Clinical Perspectives on Atypical Antipsychotics for Treatment of Agitation

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In the past, the use of atypical antipsychotics in treating acute agitation was limited by a lack of data in behavioral emergencies and by the lack of intramuscular formulations or alternate rapid-acting oral formulations. This article evaluates current data from studies of atypical antipsychotics in agitated patients in both short- and long-term care settings. For patients with underlying psychosis, intramuscular atypical antipsychotics are effective and help ease the transition from intramuscular therapy in the acute care setting to oral dosing in inpatient or community settings. Evidence exists that atypical antipsychotics demonstrate antiagitation effects in schizophrenic patients for as long as 10 weeks and that overall clinical response may be partly mediated by these antiagitation properties. Intramuscular and oral atypical antipsychotics effectively treat acute agitation in both emergency and long-term care settings. For bipolar patients, these agents are valid therapeutic options for acute as well as longer-term alleviation of manic symptoms, including agitation. Safety concerns, however, limit their use in agitated elderly patients with dementia. *(J Clin Psychiatry 2006;67[suppl 10]:22–31)*

Agitation is a common component of many psychiatric disorders.[1] It is traditionally listed among the "positive" symptoms of schizophrenia,[2] as well as among the behavioral and psychological symptoms of dementia.[3] In addition, agitation is a frequent presenting complaint in the psychiatric emergency setting, especially among patients with schizophrenia[4] or bipolar mania.[5]

The Psychopharmacological Drugs Advisory Committee of the U.S. Food and Drug Administration (FDA)[6] has emphasized the following key issues regarding the existence of the clinical entity "agitation":

- There needs to be agreement on a definition and diagnostic criteria for agitation.
- It is necessary to establish that agitation is the result of a common pathophysiologic mechanism regardless of disease state.
- A drug would need to be studied in several different disease models to demonstrate efficacy in managing agitation.

Although the development of diagnostic instruments, such as the Positive and Negative Syndrome Scale-Excited Component (PANSS-EC),[7] the Young Mania Rating Scale (YMRS),[8] and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD),[9] has contributed significantly to the definition and assessment of "agitation" in the clinical setting, these scales have found their greatest utility in the assessment of interventions, rather than in epidemiologic and pathophysiologic research.[1] To date, the pathophysiologic mechanisms behind agitation remain elusive, with research focusing on abnormalities in several different neurotransmitter systems (dopamine, norepinephrine, and γ-aminobutyric acid)[1] and on functional impairments[10] and/or microanatomic alterations in the frontal lobe.[11] Despite the lack of agreement regarding either a precise pathophysiology or even an immutable, uniform definition for "agitation" across disease states, important advances have taken place over the past decade in the treatment of the behavioral disturbance known as "agitation" as it appears in several different forms of mental illness. In particular, the development of atypical antipsychotic agents has been a boon to clinicians across a wide range of specialties and subspecialties who face the daily challenge of dealing with agitated patients in either the acute or chronic care setting.

ATYPICAL ANTIPSYCHOTICS IN THE ACUTELY AGITATED PATIENT

For decades, conventional antipsychotics and/or benzodiazepines have been the mainstay of treatment for acute psychosis, although the poor tolerability of conventional antipsychotics compromised their usefulness for both short- and long-term management.[12] Prior to the development of atypical antipsychotics, traditional therapy

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for acute agitation generally consisted of a combination of a conventional/typical antipsychotic (usually 5 mg of haloperidol) and a benzodiazepine (usually 2 mg of lorazepam) administered intramuscularly.[13] Unfortunately, it was soon well recognized that the use of these medications carried the potential for serious, and occasionally life-threatening, side effects. With haloperidol, these included extrapyramidal symptoms (EPS), cardiac arrhythmias, and neuroleptic malignant syndrome.[14] With benzodiazepines, the risks included respiratory depression, ataxia, excessive sedation, and paradoxical disinhibition.[14] Akathisia—the most common manifestation of EPS—is a particular problem with haloperidol and other first-generation agents because it can be difficult to differentiate from agitation.

