for that side effect. For example, if a patient is overweight, that patient should be treated with a drug that does not cause weight gain. Similarly, if a young muscular patient may be at high risk for EPS, that patient should be treated with a drug that has a low propensity for EPS.

Acute Versus Long-Term Treatment

Dr. Strakowski offered that the treatment used in acute mania or psychosis is not necessarily the treatment that will be used long term. In most patients with bipolar disorder, the type of treatment changes throughout the course of illness and the demands of the illness require a fairly dynamic and flexible treatment plan. The treatment goal is to always strive toward a single mood stabilizer, and for some patients that may be a second-generation antipsychotic. However, the reality is that most bipolar patients will receive some combination of mood stabilizers, antipsychotics, and, perhaps, antidepressants as treatment. Similarly, in schizophrenia, clinicians should attempt to strive toward a single antipsychotic, but as is the case with bipolar patients, most schizophrenic patients will be treated with different combinations over time. Fortunately, a completely expanded treatment armamentarium for bipolar disorder is now available, which provides opportunities for novel interventions that may not have been identifiable even a decade ago.

Conclusion

Dr. Strakowski concluded by asserting that clinicians cannot become imprecise diagnosticians because second-generation antipsychotics can be used to treat bipolar disorder and schizophrenia. Instead, they must recognize that these are nonspecific treatments, and if more specific (and ideally more effective) treatments are to be developed, clinicians have to continue to refine their ability to distinguish among different psychiatric disorders.

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Long-Term Treatment of Schizophrenia: Moving From a Relapse-Prevention Model to a Recovery Model

John M. Kane, M.D., spoke on the long-term treatment of schizophrenia, focusing specifically on treatment strategies to achieve functional recovery in patients with schizophrenia.

Functional Recovery as an Outcome for Long-Term Treatment

Dr. Kane started by stating some of the challenges in the long-term treatment of schizophrenia: ensuring response of symptoms to treatment, ensuring treatment adherence, and facilitating psychosocial and vocational functioning. The ultimate outcome of long-term treatment is functional recovery, which is achieved through the integration of relapse

prevention with psychosocial and vocational therapies.

Dr. Kane opined that, so far, psychiatrists have fallen short in terms of producing ideal levels of functional recovery. He cited data from a study[1] of patients with first-episode schizophrenia that suggested that the patients had a relatively low rate of recovery over a 5-year period, despite participating in what Dr. Kane considered a well-staffed research program using state-of-the-art treatment, albeit with conventional antipsychotic drugs.

Strategies for Enhancing Recovery

Dr. Kane offered several strategies for enhancing the likelihood of recovery. First, treatment should be improved through the use of antipsychotic medications that are more broadly effective and better tolerated, so patients will be more likely to maintain wellness and adhere to treatment. Next, care should be integrated more efficiently across patient service delivery systems and among providers. Finally, communication should be improved between clinicians and patients, clinicians and other caregivers, and clinicians and patients' families.

Reducing relapse rates. Focusing on pharmacotherapy as a recovery strategy, Dr. Kane pointed to data that suggest that relapse rates in patients with schizophrenia may be reduced with the second-generation antipsychotics. Leucht et al.[2] reviewed 11 studies, with a total of over 2000 patients, on the prevention of schizophrenic relapse in patients who were treated with newer antipsychotics; the authors concluded that these agents may reduce relapse. According to this analysis, compared with conventional antipsychotics, second-generation agents had statistically significant lower relapse rates. In terms of treatment failure, 49% of patients treated with second-generation antipsychotics dropped out of the studies early, whereas 66% of patients treated with conventional agents did so.

Improving treatment adherence. Dr. Kane reiterated that among patients with schizophrenia, nonadherence to treatment is often a factor in their relapse but adherence may be improved with second-generation medications. An analysis[3] of pharmacy refill records for a 12-month period revealed that the adherence rate was higher in patients taking the second-generation agents risperidone (N = 80), olanzapine (N = 63), and quetiapine (N = 28) than in patients taking the conventional agents haloperidol (N = 57) and perphenazine (N = 60). At 6 months, patients taking the second-generation antipsychotics had a significantly ($p = .05$) higher adherence rate, and although these patients maintained that higher rate at 12 months, the difference was no longer significant. Even with second-generation medications, adherence is not ideal. In this analysis, patients taking second-generation agents went without medication for approximately 4 days per month.

