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The Utility of Intramuscular Ziprasidone in the Management of Acute Psychotic Agitation

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Many psychiatric illnesses, including chronic schizophrenia, bipolar disorder, and dementia, are characterized by episodes of acute agitation, making administration of oral agents difficult or impossible. Ziprasidone, the first atypical antipsychotic available in both intramuscular (IM) and oral formulations, has demonstrated significant control of acute agitation within 15 minutes, as seen in two 24-hour studies in patients with schizophrenia. Improvement was maintained for ≥ 4 hours, and a low incidence of extrapyramidal symptoms, akathisia, and dystonia as well as no excessive sedation were observed. Also, two 7-day studies (n = 132 and n = 306) and one 6-week study (n = 567) of sequential IM/oral ziprasidone versus IM/oral haloperidol in patients with psychotic disorders found IM ziprasidone more effective than IM haloperidol within 3 days of IM treatment; both drugs produced further comparable improvements in efficacy parameters after transition to oral therapy. IM ziprasidone was associated with a lower incidence of movement disorders than was haloperidol in all of these studies. Overall, discontinuations were similar for IM ziprasidone and haloperidol in the comparative trials, including the sequential IM/oral studies. However, in the 6-week sequential IM/oral trial, the rate of discontinuation due to adverse events was twice as high among haloperidol vs ziprasidone patients. This report focuses on the pharmacology, clinical efficacy, and tolerability of IM ziprasidone, and provides an overview of the utility of other commonly used antipsychotics in the management of acute psychotic agitation.

Keywords IM ziprasidone; Psychotic agitation; Schizophrenia.

INTRODUCTION

Episodes of acute psychotic agitation remain one of the most difficult daily challenges facing clinicians. They represent a critical time in a patient's treatment during which the way the agitation is managed may have a bearing on the therapeutic alliance between patient and clinician. Acute psychotic agitation often occurs in patients suffering from a number of psychiatric illnesses, including chronic schizophrenia, schizoaffective disorder, bipolar disorder, and dementia. These psychiatric emergencies demand immediate intervention. The goal of acute intervention in these patients is always to decrease any behaviors that put the individuals at risk of hurting themselves or others. The clinician needs to ascertain whether the patient will respond to redirection or to being removed from his or her present environment. Clinicians should always treat agitation in the least restrictive manner possible. In episodes in which agitation fails to respond to these initial interventions, or in episodes of severe agitation, the clinician must consider immediate intervention with a rapidly acting medication. Acutely agitated patients may become uncooperative or even violent, making treatment with an oral medication a clinically difficult or even impossible task (1). Consequently, conventional intramuscular (IM) antipsychotics, such as haloperidol (2), which are often used as first-line agents or concomitantly with a benzodiazepine (e.g., lorazepam), have traditionally been used to control agitation in this cohort of patients. However, conventional antipsychotics such as haloperidol, given as IM injections, can have undesirable effects: haloperidol can induce extrapyramidal symptoms (EPS), such as

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acute dystonia, which may cause distress to the patient and possibly dim prospects for patient adherence to long-term therapy, and akathisia, which may be misinterpreted as further worsening of agitation. Benzodiazepines are generally well tolerated, but can sometimes result in excessive sedation, ataxia, confusion, and, in rare instances, respiratory depression (2).

The newer atypical antipsychotics are increasingly being used in first-line oral treatment of schizophrenia. They are comparable to the older conventional drugs in effectiveness in controlling the positive and negative symptoms of the disease, while carrying a reduced potential for inducing EPS. However, until recently, no atypical antipsychotic has been available for IM administration.

In the emergency treatment of acute psychotic agitation, the ideal IM atypical antipsychotic would offer rapid tranquilization without profound dysphoric sedation (to facilitate interview/evaluation) and would be devoid of producing movement disorders, which frighten patients and may negatively affect future compliance. In addition, an easy and effective transition from IM to longer-term oral therapy is another desirable feature of an IM atypical antipsychotic (3).

Ziprasidone is the first atypical to be introduced in a rapidly acting IM formulation and in an oral formulation. Thus, it is currently unique among the atypicals in addressing the entire unique treatment continuum from crisis management to acute and chronic therapy. The following will focus on the pharmacologic, clinical efficacy, and tolerability/safety data for IM ziprasidone and provide an overview of the utility of other commonly used antipsychotics in the management of acute psychotic agitation.

ZIPRASIDONE PHARMACOLOGY OVERVIEW

Ziprasidone has a unique pharmacologic profile. It has a high affinity for 5-HT (serotonin; 5-HT_{2A}, 5-HT_{2c}, 5-HT_{1A}, and 5-$HT_{1B/1D}$) and dopamine D_2 receptors, and inhibits neuronal uptake of 5-HT and norepinephrine (4). These characteristics predict clinical efficacy against positive, negative, and affective symptoms of schizophrenia (4). Ziprasidone's receptor-binding activities are also associated with its low potential for inducing EPS, cognitive deficits, and weight gain (4).