Although atypical antipsychotics demonstrated more favorable side-effect profiles compared with older conventional therapies,[4] initially these drugs were not available in intramuscular (IM) formulations, a fact that limited their use in the treatment of agitation in the acute care setting.[12] In addition, as of the year 2000, none of the atypical antipsychotics (in their older, slower formulations) had a relevant supporting record of published data regarding their use in behavioral emergencies.[15]

Once newer atypical antipsychotics (e.g., ziprasidone) became available in IM formulations, preliminary studies[16,17] demonstrated their efficacy and good tolerability in the treatment of acute agitation associated with psychotic disorders. By 2003, olanzapine was also available as an IM preparation, joining IM ziprasidone as a novel and efficacious treatment option for patients experiencing acute psychotic episodes.[12] Currently, a total of 3 atypical antipsychotics are available in rapid-acting forms that can be employed in the treatment of behavioral emergencies: olanzapine (IM and orally disintegrating tablets), ziprasidone (IM only), and risperidone (orally disintegrating tablets).[5,18] In general, these atypical antipsychotics are as effective as typical antipsychotic drugs but with the advantage of a reduced incidence of side effects, such as akathisia, dystonia, and tardive dyskinesia.[4,18] In addition, the availability of the new rapid-acting forms of atypical antipsychotic agents also makes the eventual transition from the IM to the oral route easier and better tolerated.[18]

In the psychiatric emergency setting, the decision as to whether the medication used should be an atypical antipsychotic or an older conventional agent hinges on considerations of mental health history, the need for synergistic sedating properties, and the drug's potential side effect profile.[19] For example, in the acutely agitated patient with a known psychiatric illness for which antipsychotics are indicated, current clinical guidelines from the American College of Emergency Physicians (ACEP)[20] recommend the use of an antipsychotic (typical or atypical) as effective monotherapy for both the management of agitation and initial drug therapy. For agitated patients who are cooperative, ACEP guidelines[20] alternately suggest the use of an oral antipsychotic and an oral benzodiazepine.

A similar list of treatment recommendations for behavioral emergencies has recently been compiled by Allen and colleagues,[5] who employed a 61-question survey of 50 psychiatric experts (96% survey completion rate). These recommendations, which were designed as a 2005 update to the group's earlier 2001 Expert Consensus Guidelines,[21] emphasized that the use of various atypical antipsychotics should be dictated by the specific circumstances surrounding different behavioral emergencies.[5] For example, oral olanzapine alone, oral risperidone alone or in combination with a benzodiazepine, or the traditional combination of haloperidol plus a benzodiazepine for acute oral treatment of agitation related to schizophrenia or mania were recommended first-line treatments.[5] Alternatively, the newer treatment recommendations also strongly supported the combination of divalproex plus an antipsychotic in patients with presumed mania.[5] In circumstances that necessitated the use of IM formulations in patients with presumed schizophrenia, the new Expert Consensus Guidelines[5] favored IM olanzapine alone, IM ziprasidone alone, IM haloperidol plus a benzodiazepine, or IM olanzapine plus a benzodiazepine.

A 1999 survey[22] sponsored by the American Association for Emergency Psychiatry indicated that a majority of medical directors supported the use of the atypical antipsychotics in the management of agitated, hostile patients with no available psychiatric history. More recently, however, both the 2005 Expert Consensus Guidelines[5] and the ACEP[20] guidelines favor the use of either an IM benzodiazepine or IM haloperidol over the newer atypical antipsychotics. Both expert groups[5,20] recommend the older, traditional therapeutic approach in situations in which either no history is available for the patient or the patient's underlying illness is undifferentiated.