Advances in Antipsychotic Treatment for Recovery

Dr. Kane reminded clinicians that, because the second-generation medications have safety and tolerability advantages over the conventional antipsychotics, the likelihood of improving the rate of functional recovery for patients with schizophrenia is possible, assuming clinicians can provide appropriate medical monitoring and management.

Dr. Kane echoed others' hope that recent advances with newer-generation antipsychotics show promise for facilitating recovery of patients with schizophrenia. Aripiprazole has been found to be an effective long-term maintenance treatment for schizophrenia.[4] In a 52-week multicenter, randomized, double-blind trial, patients (N = 1294) were assigned to treatment with aripiprazole or haloperidol. More aripiprazole-treated patients responded and continued treatment than did haloperidol-treated patients. Negative and depressive symptoms were significantly ($p < .03$) improved with aripiprazole over haloperidol.

Another advance is the development of a long-acting injectable form of risperidone, which is available in many countries and should be available soon in the United States. Long-acting risperidone was administered to schizophrenic patients (N = 615) during a 12-month trial.[5] Three different doses—25 mg, 50 mg, or 75 mg—were used, and patients in all dose-groups improved. Total scores on the PANSS improved significantly ($p < .01$), as did scores on the positive ($p < .01$) and negative ($p < .001$) factors.

Conclusion

Dr. Kane summed up his presentation by suggesting that effective medication treatment is the enabler that makes the recovery of function possible. The success of rehabilitation or psychosocial treatment is dependant upon sound pharmacotherapy. Therefore, increasing the rates of functional recovery in schizophrenia is a matter of taking advantage of new developments in antipsychotic treatment and ensuring that they are integrated with other forms of treatment that are not always readily available to all patients, such as psychosocial and vocational therapies. With all these elements in place, moving from a relapse-prevention model to a recovery model in schizophrenia treatment is possible.

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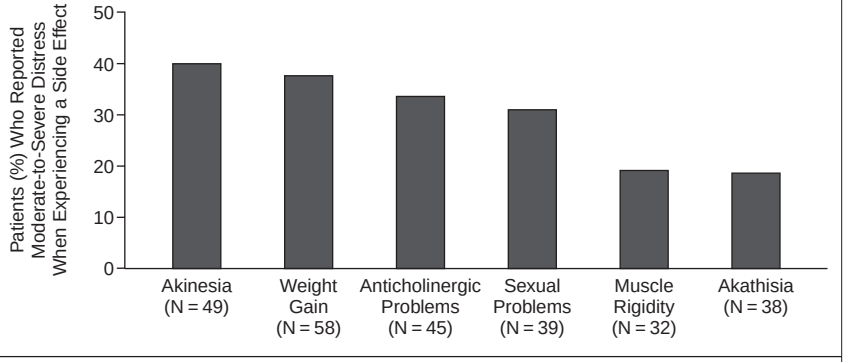
Figure 2. Rank Order of Side Effects That Elicited Moderate-to-Severe Distress in a Study of 99 Outpatients With Stable Schizophrenia Treated With Conventional Antipsychotics or Risperidone[a]



[a]Data from Weiden and Miller.[1]

Safety and Tolerability of Long-Term Antipsychotic Therapy

Stephen R. Marder, M.D., spoke about how safety and tolerability of antipsychotic therapy can influence the long-term outcomes of patients with schizophrenia. For example, patients who are unable to tolerate the side effects of an antipsychotic might discontinue their treatment and experience a recurrence of psychotic symptoms. Even if patients regularly take an antipsychotic, the benefits on mental health might be outweighed by the negative effects on physical health. To ensure that patients with schizophrenia control their psychotic symptoms without greatly impacting their physical health, Dr. Marder outlined some common side effects of antipsychotics, monitoring recommendations, and the degree to which currently used antipsychotics are associated with these side effects.