Ziprasidone treatment has not demonstrated sustained elevations of prolactin levels, which are thought to arise from dopamine D_2 receptor blockade of the tuberoinfundibular pathway during treatment with conventional antipsychotics (5). Among the potential undesirable consequences associated with hyperprolactinemia are amenorrhea and sexual dysfunction, which may interfere with patient adherence to treatment.

IM ziprasidone exhibits predictable pharmacokinetics. Peak serum concentration (C_{max}) is attained quickly, consistent with ziprasidone's rapid onset of clinical effect. Observed time to maximum serum concentration (T_{max}) is <1 hour (6). A short elimination half-life ($t_{1/2}$ <3 hours) after multiple IM dosing results in little or no drug accumulation (7). The bioavailability of IM ziprasidone is 100%, with dose-proportional exposure (6).

EFFICACY: ZIPRASIDONE IM CLINICAL TRIAL OVERVIEW

Efficacy in 24-Hour Studies

The primary goals of treatment in patients with acute psychotic agitation are the achievement of rapid and sustained efficacy, a smooth transition from IM to oral dosing as early as possible, and overall improvement in disease severity. Although agitation can occur across multiple disease states, the initial trials with ziprasidone IM were performed in patients with schizophrenia or schizoaffective disorder. Two 24-hour, double-blind, randomized trials demonstrated that IM ziprasidone achieves rapid control of acute psychotic agitation (8,9), and the results of these trials indicate optimal response with a 20-mg dose. Daniel and colleagues (8) compared treatment with up to 4 injections of IM ziprasidone 20 mg or IM ziprasidone 2 mg (used as a control) over a 24-hour period in 79 acutely agitated patients with psychosis. Several validated instruments were used to assess treatment efficacy, including the Behavioral Activity Rating Scale (BARS™), the Clinical Global Impression of Severity (CGI-S) Scale, and the Positive and Negative Symptom Scale (PANSS). The BARS was developed as a tool to rapidly evaluate agitation level, and can be administered frequently based on clinical observation (10). Patients are given a score on a 7-point scale in which 1 corresponds to "difficult or unable to rouse" and 7 to "violent."

In examining this data set (8,9), it is important to be aware of the methodologic issues that present themselves to investigators evaluating agitation. Because ziprasidone IM is a newer formulation, studies of its efficacy must evaluate it in comparison with a control. An additional requirement is that patients need to provide written informed consent to participate. As one can imagine, it is difficult to include the most agitated patients in this type of controlled design because such individuals cannot sign informed consent. As a result, the level of agitation in these studies is lower than some of the patients physicians treat in emergency settings.

The mean baseline BARS score in the study by Daniel and colleagues (8) was 5.0 (overt and active), and no patient had a baseline BARS score of 7 or 1 (Figure 1). Improvement in agitation was noted as early as 15 minutes following the initial 20 mg IM dose of ziprasidone. At 30 minutes following the initial 20 mg dose, BARS scores had decreased significantly from baseline ($p < 0.01$ vs the 2 mg group) to a score of approximately 4.0 (quiet and awake).

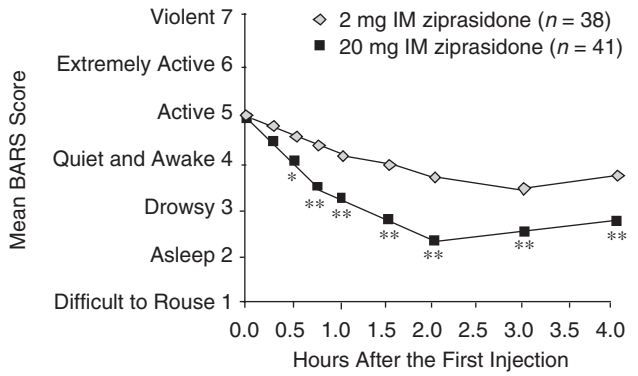

Figure 1 Mean BARS scores 0–4 hours after the initial injection of IM ziprasidone 2 mg and 20 mg. *$p < 0.01$ vs 2 mg. **$p < 0.001$ vs 2 mg. (Adapted with permission from Daniel et al. [8].)

Maximal response was attained at 2 hours following the initial 20 mg dose: 90.2% of patients met the a priori criteria for response (a reduction of ≥2 points on the BARS) compared with 34.2% of patients in the 2 mg group ($p < 0.001$). Significant reductions in scores were sustained at ≥4 hours following the initial 20 mg IM ziprasidone dose ($p < 0.001$ vs the 2 mg dose). Consistent with the improvements in BARS scores were significant reductions in PANSS Agitation items ($p < 0.05$) and CGI-S scores ($p < 0.001$) at 4 hours after the initial 20 mg IM injection.