An overview of manufacturers' dosing recommendations for the rapid-acting IM formulations of ziprasidone and olanzapine has been provided in Table 1.[23–27] For each of these medications, special dosing considerations exist in select patient populations (e.g., in elderly or debilitated patients or patients with hepatic or renal impairment). In addition, it should be noted that IM ziprasidone has a capacity to prolong the QT/QTc interval,[23] while IM olanzapine may produce postural hypotension.[24]

LONGER-TERM TREATMENT OF AGITATION IN SCHIZOPHRENIA

Dosing recommendations for atypical antipsychotics in schizophrenia are provided in Table 2.[28–32] Since the year 2000, atypical antipsychotics have been considered first-line treatments for the major psychoses.[15] These drugs were hailed as a major advance over conventional

Table 1. Dosing Guidelines for Atypical Antipsychotics Used Commonly in Behavioral Emergencies

Formulation[a]	Dosing Method	Dosing Limits	Other Considerations
Ziprasidone IM[23] (Geodon [ziprasidone mesylate for injection for IM use only])	Dosing is in 10- to 20-mg increments 10-mg dose may be administered every 2 hours 20-mg dose may be administered every 4 hours	Maximum daily dose is 40 mg	IM administration for more than 3 days has not been studied Coadministration of ziprasidone IM is not recommended in schizophrenic patients already taking oral ziprasidone Ziprasidone IM has not been systematically evaluated in elderly patients or patients with hepatic or renal impairment Ziprasidone IM should be administered with caution in patients with impaired renal function Ziprasidone has a greater capacity to prolong QT/QTc interval than several other antipsychotic drugs
Olanzapine IM[24] (Zyprexa IntraMuscular [olanzapine for injection])	Efficacy for agitation lies within a dose range of 2.5–10 mg Recommended dose is 10 mg Lower dose (5 or 7.5 mg) may be considered when clinical factors warrant Consider 5-mg dose for geriatric patients or when other clinical factors warrant 2.5-mg dose may be warranted in debilitated patients, patients predisposed to hypotensive reactions, or pharmacodynamically sensitive patients	Safety has not been established for total daily dose > 30 mg Maximum dosing is 3 doses of olanzapine IM administered 2–4 hours apart	Efficacy of repeated IM doses has not been systematically evaluated in controlled clinical trials Maximum dosing of olanzapine IM may be associated with a substantial occurrence of significant orthostatic hypotension Patients requiring subsequent doses of olanzapine IM should be assessed for postural hypotension prior to dose administration Administration of additional doses of olanzapine IM is not recommended in patients already showing clinically significant postural change in systolic blood pressure
Olanzapine oral[25] (Zyprexa Zydis [olanzapine orally disintegrating tablets])	Recommended dose is 10 mg PO every 2 hours until the occurrence of endpoint of clinical effectiveness or limiting side effects[26]	Maximum dose is 40 mg for rapid pharmacologic treatment of agitation[26]	Recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition toward hypotensive reactions, who otherwise exhibit a combination of factors that may result in lower metabolism of olanzapine (e.g., nonsmoking female patients ≥ 65 years of age), or who may be more pharmacodynamically sensitive to olanzapine; when indicated, dose escalation should be performed with caution in these patients[26]
Risperidone oral[27] (Risperdal M-Tab [risperidone orally disintegrating tablets])	Recommended dose is 2 mg PO every 2 hours until the occurrence of endpoint of clinical effectiveness or limiting side effects[26]	Maximum dose is 12 mg for rapid pharmacologic treatment of agitation[26]	Decreased dosage is recommended for the following special populations: elderly or debilitated patients, patients with severe hepatic or renal impairment, patients predisposed toward hypotension, and patients for whom hypotension would pose a risk Decreased dosing increments or increased dosing intervals may be indicated in the above special populations[27]

[a]Geodon is a registered trademark of Pfizer; Zyprexa is a registered trademark of Eli Lilly; Zydis is a registered trademark of Cardinal Health or one of its subsidiaries; and Risperdal is a registered trademark of Janssen.
Abbreviation: IM = intramuscular.

