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Pharmacological Management of Acute Agitation

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Abstract

Acute agitation occurs in a variety of medical and psychiatric conditions, and when severe can result in behavioural dyscontrol. Rapid tranquillisation is the assertive use of medication to calm severely agitated patients quickly, decrease dangerous behaviour and allow treatment of the underlying condition. Intramuscular injections of typical antipsychotics and benzodiazepines, given alone or in combination, have been the treatment of choice over the past few decades.

Haloperidol and lorazepam are the most widely used agents for acute agitation, are effective in a wide diagnostic arena and can be used in medically compromised patients. Haloperidol can cause significant extrapyramidal symptoms, and has rarely been associated with cardiac arrhythmia and sudden death. Lorazepam can cause ataxia, sedation and has additive effects with other CNS depressant drugs.

Recently, two fast-acting preparations of atypical antipsychotics, intramuscular ziprasidone and intramuscular olanzapine, have been developed for treatment of acute agitation. Intramuscular ziprasidone has shown significant calming effects emerging 30 minutes after administration for acutely agitated patients with

schizophrenia and other nonspecific psychotic conditions. Intramuscular ziprasidone is well tolerated and has gained widespread use in psychiatric emergency services since its introduction in 2002. In comparison with other atypical antipsychotics, ziprasidone has a relatively greater propensity to increase the corrected QT (QTc) interval and, therefore, should not be used in patients with known QTc interval-associated conditions. Intramuscular olanzapine has shown faster onset of action, greater efficacy and fewer adverse effects than haloperidol or lorazepam in the treatment of acute agitation associated with schizophrenia, schizoaffective disorder, bipolar mania and dementia. Intramuscular olanzapine has been shown to have distinct calming versus nonspecific sedative effects. The recent reports of adverse events (including eight fatalities) associated with intramuscular olanzapine underscores the need to follow strict prescribing guidelines and avoid simultaneous use with other CNS depressants. Both intramuscular ziprasidone and intramuscular olanzapine have shown ease of transition to same-agent oral therapy once the episode of acute agitation has diminished. No randomised, controlled studies have examined either agent in patients with severe agitation, drug-induced states or significant medical comorbidity. Current clinical experience and one naturalistic study with intramuscular ziprasidone suggest that it is efficacious and can be safely used in such populations. These intramuscular atypical antipsychotics may represent a historical advance in the treatment of acute agitation.

This review aims to provide a succinct, clinically oriented guide for the pharmacological management of acute agitation, based on scientific literature as well as current clinical practice. An electronic search of English-language literature using MEDLINE (1960–2004) was conducted using search terms 'agitation', 'psychiatric emergency', 'psychosis' and 'rapid tranquillisation'. A manual search of relevant articles was also conducted. Experts from distinct regions of the US in the field of emergency psychiatry and emergency medicine were surveyed for their clinical experience and current practice in agitation management.

1. Causes and Clinical Manifestations of Agitation

Agitation can be defined broadly as a state of motor restlessness accompanied by mental tension. Signs of mounting tension can include pacing, hand wringing, intense staring, clenching fists, pressured speech, mutism, yelling, banging objects or threatening others. Patients with lesser degrees of agitation can be treated with psychological and environmental methods to ease anxiety and tension. When agitation becomes severe it may be accompanied by behavioural dyscontrol where the threat of property damage, assualtiveness to others or self-inflicted injury become immediate treatment concerns. Under these conditions the assertive use of medication to tranquillise the patient may be required to decrease potential damage, increase safety and treat the underlying clinical condition. Rapid tranquillisation is the process of immediate use of moderate doses of medication, with or without consent, to calm the patient quickly.[1]

Acutely agitated patients usually have major psychiatric or medical illnesses that are driving the agitation. Severe agitation is seen most commonly in psychotic illnesses such as schizophrenia, schizoaffective disorder and the manic phase of bipolar disorder, where disturbances of thought or affect modulation result in impaired reality perceptions. Hallucinations, paranoid delusions and intensely irritable, angry or expansive mood are fertile conditions for development of acute agitation.