Lesem and colleagues (9) studied 117 patients randomly assigned to receive up to 4 injections of IM ziprasidone 10 mg or the 2 mg control dose over 24 hours. As in the Daniel study (8), rapid improvement in agitation was noted; in this study, reductions in BARS scores were significant at 15 minutes following the initial injection ($p < 0.05$ vs the 2 mg dose) (Figure 2). In patients receiving IM ziprasidone

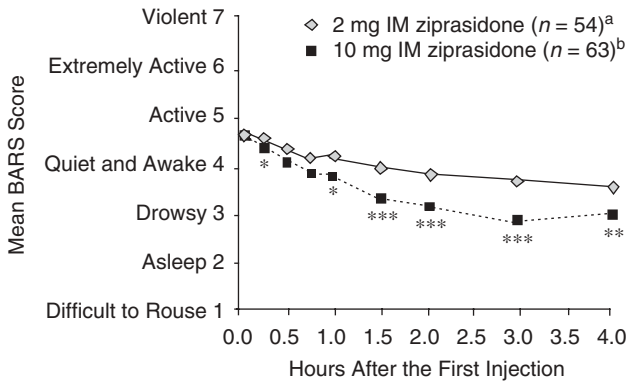

Figure 2 Mean BARS scores 0–4 hours after the initial injection of IM ziprasidone 2 mg and 10 mg. [a]At baseline, $n = 54$; at 2 hours, $n = 54$; at 4 hours, $n = 45$. [b]At baseline, $n = 63$; at 2 hours, $n = 62$; at 4 hours, $n = 55$. *$p < 0.05$ vs 2 mg. **$p < 0.01$ vs 2 mg. ***$p \leq 0.001$ vs 2 mg. (Adapted with permission from Lesem et al. [9].)

10 mg, reduced symptoms of acute agitation from a baseline mean BARS score of approximately 5 to <4.0 within 1 hour of the initial dose ($p < 0.05$ vs 2 mg dose). The BARS responder rate (improvement in BARS score of ≥2 points) for IM ziprasidone 10 mg was lower than that observed in the Daniel trial (8) for the 20 mg dose but was still significantly greater than the control dose. At 2 hours following the initial dose, 57.1% of patients who received IM ziprasidone 10 mg were responders compared with 29.6% of those who received the 2 mg dose ($p \leq 0.001$). Significant improvement in BARS scores with IM ziprasidone 10 mg was sustained for ≥4 hours after the first injection ($p < 0.01$ vs 2 mg dose).

Sequential Ziprasidone IM/Oral versus Haloperidol IM/Oral Therapy

In a 7-day, open-label, multicenter, randomized study by Brook and colleagues (11), patients with acute psychotic agitation were randomized to 3 days of flexible-dose IM ziprasidone ($n = 90$) or IM haloperidol ($n = 42$), followed by oral treatment through day 7. The initial IM ziprasidone dose was 10 mg; subsequent IM doses of 5–20 mg, given every 4–6 hours as needed up to a maximum of 80 mg/day, were followed by oral ziprasidone 80–200 mg/day. Initial doses of IM haloperidol were 2.5–10 mg, given every 4–6 hours as needed up to a maximum of 40 mg/day, followed by oral haloperidol 10–80 mg/day.

Efficacy assessments, conducted by blinded raters, included scores on the Brief Psychiatric Rating Scale (BPRS) and CGI-S at baseline, daily during IM treatment, and at study endpoint (11). Approximate mean percentage reductions at the end of the IM treatment phase in BPRS Total (Figure 3), BPRS Agitation, and CGI-S scores for IM ziprasidone vs IM haloperidol demonstrated consistently superior efficacy for IM ziprasidone—14% versus 7% ($p < 0.05$), 19% versus 8% ($p < 0.01$), and 10% versus 3% ($p < 0.01$), respectively. Values at study endpoint, following transition to and completion of 4 days of oral treatment, showed further reductions in all 3 scales for both drugs. Improvements were significantly different on the CGI-S scale (approximately 18% change from baseline for oral ziprasidone vs 8% for oral haloperidol, $p < 0.05$), and comparable for both drugs on the BPRS scales. Patients were able to transition from IM to oral ziprasidone with sustained or improved efficacy. This study also demonstrated the safety and tolerability of ziprasidone IM up to 80 mg in a 24-hour period (which is reassuring for clinicians, as it is twice the recommended total daily dose).