Table 2. Dosing of Atypical Antipsychotics in Schizophrenia

Antipsychotic[a]	Initial Dosing	Maintenance
Aripiprazole[28] (Abilify [aripiprazole tablets and oral solution])	Recommended starting and target dose is 10–15 mg/day Aripiprazole has been systematically evaluated and shown to be effective in a dose range of 10–30 mg/day; however, doses > 10 or 15 mg/day were not shown to be more effective than 10 or 15 mg/day Dosage increases should not be made before 2 weeks	Benefits have been seen with a maintenance dose of 15 mg/day over a period of up to 26 weeks
Olanzapine[29] (Zyprexa [olanzapine tablets])	Administered on a qid schedule Initial dose is generally 5–10 mg, with a target dose of 10 mg/day within several days Efficacy has been demonstrated at 10–15 mg/day, but doses > 10 mg/day were not shown to be more effective than 10 mg/day Safety of doses > 20 mg/day has not been evaluated in clinical trials	Doses of 10–20 mg/day have effectively maintained treatment response in patients with schizophrenia
Quetiapine[30] (Seroquel [quetiapine fumarate tablets])	Initial dose is 25 mg bid, with increases in increments of 25–50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300–400 mg/day by the fourth day, given bid or tid Further dose adjustments, if indicated, should generally occur at intervals of not less than 2 days When dosage adjustments are necessary, dose increments/decrements of 25–50 mg bid are recommended	Efficacy was demonstrated at a dose range of 150–750 mg/day In 1 study, doses > 300 mg/day were not demonstrated to be more effective than the 300-mg/day dose; however, in other studies, doses in the range of 400–500 mg/day appeared to be needed The safety of doses > 800 mg/day has not been evaluated in clinical trials
Risperidone[31] (Risperdal [risperidone tablets/oral solution])	Administered bid or qid Early trials used a 1-mg bid initial dose, increased to 2 mg bid on the second day, and 3 mg bid on the third day Subsequent studies showed that doses of up to 8 mg qid were also safe and effective	A dose of 2–8 mg qid was effective at delaying relapses
Ziprasidone[32] (Geodon [ziprasidone hydrochloride oral capsules])	Initial daily dose is 40 mg bid, increased to 60 or 80 mg bid on the second day Subsequent increases in dosage up to 80 mg bid may be made on the basis of individual clinical status Dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days A dose > 80 mg bid is not generally recommended The safety of doses > 100 mg bid has not been systematically evaluated in clinical trials	Efficacy in schizophrenia has been maintained for periods of up to 52 weeks at a dose of 20–80 mg bid No additional benefit was demonstrated for > 20 mg bid

[a]Abilify is a registered trademark of Otsuka; Zyprexa is a registered trademark of Eli Lilly; Seroquel is a registered trademark of AstraZeneca; Risperdal is a registered trademark of Janssen; and Geodon is a registered trademark of Pfizer.

antipsychotics in the treatment of schizophrenic illness because of the reduced risk of adverse effects, higher rates of patient compliance, and potential superior treatment outcomes.[14] With respect to the symptom of agitation, there have been relatively few long-term studies or head-to-head comparisons that specifically have assessed the ability of atypical antipsychotics to decrease agitation in patients with schizophrenia over weeks or months.[33] For example, in a 2004 trial, Kinon's group[34] demonstrated that olanzapine produced a dramatic decrease (up to 18 points) in mean PANSS agitation scores over a 3-week treatment period. In a longer study (14 weeks) that compared 4 antipsychotics—clozapine, olanzapine, risperidone, and haloperidol—Volavka's group[35] concluded that atypical antipsychotics were superior to haloperidol in treatment-resistant inpatients (N = 157) with chronic schizophrenia or schizoaffective disorder, especially in the first 24 days of therapy. In their study,[35] which used PANSS scores as an endpoint, risperidone and olanzapine were more efficacious in patients with less aggressive behavior, whereas clozapine was more effective in patients with higher levels of aggression.

Most recently, Marder[36] used drug-manufacturer data sets (a total of 9 FDA registration and postmarketing trials) to compare baseline levels of agitation (high or low) to clinical outcomes in patients with schizophrenia. Based on assessments of PANSS total score, Marder[36] concluded that the atypical antipsychotics risperidone, olanzapine, ziprasidone, and aripiprazole showed continued efficacy in agitated patients with schizophrenia over periods as long as 8 weeks. In contrast to the findings of Volavka's group,[35] the antiagitation effect of the atypical antipsychotics in this study was found to be especially prominent in schizophrenic patients who had higher levels of baseline agitation (baseline PANSS-EC score ≥ 15, with a minimum score of 4 for excitement, hostility, tension, uncooperativeness, or poor impulse).