Patients in drug intoxication states (most commonly sympathomimetic stimulants such as cocaine or amphetamines) or alcohol intoxication may present with severe agitation, sometimes also resulting in psychosis. Withdrawal from alcohol may exacerbate acute agitation, as patients in this condition have generalised malaise, poor attention and heightened irritability of the CNS. Less frequently, alcohol withdrawal evolves into delirium tremens, characterised by disorganised thought processes and a fluctuating level of arousal, predisposing such a patient to agitation.[2]

Patients with some personality disorders are more prone to acute agitation because of decreased stress tolerance and poor impulse control.[3,4] Borderline personality disorder is characterised by intense fluctuations in mood, often precipitated by relationship conflicts. A patient with antisocial personality is less likely to have conscious awareness of underlying dysphoric mood states, but nonetheless becomes agitated as a result of them. Post-traumatic stress disorder is accompanied by increased CNS arousal, dysphoric mood and trauma-linked flashbacks, all of which may predispose to acute agitation.

Finally, any medical condition causing brain dysfunction may cause agitation, primarily through confusion, poor attention, dysregulation of affective processes, sympathetic stimulation or generalised mental disorganisation. Examples of such medical conditions include medication toxicity, any infection/fever in the elderly, thyrotoxicosis, meningitis, encephalitis, brain trauma (including cerebrovascular accidents) and dementia.

Agitation is poorly understood at the level of cellular physiology. Generally, pathological increases in dopamine and noradrenaline (norepinephrine), and decreases in GABA are seen as underlying conditions for agitation.[5] Both hyper- and hyposerotonergic states have been implicated in agitation.[6] None of these neurotransmitter systems exist in isolation. For example, GABA has modulating effects on dopamine transmission in both mesolimbic and nigrostriatal regions.[7,8]

2. Pharmacological Treatments

Early treatments for acute agitation focused on getting the patient into a stuporous or unconscious state (sleep or otherwise). Prior to the development of antipsychotic medication, pharmacological treatments for agitation included insulin coma therapy, barbiturates, bromides and various anaesthesia cocktails.[9] These treatments frequently resulted in adverse sequelae, including serious medical morbidity and, rarely, mortality. Although these treatments reduced the level of arousal in agitated patients, the underlying psychopathological state, in particular psychosis, was left untreated.

Initially, sleep was considered a therapeutic endpoint for calming an extremely agitated patient. Some tranquillisation protocols kept patients asleep for several days, allowing wakefulness only for eating, drinking and elimination functions (some reports from the Russian literature describe this as 'artificial hibernation').[10,11] Although sleep appeared to confer some therapeutic benefit, cumulative clinical experience and tranquillisation research showed that sleep was not essential for improvement in agitation or decrease in core psychotic symptoms. In fact, an emerging opinion among clinicians was that excessive sedation was an unwanted side effect of treatment, interfering with the initial psychiatric and medical examination, and decreasing the ability of the patient to participate in tests, procedures or crisis intervention. Thus, tranquillisation, as a calming process separate from total sleep induction, is now viewed as the therapeutic endpoint for treatment of agitation, although some recent published protocols still view deep sleep as a legitimate target.[12,13] A quantum advance in tranquillisation of patients with acute agitation was ushered in with the discovery of antipsychotic medication ('typical antipsychotics'). Treatment with typical antipsychotic medication not only calmed the patient, but treated underlying psychotic states, usually without serious or life-threatening adverse effects. In psychotic agitation an additive, reciprocal relationship exists between the general state of arousal and the psychotic process: increasing agitation worsens psychosis and vice versa.