In a 7-day, open-label, multicenter study ($N = 306$) by Swift and colleagues (12), hospitalized patients with psychotic disorders (agitation was not a criterion for entry) were randomized to 3 days of fixed-dose IM ziprasidone or

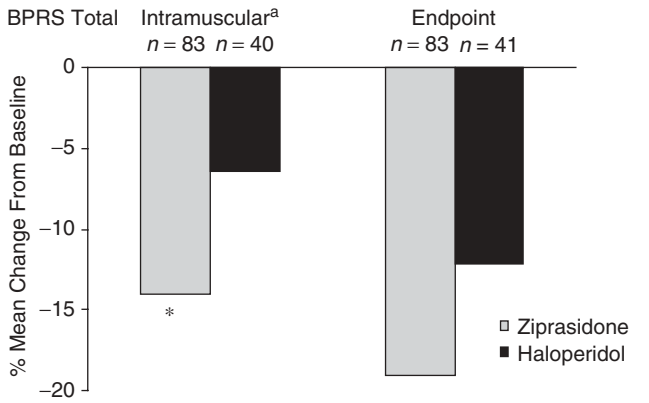

Figure 3 Mean percentage change from baseline in efficacy variables following IM dosing and at endpoint with ziprasidone and haloperidol in sequential IM/oral therapy. Flexible IM ziprasidone given as 10 mg initially, then 5–20 mg as needed to a maximum of 80 mg/day for 3 days, followed by 80–200 mg/d orally through day 7. Flexible IM haloperidol given as 2.5–10 mg initially as needed to a maximum of 40 mg/d for 3 days, followed by 10–80 mg/day orally through day 7. BPRS Total. [a]"Intramuscular" denotes last observations after IM injection and before oral administration. The number of patients included in the analysis (*n*) represents patients who were assessed at baseline and had ≥ 1 postbaseline assessment on IM treatment and at endpoint. *$p < 0.05$ (ziprasidone vs haloperidol). (Reproduced with permission from Brook et al. [11].)

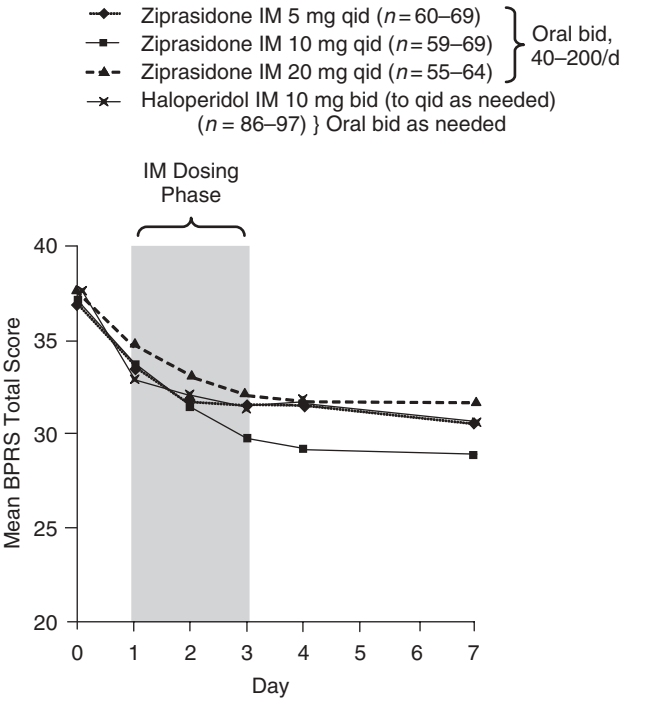

Figure 4 Mean BPRS total scores (observed cases) during IM and oral treatment in 7-day open-label study of ziprasidone and haloperidol in patients with psychotic disorders. (Data from Swift et al. [12].)

flexible-dose IM haloperidol, followed by oral treatment for 4 days with either drug. Although the primary objective of this study was to assess the safety and tolerability of IM ziprasidone, assessments of efficacy were conducted. Doses of IM ziprasidone were 5 mg ($n = 69$), 10 mg ($n = 71$), or 20 mg ($n = 66$) four times daily, and doses of IM haloperidol were 10 mg twice daily up to 10 mg four times a day as needed ($n = 100$). Oral treatment consisted of ziprasidone twice daily (40–200 mg/day) or haloperidol twice daily (adjusted according to clinical need). Short-term IM management of psychotic symptoms and ease of transition from IM to oral treatment were evaluated.

On day 1, mean reduction in BARS score 30 minutes after each injection of each dose of IM ziprasidone (≥0.4) was at least double that observed with IM haloperidol (≥0.2), suggesting a more rapid onset of action for IM ziprasidone versus IM haloperidol (12). In this study, patients also underwent evaluation using the BPRS, and in all groups, BPRS Total scores at 7 days were comparable to those after 3 days, indicating sustained symptom control after transition to oral therapy (Figure 4).

Using a randomized, parallel-group, assessment-blind, flexible-dose design, Brook and colleagues (13) conducted a 6-week multicenter study in patients with acute exacerbation of schizophrenia or schizoaffective disorder; agitation was not a criterion for entry. (A double-blind design was not used because of substantial differences in the appearance and volume of IM ziprasidone and IM haloperidol.) Patients received IM ziprasidone 10 or 20 mg initially to a maximum of 40 mg/day for up to 3 days, followed by oral ziprasidone 40–80 mg twice daily for the remainder of the study, or they received IM haloperidol 2.5 or 5 mg initially to a maximum of 10 mg/day for up to 3 days, followed by oral haloperidol 5–20 mg twice daily for the remainder of the study. Primary efficacy outcomes were change from baseline to endpoint in BPRS, CGI-S, and CGI-Improvement (CGI-I), and secondary outcomes included change from baseline in Covi Anxiety Scale scores. Efficacy was assessed in 429 patients treated with ziprasidone and 138 patients treated with haloperidol.