Specifically with respect to ziprasidone, Schooler and colleagues[37] recently presented findings regarding the long-term antiagitation efficacy of this drug in schizophrenic patients with differing levels of agitation at baseline. Based on assessments of patients' Clinical Global Impressions (CGI)[38] scale scores from two 10-week, randomized, placebo-controlled trials, these researchers[37] concluded that ziprasidone therapy produced a significant effect on the CGI scores in patients with both high and low levels of agitation at baseline. In this study,[37] a quantitative effect was found between agitation severity at baseline and the effects of ziprasidone treatment, indicating a relationship between agitation and treatment response. Moreover, based on the results of mediator analyses, it appeared that the overall response to ziprasidone observed in this long-term study might have been mediated, at least in part, by the antipsychotic's effects on schizophrenic patients' agitation symptoms.[37]

TREATMENT OF AGITATION IN MANIA

Beyond their use as schizophrenia therapy, atypical antipsychotics have been increasingly recognized as beneficial therapies for other types of psychiatric illnesses. As of the year 2000, investigators had already begun using the atypical antipsychotics as adjunctive therapy in the treatment of patients with bipolar disorder who were highly agitated, psychotic, or severely manic.[39] This prescribing practice was primarily based on results from open-label trials and case reports because, at that time, very few controlled clinical trials had established the efficacy of atypical antipsychotics in this "off-label" indication.[40] Conversely, the use of atypical antipsychotics as first-line therapy for mania was not recommended because of safety concerns since, at the time, there was a paucity of evidence regarding the propensity of these agents to cause tardive dyskinesia.[39]

As the third millennium progressed, however, it became increasingly apparent that remission rates associated with traditional mood stabilizers (lithium and divalproex) were clearly inadequate with respect to the treatment of patients with bipolar mania.[41] As a result, drug manufacturers and independent investigators responded to this clinical need by conducting a series of randomized controlled clinical trials to support the use of atypical antipsychotics in the bipolar-manic population. Table 3 summarizes some of the major studies[42–53] (conducted between 2002 and 2006) currently available to support the use of atypical antipsychotics in the ongoing treatment of mania associated with bipolar disorder. It also provides data from double-blind, controlled clinical trials for a number of clinically significant efficacy measures, including the YMRS, CGI, Montgomery-Asberg Depression Rating Scale (MADRS),[54] PANSS, and Global Assessment Scale (GAS).[55] These trials support the use of atypical antipsychotics in the acute and maintenance treatment of mania, both as effective alternatives to the mood stabilizers (lithium or divalproex) in monotherapy and in combination with the mood stabilizers.[8,56] In a 2005 review, Yatham[8] concluded that the sum of the evidence suggested that olanzapine, risperidone, quetiapine, aripiprazole, and ziprasidone all are effective in the treatment of acute mania, with no significant difference in antimanic efficacy among these agents. Most recently, however, in a head-to-head comparison of 4 antipsychotics (risperidone, olanzapine, ziprasidone, and aripiprazole) involving 8 clinical trials, Sachs[57] suggested that among the atypical antipsychotics, risperidone and aripiprazole may actually show the most consistent and clinically significant efficacy in bipolar mania when statistically significant decreases in total YMRS scores are used as a yardstick.[57] If, however, treatment response is defined as a ≥ 50% decrease in total YMRS scores compared to baseline,[58,59] then based on Sachs's data comparisons, only risperidone

Table 3. Randomized, Double-Blind Trials of Atypical Antipsychotics in the Longer-Term (≥ 3 weeks) Treatment of Bipolar Mania Conducted Between 2002 and 2006