Importance of Attending to Side Effects

Dr. Marder advised that clinicians who prescribe long-term treatment for patients with schizophrenia must routinely monitor and control medication side effects to make certain that patients continue to take their antipsychotic and have good physical health. As Dr. Marder explained, a patient's subjective view of an antipsychotic is often shaped by the side effects that the patient experiences. Therefore, if patients with schizophrenia tell their clinicians that they like a particular antipsychotic, the reason could be that they like the side effect profile of the drug. Alternatively, if patients dislike an antipsychotic, the reaction could be caused by discomfort related to a side effect.

To address the value of examining patients' distress in response to side effects, Dr. Marder cited a study by Weiden and Miller.[1] The authors asked 99 outpatients with schizophrenia who were stable on first-generation antipsychotic or risperidone treatment not only whether they were experiencing a side effect but also how much distress the side effect caused them. The side effect that was most disturbing to patients during chronic treatment was akinesia, followed closely by weight gain, anticholinergic problems, and sexual problems (Figure 2). However, some patients felt no or only mild distress related to a side effect they experienced. Weiden and Miller pointed out that objective physical findings might not correlate with subjective distress. Dr. Marder concluded that by asking how much a side effect actually upsets individual patients, clinicians will be better able to determine whether or not the patient is likely to continue taking the drug over the long term.

In addition to influencing compliance, side effects can affect patients' physical health. Dr. Marder reported that the impact of antipsychotics on physical health is of great concern because patients with schizophrenia already have increased risk for mortality compared with the general population. He referenced a review by Harris and Barraclough,[2] which found that individuals with schizophrenia have about a 20% shorter life expectancy than the general population. Dr. Marder explained that in 2000, the average life expectancy was 77 years for the general U.S. population[3] but would have been only 62 years for people with schizophrenia. Although the increased risk for suicide in patients with schizophrenia contributes to the greater mortality, natural causes such as circulatory, digestive, respiratory, and genitourinary diseases add to patients' risk.[2] Dr. Marder added that increased risk for developing those diseases is a side effect of some antipsychotics.

Safety and Tolerability Profiles of Antipsychotics

Dr. Marder reported that many antipsychotics are associated with the same side effects, but the antipsychotics differ in the degree of risk for these adverse effects, including weight gain, dyslipidemia, elevated prolactin level, and EPS (Table 4). During his discussion, Dr. Marder provided some specific examples.

The risk for weight gain varies greatly among antipsychotics according to a report by Allison and coworkers.[5] The newer-generation antipsychotics clozapine and olanzapine and the first-generation antipsychotics thioridazine and mesoridazine were associated with the greatest weight gains while ziprasidone, fluphenazine, and haloperidol were associated with the lowest. Aripiprazole, the newest antipsychotic, was not included in that comparison because the drug was not available at the time. The results of a recent 26-week randomized double-blind study[6] in 310 patients with stable chronic schizophrenia showed that

Table 4. Frequency of Side Effects of Newer-Generation Antipsychotics[a]

Side Effect	Aripiprazole	Clozapine	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Weight gain	±	+++	+++	+	+	±
Dyslipidemia	±	+++	+++	++	+	±
Diabetes mellitus	±	+++	+++	+	+	±
QTc prolongation	±	++	+	+	+	++
Decrease in orthostatic blood pressure	±	+++	+	++	++	±
Elevated prolactin level	±	±	±	±	+++	±
Extrapyramidal symptoms	± to +	±	± to + *	±	± to + *	± to + *
Tardive dyskinesia	± (?)	±	± (?)	± (?)	± to +	± (?)
Somnolence	±	+++	+	++	±	±

[a]Adapted, with permission, from Jibson and Tandon.[4]
Symbols: * = dose related; (?) = not clearly established; ± = no to minimal, + = occasional, ++ = frequent, +++ = substantial occurrence of side effect compared with placebo rates.

weight gain was comparable for aripiprazole and placebo. Another 26-week double-blind trial[7] compared weight changes in 317 patients randomly assigned to treatment with aripiprazole or olanzapine for acute relapse of schizophrenia. Patients taking olanzapine gained a mean weight of 4.2 kg (9.3 lb) while those taking aripiprazole lost a mean weight of 1.4 kg (3.1 lb), a significant difference ($p < .001$).