At the end of the 3-day IM treatment phase, patients treated with ziprasidone showed significant improvement versus haloperidol in overall psychiatric rating (BPRS Total, $p < 0.01$) and anxiety rating (COVI Anxiety, $p < 0.01$) scales (13). Improvement in CGI-S and CGI-I scales were comparable for both groups at the end of IM dosing. Values on all scales were sustained or improved for both drugs during the oral treatment phase, and comparable improvements in efficacy measures were noted for both groups at the 6-week study endpoint. The absence of statistically significant differences in study endpoints between ziprasidone and haloperidol confirmed comparable clinical efficacy for

ziprasidone and haloperidol and effective transition from IM to oral dosing for both drugs.

ZIPRASIDONE SAFETY AND TOLERABILITY

Safety has been established for IM ziprasidone up to 80 mg/day for up to 3 days. Most treatment-emergent, adverse events (AEs) in all studies were mild or moderate in severity. The most common AEs among patients receiving 10- or 20-mg IM doses of ziprasidone, occurring in >5% of patients in the short-term fixed-dose trials, were somnolence (20%), headache (13%), nausea (12%), and dizziness (10%) (Table I) (14). In comparison, in oral placebo-controlled studies of up to 6 weeks' duration, the most commonly observed events occurring with ziprasidone at an incidence of >5% were somnolence (14%), respiratory disorder (8%), and EPS (5%) (6).

Discontinuations due to treatment-emergent AEs occurred in 3.2% of patients who received IM ziprasidone 10 mg and in no patients who received IM ziprasidone 20 mg in the 24-hour, fixed-dose studies (8,9). Discontinuation rates were similar for both IM ziprasidone and IM haloperidol in the comparative trials, including the sequential IM to oral studies (11–13). Rates of discontinuation due to lack of efficacy were low (<5%) for both ziprasidone and haloperidol. In the 6-week study by Brook and colleagues (13), the rate of discontinuation due to AEs was approximately twice as high with haloperidol as with ziprasidone (9.6% vs 4.2%) (15). Clinically significant changes in blood pressure and heart rate occurred infrequently in the IM ziprasidone studies and did not constitute a treatment limitation (15).

Because IM ziprasidone employs a cyclodextrin excipient that is cleared by renal filtration, IM ziprasidone should be administered with caution to patients with impaired renal function (6).

Extrapyramidal Symptoms

The critical tolerability issue in the use of antipsychotic medications to control acute psychotic agitation is incidence of associated movement disorders. The incidence and perceived distress of EPS are often among the rate-limiting factors in the treatment of agitation. In a review of clinical trial data (15), IM ziprasidone was associated with a significantly lower incidence of movement disorders (EPS, akathisia, dystonia, hypertonia) than IM haloperidol ($p < 0.0001$). In the 24-hour study by Daniel and colleagues (8), no occurrence of EPS, dystonia, or akathisia was noted. Similarly, in the 24-hour study by Lesem and associates (9), no patients exhibited acute dystonia, although one patient who received the 10 mg dose experienced akathisia. Patients in both 24-hour studies were calmed but not excessively sedated (8,9).

As measured by the Simpson-Angus Scale and the Barnes Akathisia Scale (BAS) in the 7-day open-label study by Brook and colleagues (11), movement disorder scores improved with IM and oral ziprasidone, but deteriorated with haloperidol (Figure 5). Incidence of movement disorders in this study, including akathisia, dystonia, EPS, and hypertonia, was ≤4% in patients treated with ziprasidone, compared with 12–38% in patients treated with haloperidol.

In the 7-day, open label study of sequential IM/oral treatment by Swift and associates (12), the incidences of EPS, dystonia, akathisia, and hypertonia were notably higher with IM haloperidol than with IM ziprasidone. The lower liability for movement disorders with ziprasidone compared with haloperidol was also apparent during oral treatment. One patient discontinued IM ziprasidone due to treatment-related

Table I Treatment-Emergent Adverse Events Occurring in >5% of Patients in Short-Term, Fixed Dose, IM Trials[a]

	Patients reporting event (%)	
	Ziprasidone, 10 mg ($n = 63$)	Ziprasidone, 20 mg ($n = 41$)
Somnolence	8	20
Headache	13	5
Nausea	8	12
Dizziness	3	10

[a]Data from FDA Psychopharmacological Drugs Advisory Committee, Briefing Document for Ziprasidone Mesylate for Intramuscular Injection; February 15, 2001 (14).