Antipsychotic	Disease Entity and Study Design, Duration, and Size	Outcome	Adverse Events Associated With the Atypical Antipsychotic	Publication (Year)
Risperidone				
Mean modal dose: Risperidone (3.8 mg/d) Haloperidol (6.2 mg/d)	Bipolar disorder with manic or mixed episode RDBPC Patients treated with a mood stabilizer + risperidone or a mood stabilizer + haloperidol 3 weeks N = 156	High discontinuation rates: 53% for haloperidol 49% for placebo 35% for risperidone YMRS scores improved in both the risperidone and haloperidol groups compared with placebo Risperidone was more efficacious than a mood stabilizer alone Efficacy of risperidone plus a mood stabilizer was comparable to haloperidol plus a mood stabilizer	Percentage of patients who required antiparkinsonian medications: 38% haloperidol 17% risperidone 8% placebo group	Sachs et al (2002)[42]
Risperidone flexible dose (1–6 mg/d)	Bipolar I with manic or mixed episode RDBPC 3 weeks N = 290	At weeks 1 and 2 and study endpoint, risperidone produced significant improvements compared with placebo in YMRS, CGI, MADRS, PANSS, and GAS scores	EPS were the most frequently reported adverse event in the risperidone group	Khanna et al (2003)[43]
Risperidone mean modal dose (4.4 mg/d)	Mania RDBPC 3 weeks N = 259	Risperidone produced significant improvement in YMRS scores beginning at day 3 compared with placebo Risperidone also produced significant improvements in CGI severity rating, PANSS, and GAS scores	Somnolence was the most common adverse event in the risperidone group EPS Rating Scale scores were significantly greater in risperidone-treated patients than in the placebo group	Hirschfeld et al (2004)[44]
Risperidone (1–6 mg/d) Haloperidol (2–12 mg/d)	Acute bipolar mania RDBPC for 3 weeks followed by RDBAC (haloperidol) for 9 weeks N = 438	At week 3, YMRS score reductions from baseline were greater with risperidone than placebo There were no significant differences in YMRS scores between risperidone and haloperidol	EPS occurred less frequently with risperidone than haloperidol	Smulevich et al (2005)[45]
Olanzapine				
Olanzapine (5–20 mg/d) Divalproex (500–2500 mg/d)	Bipolar disorder with acute mania or mixed episodes RDBAC olanzapine vs divalproex 3 weeks N = 248	Olanzapine treatment produced greater improvement in YMRS scores Quetiapine treatment produced more remissions (47.2%) than divalproex treatment (34.1%) and a significantly greater proportion of patients who achieved protocol-defined remission	Adverse events occurring more frequently (> 10%) with olanzapine included dry mouth, increased appetite, and somnolence There was higher mean weight gain with olanzapine (2.5 kg) than with divalproex (0.9 kg)	Tohen et al (2002)[46]
Olanzapine (2.5–10.0 mg IM)	3 studies of acutely agitated patients RDBPC and RDBAC Schizophrenia, N = 311 Bipolar mania, N = 201 Dementia, N = 206	Excluding asleep patients, agitation remained significantly more reduced with olanzapine than placebo Among active treatment groups, the rates of scores reaching calm states were faster during treatment with olanzapine	The sedating effects of olanzapine were comparable to haloperidol or lorazepam	Battaglia et al (2003)[47]
Olanzapine (5–20 mg/d) Haloperidol (3–15 mg/d)	Bipolar mania RDBAC Olanzapine vs haloperidol 12 weeks N = 453	Based on the YMRS, rates of remission were similar for olanzapine (52.1%) and haloperidol (46.1%)	Olanzapine had lower rates of EPS than haloperidol but more weight gain	Tohen et al (2003)[48]

continued

Table 3. Randomized, Double-Blind Trials of Atypical Antipsychotics in the Longer-Term (≥ 3 weeks) Treatment of Bipolar Mania Conducted Between 2002 and 2006 (cont.)