Many pharmacological strategies in acute agitation now target one or both components of this relationship. Although some authors caution that several weeks are required for 'true' antipsychotic medication effect, most published studies show decrease in measurable psychotic symptoms (including hallucinations, delusions, disorganised thinking, disturbance in affect) within minutes to hours of assertive medication management of agitation.[14]

3. Typical Antipsychotics

All typical antipsychotics inhibit dopaminergic transmission in the brain, and this activity has clearly established anti-agitation effects in humans and other animals.[15] Early protocols used large doses of low-potency antipsychotics, such as chlorpromazine, for rapid tranquillisation.[16] Excessive sedation, clinically significant hypotension, irritation at the injection site and cardiac arrhythmias (associated with histaminic, cholinergic and α-adrenergic antagonistic effects) led to less use of low-potency antipsychotics. The relatively better tolerated high-potency antipsychotics became the standard treatment of acute agitation.[17]

For patients with severe agitation who are unwilling to take medication, intramuscular injection formulations of typical antipsychotics have been employed most often for rapid tranquillisation. Typical antipsychotics given intramuscularly result in higher maximum plasma concentrations (no hepatic 'first-pass' effect) in a shorter period of time, usually with a concomitant faster onset of action. In two studies comparing intramuscular and oral typical antipsychotics in the treatment of agitated patients willing to take medication and comply with the treatment protocol, both routes of administration were considered effective.[18,19] The intramuscular typical antipsychotics had a faster onset of action and fewer doses were required within the first 3 hours, whereas there were no significant differences in agitation when measured at 4 and 24 hours.

3.1 Haloperidol

Haloperidol, a high-potency butyrophenone, has a relatively low incidence of sedation or hypotension, and can be administered orally, intramuscularly or intravenously. Haloperidol given intramuscularly or intravenously has an onset of action within 30–60 minutes, elimination half-life of 12–36 hours and duration of effect lasting for up to 24 hours when given for acute agitation.[20] Although initially high doses of haloperidol were favoured for rapid tranquillisation, more recent evidence has supported a therapeutic window for haloperidol, with initial doses of 10–20 mg/24 hours most likely to be effective with the least number of adverse effects.[21-23] Taken collectively, the worldwide published literature suggests haloperidol is one of the most frequently used typical antipsychotics for treatment of acute agitation at this time.

Most problematic consequences of haloperidol use are extrapyramidal symptoms (EPS), including dystonia, akathisia and Parkinson-like effects. Dystonic reactions occur commonly with intramuscular haloperidol, are dose-dependent, most common in muscular young men, and respond to treatment with anticholinergic medications such as benzatropine, diphenhydramine or trihexyphenidyl. Dystonia (including laryngospasm) can be painful and is distressing to patients; thus, anticholinergic medications are sometimes given prophylactically with the initial intramuscular injection of haloperidol.

Akathisia is motor restlessness accompanied by anxiety; treatment-emergent akathisia may make agitation worse and may be difficult to distinguish from agitation. Although akathisia is relatively uncommon in the acute phase of treatment (first 24 hours), it must be addressed quickly and can be lessened by addition of a benzodiazepine.[24]

All typical antipsychotics have quinidine-like cardiac effects (increase corrected QT [QTc] interval) and, thus, potential for inducing cardiac arrhythmias.[25] Among the typical antipsychotics, haloperidol has a relatively lower propensity for increasing QTc, although several published reports have linked haloperidol with cardiac arrhythmia.[26] There are reports of sudden death occurring during tranquillisation with typical antipsychotics, including haloperidol, although a direct link remains unsettled as most reported cases have multiple possible

causative factors.[27,28] All typical antipsychotics can lower the seizure threshold, although low-potency antipsychotics have greater effect than high-potency antipsychotics. Haloperidol exhibits a relatively low risk in this regard.

Neuroleptic malignant syndrome is a rare complication of typical antipsychotic use (0.2% of patients treated), which is worsened when relatively large amounts of drug are given over short periods of time.[29] (Neuroleptic malignant syndrome has been reported with atypical antipsychotic use, although the frequency of occurrence appears less than with typical antipsychotics.[30]) Any patient treated for acute agitation should have periodic vital signs monitored as well as examinations for EPS, particularly muscular rigidity.