Recent research has also compared the risk for hyperlipidemia among antipsychotics. When Lambert et al.[8] analyzed a Medi-Cal database of 4371 patients with schizophrenia, the researchers found that clozapine and olanzapine but not quetiapine or risperidone were associated with a substantially greater risk for hyperlipidemia than were first-generation antipsychotics. In the study[7] of aripiprazole and olanzapine, hyperlipidemia occurred more often in the group taking olanzapine than in the group taking aripiprazole.

Dr. Marder noted that because each antipsychotic has a unique side effect profile, switching the antipsychotic might be a useful intervention for patients who are unable to tolerate an adverse effect of their current medication.

Monitoring for Side Effects

Compared with the general population, patients with schizophrenia are, as a group, at higher risk for conditions such as hyperlipidemia and type 2 diabetes mellitus. Taking antipsychotics associated with these illnesses further raises patients' risk. Dr. Marder advised that clinicians should always ask patients about side effects to determine subjective distress and also test for side effects to determine medications' effects on physical health. He highlighted recommendations developed at the Mount Sinai consensus conference.[9]

Weight gain/unfavorable body mass index. Clinicians should be aware of their patients' body mass index (BMI), and patients should be weighed at every clinical visit for the first 6 months after therapy with a new antipsychotic is begun and then every 6 months thereafter.

Dyslipidemia. Cholesterol and triglyceride levels should be checked before patients begin treatment with a new antipsychotic and every year thereafter for most patients, especially those who gain more than 7% of their body weight while taking the medication. If abnormal lipid levels are found, psychiatrists should ensure that patients with schizophrenia receive standard recommended treatment such as therapy with a cholesterol-lowering drug.

Type 2 diabetes mellitus. Baseline glucose level should be tested for all patients before they start a new antipsychotic. For individuals who have a significant risk factor for diabetes, such as a gain of more than 7% of their body weight or a family history of diabetes, fasting glucose or hemoglobin A_{1C} level should be monitored 4 months after starting an antipsychotic and then yearly.

Cardiovascular disease. Because patients with schizophrenia are at high risk for obesity, hyperlipidemia, and type 2 diabetes mellitus, they are also at great risk for cardiovascular disease. In general, an electrocardiogram will be unnecessary. However, patients taking thioridazine, mesoridazine, or ziprasidone, which can substantially prolong the QTc, should receive an electrocardiogram at baseline and every year after.

Elevated prolactin level. A marked increase in prolactin level can cause intolerable sexual side effects that lead to treatment discontinuation. Therefore, clinicians should question patients about sexual side effects yearly. Women should be asked about changes in menstruation, libido, and unexpected lactation. Men should be asked about changes in libido and erectile and ejaculatory functioning.

Movement disorders. Movement disorders such as EPS and tardive dyskinesia are associated, to some degree, with every antipsychotic. Rating scales may be useful in identifying these conditions. All patients should be monitored for EPS at baseline, at every visit as long as symptoms are present, and then yearly if symptoms are not a problem. Symptoms of tardive dyskinesia should be assessed at baseline and every 6 months for patients taking first-generation antipsychotics and every year for patients taking a newer-generation antipsychotic.

Conclusion

Dr. Marder concluded his presentation by saying that to ensure good long-term outcomes in schizophrenia, the clinician must be aware of which antipsychotic side effects each patient is experiencing and how the side effects are impacting the individual's physical health.

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Newer-Generation Antipsychotics for the Management of Psychosis in Older Patients With Dementia

J. Michael Ryan, M.D., spoke about the prevalence of neuropsychiatric symptoms in older patients with dementia and psychosis. He addressed considerations for using antipsychotic therapy in this special population, including the efficacy and safety of treatment with some newer-generation antipsychotics for these patients.

Prevalence of Neuropsychiatric Symptoms in Older Patients With Dementia

Dr. Ryan noted that until Lyketsos et al.[1] published a population-based study in 2000, little was known about the prevalence of neuropsychiatric symptoms in community-dwelling older patients with dementia. Lyketsos and colleagues identified neuropsychiatric symptoms in 1002 patients aged 65 years or older using the Neuropsychiatric Inventory (Table 5). The 1-month prevalence of any neuropsychiatric symptom in participants with dementia was 60%. About 19% of the subjects with dementia had delusions, and about 14% experienced hallucinations.