Antipsychotic	Disease Entity and Study Design, Duration, and Size	Outcome	Adverse Events Associated With the Atypical Antipsychotic	Publication (Year)
Ziprasidone				
Ziprasidone (40–80 mg bid)	Bipolar mania RDBPC Inpatients 21 days N = 202	There were significant improvements in YMRS, CGI, and MRS scores from day 2 onward	Discontinuations: 5.8% ziprasidone 1.5% placebo	Potkin et al (2005)[49]
Ziprasidone (40–80 mg bid)	Bipolar I patients with manic or mixed episode RDBPC 3 weeks N = 201	There were significant improvements in SADS (includes MRS) and CGI severity scale scores within 2 days Improvement was maintained for the 3-week study duration	Ziprasidone tolerability was generally comparable to placebo	Keck et al (2003)[50]
Aripiprazole				
Aripiprazole (30 mg/d except when reduced to 15 mg/d for tolerability)	Bipolar patients with manic or mixed episode RDBPC 3 weeks N = 262	There were statistically significant improvements in YMRS scores compared with placebo	Aripiprazole was not associated with elevated serum prolactin or QTc elevation	Keck et al (2003)[51]
Aripiprazole 15 or 30 mg/d	Bipolar I disorder patients recently hospitalized and treated for a manic or mixed episode RDBPC 6–18 weeks N = 633	Superior to placebo in delaying time to relapse Aripiprazole-treated patients had significantly fewer relapses (25%) vs placebo (43%)	Akathisia, pain in the extremities, tremor, and vaginitis were more common in aripiprazole-treated patients than placebo	Keck et al (2006)[72]
Quetiapine				
Quetiapine (titrated to maximum of 450 mg/d by day 7) Divalproex (initial dose 20 mg/kg/d; serum level 80–130 mg/dL)	Adolescents with bipolar disorder and mania RDBPC Quetiapine in combination with divalproex 6 weeks N = 30	The quetiapine + divalproex group had significantly greater reductions in YMRS scores compared with the placebo + divalproex group The YMRS response rate was significantly greater in the quetiapine + divalproex group (87%) than in the placebo + divalproex group (53%)	There were no significant between-group differences in safety measures Sedation (mild or moderate) was more common in quetiapine + divalproex group than in the placebo + divalproex group	Delbello et al (2002)[52]
Quetiapine (rapidly dosed to a maximum of 800 mg/d) Lithium (dosed to 0.7–1.0 mEq/L) Divalproex (dosed to 50–100 μg/mL)	Bipolar disorder and acute mania RDBPC (1) Quetiapine + divalproex or lithium, or (2) placebo + divalproex or lithium 3 weeks N = 191	Quetiapine combined with either divalproex or lithium showed superior efficacy (as measured by the YMRS) compared with either lithium or divalproex monotherapy	Common adverse events (≥ 10%) in patients who received quetiapine included somnolence, dry mouth, asthenia, and postural hypotension	Sachs et al (2004)[53]

Abbreviations: CGI = Clinical Global Impressions scale; EPS = extrapyramidal symptoms; GAS = Global Assessment Scale; MADRS = Montgomery-Asberg Depression Rating Scale; MRS = Mania Rating Scale; PANSS = Positive and Negative Syndrome Scale; RDBAC = randomized, double-blind, active comparator trial; RDBPC = randomized, double-blind, placebo-controlled trial; SADS = Schedule for Affective Disorders and Schizophrenia; YMRS = Young Mania Rating Scale.

and olanzapine achieved treatment response in at least 1 trial of agitated bipolar patients.[57]

Considering long-term (≥ 3 weeks) adverse events, a review of Table 3 reveals that risperidone use was associated with both somnolence and EPS, although the incidence of EPS appeared to be less than for haloperidol.[42,45] For olanzapine, weight gain was of particular significance,[46,48] while, for quetiapine, there were higher rates of somnolence, dry mouth, asthenia, and postural hypotension.[53] The limited number of trials[49–51,72] involving ziprasidone and aripiprazole have all emphasized the favorable safety profile of these medications.