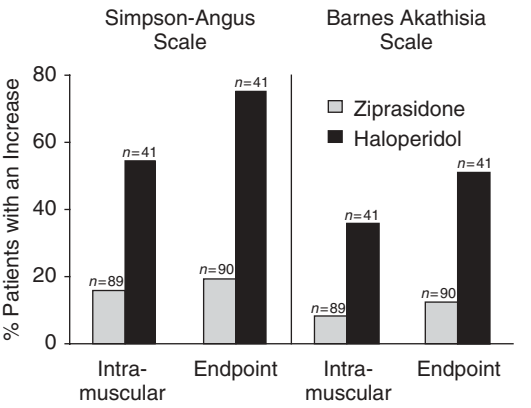

Figure 5 Percentage of patients showing a postbaseline increase in movement disorder rating scale scores: sequential treatment with IM and oral ziprasidone. Patients received up to 3 days of flexible-dose IM ziprasidone or IM haloperidol followed by oral treatment to study endpoint (day 7). Flexible IM ziprasidone given as 10 mg initially, then 5–20 mg as needed to a maximum of 80 mg/day for 3 days, followed by 80–200 mg/day orally through day 7. Flexible IM haloperidol given as 2.5–10 mg initially as needed to a maximum of 40 mg/day for 3 days, followed by 10–80 mg/day orally through day 7. (Reproduced with permission from Brook et al.[11].)

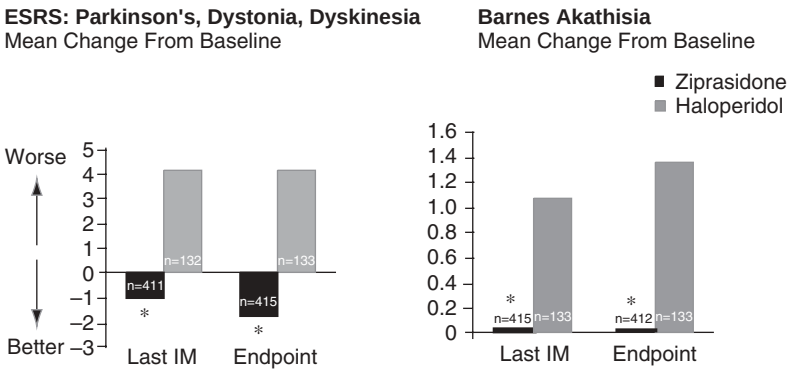

Figure 6. Mean change from baseline in ESRS and BAS total scores for IM and oral ziprasidone and haloperidol. IM ziprasidone was given10 or 20 mg initially to a maximum of 40 mg/day up to 3 days, followed by oral ziprasidone 40 mg initially then 40–80 mg b.i.d. for the remainder of the study. IM haloperidol was given 2.5 or 5 mg initially up to a maximum of 10 mg/day for up to 3 days, followed by oral haloperidol 5 mg initially then 5–20 mg b.i.d. for the remainder of the study. Increasing score indicates increasing severity of akathisia. *$p < 0.001$. (Data from Brook et al. [13].)

akathisia, and one patient discontinued IM haloperidol due to treatment-related dystonia and EPS.

Similarly, in the 6-week trial by Brook and colleagues (13), the likelihood of EPS and akathisia was greater with haloperidol than with ziprasidone—ziprasidone showed significantly greater improvement in the Extrapyramidal Symptom Rating Scale (ESRS) and in the BAS ($p < 0.001$; Figure 6).

QT_c Interval

Ziprasidone is associated with an increase in corrected cardiac QT interval (QT_c). However, in the IM ziprasidone clinical development program, no QT_c values ≥500 msec occurred with IM ziprasidone, and QT_c values >450 msec were uncommon, occurring in 1.1% of patients treated with IM ziprasidone compared with 1.3% of patients treated with IM haloperidol (14). In the 7-day, open-label studies by Brook (11) and Swift (12), the incidence of categorical QT_c increases >30 msec was 9.5% with haloperidol and 7.6% with ziprasidone. The incidence of increases >60 msec was 1.5% and 0.2% for haloperidol and ziprasidone, respectively (16). In 3 studies, including one 7-day study (11) and a 6-week study of sequential IM/oral dosing by Brook and colleagues (13), no patient had a QT_c interval >500 msec during the transition from IM to oral therapy (16).

In a study designed to examine the effects of IM ziprasidone and IM haloperidol on the QT_c interval at maximum drug concentrations (C_{max}), Miceli and colleagues (17) found that the two drugs were comparable. The frequent use of haloperidol IM in the treatment of agitation and its known safety profile offered an excellent comparator. This single-blind, multicenter, parallel-group design included 58 patients receiving chronic antipsychotic therapy. Agitation was not a criterion for enrollment in this study. Patients received 2 injections of ziprasidone 20 mg followed by 30 mg (50% above the recommended dose) or haloperidol 7.5 mg followed by 10 mg 4 hours apart. Electrocardiograms were recorded, and blood sampling for pharmacokinetic measurements was performed at 15-minute intervals within 2 hours after each injection to determine C_{max}. The mean QT_c interval, using a baseline correction factor of 0.33, was calculated as the average of three measurements obtained at the time of C_{max} (T_{max}), and before and after C_{max} for each injection for each subject.