Special Considerations for the Antipsychotic Management of Older Patients With Dementia

According to Dr. Ryan, clinicians must consider the special characteristics of older patients with dementia when choosing an antipsychotic.

Antipsychotic choice often depends on the side effect profiles of medications because older patients are often more frail and susceptible to adverse effects such as cardiovascular and metabolic complications, anticholinergic effects, EPS, tardive dyskinesia, and sedation than are younger patients. Dr. Ryan explained the potential consequences of some adverse effects. EPS and tardive dyskinesia can result in poor coordination, disfigurement, social isolation, and falls that might cause lethal injuries in older patients. Sedation may interfere with activities of daily living, and anticholinergic effects may worsen confusion and memory impairment in patients with dementia.

Comorbid medical disorders and concomitant medications also influence antipsychotic choice. In a study[2] of almost 300,000 older nursing home residents in 5 U.S. states, participants had, on average, more than 3 medical conditions. More than 20% of the subjects were taking 10 or more medications.

Safety of Newer-Generation Antipsychotics in Older Patients With Dementia

A growing body of literature has shown that newer-generation antipsychotics effectively reduce psychotic symptoms without dangerous side effects in older patients with dementia. Dr. Ryan highlighted some of the outcomes from controlled clinical trials of risperidone, olanzapine, quetiapine, and aripiprazole.

Risperidone. Katz et al.[3] conducted a 12-week double-blind, placebo-controlled trial of risperidone in 625 patients aged 55 years or older who had dementia and lived in a nursing

Table 5. Frequency of Neuropsychiatric Inventory Item Domains in 1002 Participants With or Without Dementia in a Community Study of People Aged 65 Years or Older in Cache County, Utah[a]

	With Dementia (N = 329)		Without Dementia (N = 673)	
Item Domain	N	%	N	%
Apathy	90	27.4	21	3.1
Depression	78	23.7	47	7.0
Agitation/aggression	78	23.7	19	2.8
Irritability	67	20.4	30	4.5
Delusions	61	18.5	16	2.4
Anxiety	56	17.0	38	5.6
Hallucinations	45	13.7	4	0.6
Aberrant motor behavior	47	14.3	3	0.4
Disinhibition	30	9.1	6	0.9
Elation	3	0.9	2	0.3

[a]Adapted with permission from Lyketsos et al.[1] Data for some patients are missing for some domains.

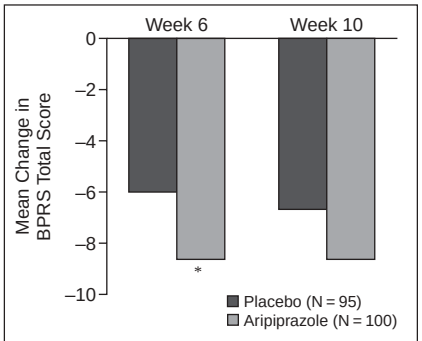
home or in a hospital for patients with chronic diseases. Compared with patients who took placebo, more patients treated with 1 or 2 mg/day of risperidone experienced ≥ 50% improvement in total Behavioral Pathology in Alzheimer's Disease rating scale scores. The side effect profile of the 3 doses of risperidone (0.5, 1.0, and 2.0 mg/day) was generally good, but dose-related increases were seen in the rates of some adverse events such as somnolence and EPS. Interestingly, the incidence of falls was lower in the groups of patients who took 0.5 or 1.0 mg/day (but not 2.0 mg/day) of risperidone than in the group who took placebo. Whether treating psychosis in dementia with an appropriate dose of an antipsychotic may reduce older patients' risk of falls is currently being investigated.

Olanzapine. In a 6-week, randomized, double-blind trial, Street and coworkers[4] compared the efficacy and safety of olanzapine and placebo in reducing psychotic symptoms in 206 subjects who ranged in age from 61 to 94 years, had Alzheimer's disease, and lived in a nursing home. The primary outcome measure was change from baseline to endpoint in Core Total (Agitation/Aggression, Hallucinations, and Delusions items) scores on the Neuropsychiatric Inventory–Nursing Home version. According to this criterion, patients treated with 5 mg/day of olanzapine experienced greater improvement (–7.6 change) than patients who received 10 mg/day (–6.1) or 15 mg/day (–4.9) of olanzapine and those who took placebo (–3.7). The only adverse events that occurred significantly ($p < .05$) more often in any olanzapine groups than in the placebo group were somnolence (a dose-related risk 4.9 to 8.2 times higher with olanzapine) and abnormal gait (7.5 to 11.2 times higher risk with olanzapine).