3.2 Droperidol

Droperidol, like haloperidol, is a high-potency butyrophenone with potent tranquillising effects. Used in the US primarily for calming patients undergoing anaesthesia and as an antiemetic, droperidol became popular as an agent for rapid tranquillisation of ambulatory psychiatric patients. Droperidol is usually administered intramuscularly or intravenously, has an onset of action within 15–30 minutes, elimination half-life of 2–4 hours and duration of effect for 6–8 hours.[31] Although larger doses have been studied, for acute agitation the usual dose of intramuscular droperidol is 5mg. Most studies comparing droperidol with haloperidol in severely agitated patients have found a slightly quicker onset of action (significant calming within 10–15 minutes), fewer injections required, greater sedation and comparable adverse effects.[32-36] One study included agitated patients with significant blood alcohol levels (average blood alcohol level >200 mg%) and found that droperidol was more rapidly effective without serious adverse effects.[37]

At the turn of the millennium, droperidol had become first choice for the initial treatment of severe agitation in many large urban emergency departments. However, in 2001 the manufacturer pulled the drug from European markets and the US FDA issued a 'black box warning' because of concerns about the risk of fatal cardiac arrhythmia caused by prolongation of the QTc interval.[38] The data underlying these decisions have been reported in an ambiguous fashion. Two recent large retrospective reviews (around 14 500 patients) showed no evidence of increased morbidity or mortality with droperidol use for treatment of acute agitation.[39,40] Nevertheless, the use of droperidol in US emergency departments has sharply declined as a result of medico-legal concerns.

3.3 Zuclopenthixol

Zuclopenthixol (zuclopenthixol acetate) is a short-acting depot thioxanthene derivative available in 70 countries; however, it is not available in the US.[41] It has an onset of action within 15–30 minutes, reaches peak serum concentration in 24–48 hours and has a duration of effect of up to 3 days.[42] Efficacy of zuclopenthixol is reported as comparable with haloperidol for acute agitation, although the strength of the research has been questioned.[43,44] Reported benefits have included fewer injections needed, longer duration of effect and cost savings by reduction of nursing hours required for management of agitation. Reported disadvantages have been greater sedation and higher incidence of EPS.

The 3-day duration of effect raises some ethical concerns, as patients in acutely agitated states requiring intramuscular medication are often not able to give informed consent and a 3-day medication effect goes beyond the immediate control of dangerousness. Also, some patients requiring such emergency treatment have relatively brief periods of illness (e.g. cocaine intoxication causing psychotic agitation often completely dissipates within 24 hours), and, therefore, would not require medication beyond the immediate control of the acute agitation. Physicians are often unable to determine the aetiology of acute agitation until after the initial treatment.

For these reasons zuclopenthixol appears to occupy a particular niche in the treatment of acute agitation (e.g. for treatment of patients with established patterns of agitation, chronic psychotic illness and prior consent to treatment with this agent), and

protocols should be established in those institutions using it.

4. Benzodiazepines

Benzodiazepines facilitate GABA neurotransmission and this action is probably responsible for tranquillisation of agitated patients. Although benzodiazepines have both sedative and anxiolytic properties, either effect may contribute to decreasing agitation.

A number of studies have compared benzodiazepines with typical antipsychotics in the treatment of acute agitation. Most studies find comparable efficacy, less EPS or other adverse effects and increased sedation.[45] Patient preference and compliance is better with benzodiazepines during the acute phase of agitation. The therapeutic effects of benzodiazepines in acute agitation appear to be tightly linked with their ability to decrease arousal, and patients studied 24 hours after initial dose show little further benefit in their psychiatric symptoms. Some research has suggested that benzodiazepines possess intrinsic antipsychotic effects, separate from tranquillisation or sedation.[46-48]

Benzodiazepines do not cause significant EPS or cardiac effects, although they can cause respiratory depression, ataxia, excessive sedation or paradoxical disinhibition. Respiratory depression during benzodiazepine treatment of agitation is uncommon, nonetheless most practitioners avoid benzodiazepine use in patients with chronic obstructive pulmonary disease or other conditions characterised by limited pulmonary reserve.[49]

Excessive sedation and ataxia from benzodiazepines can become clinically significant in the elderly patient, and dose adjustments are suggested in this population.[50] The sedative and respiratory depressant effects of benzodiazepines are additive with other CNS depressants, therefore benzodiazepines must be used with caution in those patients with alcohol (ethanol), barbiturate and opioid intoxication.