Among patients who completed the study (17), mean increases in QT_c at C_{max} were 4.6 msec for IM ziprasidone and 6 msec for IM haloperidol after the first injection, and 12.8 msec for IM ziprasidone and 14.7 msec for IM haloperidol after the second injection. No patient had a QT_c ≥500 msec or a change of ≥75 msec from baseline QT_c. These results complement, and are consistent with, data from the IM ziprasidone clinical development program (14).

COMMON OPTIONS IN THE TREATMENT OF ACUTE AGITATION

Conventional IM Antipsychotics

As mentioned, conventional IM antipsychotics have significant side effect burdens that in the acute emergency setting interfere with patient satisfaction. The sedation from low-potency agents (e.g., chlorpromazine) and the frightening symptoms of dystonia and akathisia from high-potency agents (e.g., haloperidol) result in patient and family dissatisfaction, which can negatively affect compliance with future treatment recommendations (3). Anticholinergics are often coadministered with high-potency conventional agents to manage pseudoparkinsonian symptoms; however, the combination can exacerbate cognitive disturbances (18). IM haloperidol

continues to be commonly used in the emergency department for treating agitation and aggressive behavior (19); however, because of its liability for movement disorders and tendency to induce dysphoria, it may no longer be the best choice for many patients in this population (20,21).

IM Lorazepam

IM lorazepam is the most commonly used benzodiazepine in the emergency department. It is a well-tolerated agent with a wide therapeutic index, and it has been demonstrated to be equivalent to haloperidol in the treatment of agitation without the added side effect burden of EPS. In one study, Salzman and colleagues (22) treated 60 patients with acute agitation with either haloperidol 5 mg ($n=30$) or lorazepam 2 mg ($n=30$). Both drugs were equally effective in controlling aggression, agitation, and assaultive behavior, but lorazepam-treated patients had a greater decrease in aggression ratings than did haloperidol-treated patients, and lorazepam produced significantly fewer EPS. A more recent study by Foster and associates (23) examined the efficacy of lorazepam versus haloperidol in the emergency department setting. Severely agitated patients with psychosis (n=37) were randomly assigned to 2 mg lorazepam or 5 mg haloperidol (IM or oral concentrate). The investigators found that both drugs were comparable in rapidly reducing agitation and noted that lorazepam would be an excellent alternative to haloperidol for rapid tranquilization because of its lower liability for EPS.

Lorazepam is especially useful when the etiology of the agitation is unclear and the patient may be undergoing alcohol or substance withdrawal (3,21). Although well tolerated, lorazepam may cause excessive sedation, ataxia, and respiratory depression in patients with prior histories of obstructive sleep apnea, which are potential clinical concerns. Some patients with alcohol or benzodiazepine dependence may present with agitation arising from substance withdrawal. These patients can be easily overlooked as they may present regularly to the emergency department with psychosis (20,21). Long-term treatment with benzodiazepines can produce dependence and withdrawal.

Combination IM Haloperidol/IM Lorazepam

Another common approach to managing agitation is the use of combination haloperidol and lorazepam either simultaneously or sequentially (24). Double-blind clinical trials evaluating IM haloperidol or IM lorazepam monotherapy versus IM combination haloperidol/lorazepam therapy in patients with psychotic agitation found combination therapy more effective for reducing psychotic symptoms (25,26).

In one study, Battaglia and colleagues (25) randomly assigned acutely psychotic patients ($N=98$) to receive intramuscular injections of lorazepam (2 mg), haloperidol (5 mg), or a combination of the two drugs (in one syringe). Combination therapy was most effective for reducing psychotic symptoms. Incidence of side effects did not differ between treatment groups, although patients receiving haloperidol alone tended to have more EPS. The combination was found to have a quicker onset of action in controlling agitation without an added side effect burden. There was no significant difference in the incidence of side effects between groups; however, patients on haloperidol monotherapy tended to have more EPS. Bieniek and associates (26) compared IM lorazepam with combination IM haloperidol/lorazepam in severely agitated patients presenting to the emergency department ($N=20$). Patients on combination therapy showed significantly greater improvements on agitation and hostility scales at 60 minutes postdose than did patients on lorazepam alone.

Combination IM haloperidol/lorazepam is associated with less EPS compared with haloperidol monotherapy, but EPS and dystonia are still associated with these two drugs and thus could lead to compliance issues.