Quetiapine. Tariot et al.[5] conducted subanalyses for 284 subjects with Alzheimer's disease who participated in a 10-week, randomized, double-blind, placebo-controlled, flexible-dosing trial of quetiapine and haloperidol in 378 older nursing home patients with dementia and psychotic symptoms. The mean daily dose was 120 mg/day in the quetiapine group and 2 mg/day in the haloperidol group. All patients with Alzheimer's disease had substantial improvement in total Brief Psychiatric Rating Scale (BPRS) scores but not psychotic symptoms, regardless of treatment. Treatment with quetiapine and haloperidol did, however, reduce agitation significantly more than placebo did. Improvement in functioning was significantly greater with quetiapine than haloperidol. In general, the side effect profile of quetiapine was favorable. Compared with patients who took placebo or haloperidol, fewer patients treated with quetiapine had EPS, falls, or fractures. Anticholinergic effects were more prevalent in the placebo group than in the quetiapine and haloperidol groups, but somnolence occurred more often in the active treatment groups.

Aripiprazole. Aripiprazole, at flexible doses of 2 to 15 mg/day, was recently compared with placebo in a 10-week, randomized trial conducted by De Deyn et al.[6] The 208 community-dwelling patients, who had a mean age of 82 years, had been diagnosed with Alzheimer's disease and psychosis. The mean dose of aripiprazole at endpoint was 10 mg/day. The change from baseline to endpoint in the Neuropsychiatric Inventory Hallucinations and Delusions Subscale score was not significantly greater for the aripiprazole group than for the placebo group. However, the aripiprazole group had significantly greater decreases in total BPRS score at week 6 (Figure 3) as well as BPRS Core Subscale and BPRS Psychosis Subscale scores at study endpoint. There were no side effects occurring at an incidence of greater than or equal to 10% in the aripiprazole group. The only side effect that occurred at least 5% more often in the aripiprazole than the placebo group was somnolence (8% versus 1%). Somnolence was not associated with falls and no patients discontinued treatment due to somnolence. The incidence of EPS was similar in the 2 groups as assessed by the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale. A total of 13 falls occurred during the trial, 5 with placebo and 8 with aripiprazole.

Figure 3. Mean Change From Baseline in BPRS Total Score in 195 Patients Aged 55 Years or Older With Alzheimer's Disease Randomly Assigned to Treatment With Aripiprazole or Placebo (LOCF)[a]



[a]Adapted from De Deyn et al.[6] Baseline BPRS total scores were 43.42 in the placebo group and 43.63 in the aripiprazole group.
*p = .045 vs. placebo.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.

Future research. The National Institute of Mental Health and the University of North Carolina at Chapel Hill[7] are currently recruiting patients for an effectiveness study that will compare newer-generation antipsychotics in the management of outpatients with Alzheimer's disease and clinically significant psychosis or agitation.

Conclusion

Dr. Ryan noted that managing older patients with dementia and neuropsychiatric symptoms using the newer-generation antipsychotics can be effective and safe when a medication with a favorable side effect profile is chosen and given at an appropriate dose.

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Drug names

aripiprazole (Abilify), chlorpromazine (Sonazine, Thorazine, and others), clozapine (Clozaril and others), diazepam (Diastat, Valium, and others), divalproex (Depakote), droperidol (Inapsine and others), estrogen (Cenestin, Premarin, and others), fluphenazine (Permitil, Prolixin, and others), haloperidol (Haldol and others), mesoridazine (Serentil), olanzapine (Zyprexa), perphenazine (Trilafon and others), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage

Dr. Strakowski has determined that, to the best of his knowledge, aripiprazole, quetiapine, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of mania. If you have questions, contact the medical affairs department of the manufacturer for the most recent prescribing information.

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