ALZHEIMER'S DISEASE: TREATMENT OF DEMENTIA-RELATED AGITATION

Among all patients with Alzheimer's disease (AD), the incidence of agitation is estimated to be 60% to 80%,[60] with approximately 50% of community-dwelling AD patients afflicted by the problem, versus 70% to 90% of nursing home residents.[61] In terms of human suffering, agitation and its associated symptoms (aggression, combativeness, hyperactivity, wandering, hypervocalization, and disinhibition) have long been recognized as among the most devastating and problematic behaviors in patients with AD, since these behaviors often lead to great caregiver distress and resultant institutionalization of the patient.[62]

With respect to treatment options for agitation in AD dementia, both pharmacologic and nonpharmacologic interventions have been used, but implementation of nonpharmacologic interventions often has been limited by practical considerations, especially in the managed care setting.[63] As an alternative to nonpharmacologic interventions, pharmacotherapy with antipsychotics, particularly atypical antipsychotics, has proven to be an effective strategy in the amelioration of agitation and psychosis in patients with dementia, especially when environmental manipulation has failed.[64] As of 2003, several consensus statements had been published that support the modest effectiveness of both typical and atypical antipsychotics as pharmacotherapy for the treatment of dementia-related agitation.[60] Additionally, in the 2004 Expert Consensus Guidelines,[65] a survey of 48 leading experts in the field of geriatrics showed that 90% recommended antipsychotics (risperidone, quetiapine, or olanzapine) as first-line treatment in dementia with agitation and delusions, while 60% listed antipsychotics as the first-line treatment in dementia with agitation without delusions.[65] As of 2005, risperidone was the atypical antipsychotic with the largest database of double-blind, controlled clinical trials supporting its efficacy and safety in the treatment of agitation, aggression, and psychosis associated with dementia.[66] Moreover, among all the atypical antipsychotics, the antiagitation effect of risperidone appeared to be especially prominent in patients with dementia who exhibited the highest levels of agitation at baseline.[67]

Most recently, Mintzer's group[68] has similarly demonstrated a significant antiagitation effect for aripiprazole when this drug is used on highly agitated patients with AD and associated psychosis. Based on analyses of several test instruments (Neuropsychiatric Inventory psychosis subscore [NPI-P],[68] Clinical Global Impressions-Improvement [CGI-I] scale, Cohen-Mansfield Agitation Inventory [CMAI],[69] and NPI-agitation/aggression[70]) in two 10-week, randomized, placebo-controlled trials (N = 723), Mintzer et al.[68] concluded that highly agitated patients who were treated with aripiprazole demonstrated both overall clinical improvement and significant decreases in agitation symptoms compared with placebo-treated control subjects. In this study, group differences were evident only in patients with high baseline agitation levels, a finding that was similar to the antiagitation effect seen with risperidone.[67]

In April 2004, despite substantiated clinical efficacy, the "off-label" use of atypical antipsychotics in the treatment of dementia drew the attention of the FDA as a result of reports of higher death rates, compared with placebo, among elderly patients.[71] Currently, at the FDA's request, all manufacturers of atypical antipsychotics have added a boxed warning to their drug labeling that describes this risk of fatalities and notes that atypical antipsychotics are not approved for the treatment of behavioral symptoms in elderly patients.[71]

SUMMARY AND FUTURE DIRECTIONS

As a behavioral manifestation of mental illness, agitation remains a therapeutic challenge for clinicians across a wide range of specialties, from emergency medicine to chronic psychiatric and geriatric care. Currently, rapid-acting intramuscular and oral forms of atypical antipsychotics have found a valuable place in the armamentarium of therapies used to treat acute agitation in the emergency setting, especially in patients who present with an established history of psychotic illness. For patients with underlying psychosis, these same rapid-acting formulations also help ease the transition from emergent therapy in the acute care setting to standard oral dosing in the inpatient or community milieu. In addition, when atypical antipsychotics are used in the longer term, there is mounting evidence that these drugs show continued antiagitation efficacy in patients with schizophrenia over periods as long as 8 to 10 weeks and that overall clinical response may be partly mediated by the antipsychotic's antiagitation properties.

For patients with bipolar disorder, atypical antipsychotics have found a place alongside older mood stabilizers as recognized therapeutic options for acute as well as longer-term alleviation of manic symptoms, including

agitation. Although current safety concerns limit the use of atypical antipsychotics in agitated elderly patients with dementia, future research may yet re-establish a place for the safe use of these medications in the treatment of this and other select patient populations.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), divalproex (Depakote), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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