Olanzapine Novel Formulations

The atypical antipsychotic IM olanzapine has been evaluated in several clinical trials, and have recently been approved by the US Food and Drug Administration. In four randomized, double-blind, placebo-controlled trials (27), IM olanzapine proved effective in controlling agitation in patients with schizophrenia, bipolar mania, and dementia. In one double-blind trial versus placebo and IM haloperidol in agitated schizophrenic patients (28,29), both active drugs proved more effective than placebo and comparable with each other as measured by BPRS positive subscale scores. In another double-blind trial in acutely agitated patients with bipolar mania (29,30), IM olanzapine was more effective than IM lorazepam and placebo in reducing agitation. In two 5-day single-blind trials of IM/oral olanzapine (29,31,32), BPRS positive subscale scores decreased for all olanzapine dose groups during the 3-day IM phase and continued during oral phase to endpoint.

Olanzapine was well tolerated in these trials (27,29) and as with other atypicals, it has a lower liability for movement disorders compared with conventional agents. Although not associated with QTc prolongation, bradycardia was observed in about 33% of healthy volunteers in the IM olanzapine clinical trials; fewer than 5% of agitated patients experienced sinus bradycardia (21). Most of these instances of bradycardia were accompanied by decrements in heart rate and blood pressure, which were considered benign and consistent with a self-limiting vasovagal attack likely associated with α_1 antagonism of olanzapine (21,27).

Olanzapine is also available in a rapidly dissolving oral formulation that can be suspended in noncarbonated liquid. Its speed of onset is equivalent to olanzapine tablets. The rapidly dissolving formulation may be an advantage for some patients, but it is still difficult to administer to agitated patients.

Oral Risperidone/Lorazepam vs IM Haloperidol/Lorazepam

In this naturalistic pilot study (33), the atypical antipsychotic risperidone (liquid concentrate) plus oral lorazepam ($n=30$) were compared against IM haloperidol plus IM lorazepam ($n=30$). Although not a true randomized study, both treatment groups showed similar improvements on five PANSS items (excitement, hostility, hallucinatory behavior, uncooperativeness, and poor impulse control), suggesting that oral risperidone/lorazepam was a comparable alternative to IM haloperidol/lorazepam for the short-term treatment of agitated psychotic patients who could take oral medication. No adverse events were reported in the oral group, one patient in the IM group developed acute dystonia, and one patient in the oral group required IM haloperidol for resistant agitation. Somnolence was comparable between groups (mean time to sleep about 44 minutes).

IM ZIPRASIDONE COST-EFFECTIVENESS

The cost-effectiveness of treating acute psychotic agitation with IM ziprasidone versus IM haloperidol was recently examined by Russell and colleagues (34). Using a model of patient data, costs of emergency department treatment, drug costs, and the additional emergency department costs associated with managing EPS and dystonia, these investigators found that despite the higher acquisition costs, the use of IM ziprasidone in the emergency department was more cost-effective than use of IM haloperidol. The cost savings were a direct result from lower rates of acute EPS and dystonia with IM ziprasidone, which resulted in lower emergency department costs to manage patients with acute psychotic agitation.

Pondrom and associates (35) assessed the economic impact of specifying ziprasidone as the preferred atypical antipsychotic in correctional inpatient psychiatric facilities. Data from two psychiatric units were collected and total pharmaceutical and atypical drug costs were calculated for each month from July 2000 through May 2002. Patient counts ranged from 391 to 497 in Unit A and from 487 to 534 in Unit B. Beginning in October 2001, patients receiving olanzapine, quetiapine, or >6 mg/day of risperidone were switched to ziprasidone unless contraindicated.

Respective utilization rates before and after the formulary change were ziprasidone, 0% and 45%; risperidone, 64% and 43%; olanzapine, 21% and 2%; quetiapine, 8% and 4%; and clozapine 7% and 6% (35). The formulary change significantly decreased mean monthly atypical agent expenditures from $82,257 (July 2000 to October 2001) to $59,507 (November 2001 to May 2002) ($p<0.001$). Overall pharmacy costs were reduced $40,989 per month, with projected total annual pharmacy cost savings of $491,868 (about 25%). Notably, the formulary change decreased use of concomitant antidepressant/anticholinergic medications. Switching to ziprasidone significantly reduced expenditures for atypical agents and decreased overall pharmacy costs.

SUMMARY AND CONCLUSIONS

Acute agitation in psychotic patients is a significant clinical problem for which improved treatments are clearly needed. The present utilization of typical antipsychotics is often complicated by unwanted motor side effects. Ziprasidone is the first atypical antipsychotic to be available in both rapid-acting IM and oral formulations. Clinical trial experience indicates that IM ziprasidone provides rapid control of agitation and improvement of psychotic symptoms, with a low incidence of movement disorders relative to conventional medications. Because movement disorders are highly distressing to patients and may affect adherence to long-term treatment, ziprasidone's tolerability profile may have implications beyond treatment of the acute episode. The transition from IM to oral ziprasidone therapy is well tolerated, with sustained symptom control. In addition, the use of IM ziprasidone in emergency treatment of acute psychotic agitation has been shown to be cost-effective compared with IM haloperidol (despite its higher acquisition cost), owing to the lower rates of acute EPS and dystonia associated with IM ziprasidone.

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