Paradoxical disinhibition is most likely to occur with high doses of benzodiazepines in patients with structural brain damage, mental retardation or dementia. The incidence of paradoxical disinhibition is extremely low; in fact, many experienced emergency department physicians have never witnessed it.[51]

4.1 Lorazepam

Lorazepam is the only benzodiazepine with consistent, complete and rapid intramuscular absorption. Intramuscular or sublingual lorazepam reaches peak plasma concentrations 60–90 minutes after dose. The elimination half-life is 12–15 hours and duration of effect is 8–10 hours.[52,53] Lorazepam is usually given in 1–2mg doses and may be administered orally (sublingual or oral tablet), intramuscularly or intravenously. Lorazepam is rapidly conjugated to an inactive glucuronide, requiring no involvement of the cytochrome P450 system, and has few drug-drug interactions.

These pharmacodynamic and pharmacokinetic properties of lorazepam have contributed to the widespread use of this agent in rapid tranquillisation. More than a few studies have substantiated that lorazepam has equal efficacy to haloperidol in the treatment of psychotic or manic agitation, and some have indicated superiority.[54-57] Patients tolerate lorazepam better and have less aversion to repeat dose administration. The intramuscular or intravenous preparation of lorazepam must be refrigerated, thus limiting the use of lorazepam in some underdeveloped countries. Because of additive CNS depressive effects, lorazepam should be used with caution in patients with sedative intoxication. Lorazepam may be poorly effective in patients with tolerance to alcohol or other sedatives.[58] Alternatively, lorazepam is particularly useful in patients undergoing acute alcohol withdrawal.[59,60] Lorazepam is firmly established as a front-line drug for the pharmacological management of acute agitation.

4.2 Clonazepam

Clonazepam is a high-potency benzodiazepine with a poorly understood mechanism of action, long elimination half-life (20–80 hours), and complete but inconsistent intramuscular absorption.[61] Peak oral absorption of clonazepam was in fact faster than

intramuscular absorption in one study (1.7 vs. 3.1 hours after dose).[62] Published reports on the efficacy of clonazepam in acute agitation have been mixed. A double-blind trial of intramuscular clonazepam versus intramuscular haloperidol for agitated manic psychosis found that clonazepam was effective and safely used, but slower acting.[63] A small, open-label, nonblind study showed that intramuscular clonazepam was effective for acute psychotic agitation; however, a double-blind comparison of intramuscular clonazepam with intramuscular lorazepam in acute mania found no significant therapeutic effect with clonazepam (as opposed to marked improvement with lorazepam).[64,65] Several published reports, including one double-blind, placebo-controlled trial in patients with chronic schizophrenia, have indicated that clonazepam may increase psychosis or agitation in certain individuals.[66-68] Overall, clonazepam appears to have limited efficacy in the treatment of acute agitation.

4.3 Other Benzodiazepines

Diazepam, chlordiazepoxide, midazolam and flunitrazepam have all been studied as single-agent therapy for acute agitation and shown to have tranquillising effects comparable with haloperidol.[69-71] Although effective, diazepam and chlordiazepoxide have erratic intramuscular absorption rates and active metabolites with long half-lives. Midazolam given intramuscularly in dose ranges of 2.5–15mg has rapid absorption, quick onset of action (15 minutes) and does not require refrigeration; however, most patients fall asleep and the duration of effect is short (1–2 hours).[72] One published report showed flunitrazepam to be comparable with haloperidol for aggressive psychotic behaviour, with both showing significant lowering of aggression at 30 minutes (flunitrazepam is not available in the US).[73]

5. Combination Treatments

Medication can be combined to target different components of agitation (arousal, anxiety, psychosis) much the same as oncology treatments combine therapeutic agents for various pathways of the immune system. Combining agents can result in additive or synergistic effects, either therapeutically or adversely. Barbiturates have been combined with typical antipsychotic agents with success, for example, studies have shown faster reduction in agitation and earlier achievement of therapeutic goals with the combination treatment.[74,75] Barbiturates (e.g. phenobarbital sodium) may cause significant respiratory depression; therefore, benzodiazepines have been used more often in combination treatments.

Most studies combining typical antipsychotic agents with benzodiazepines have shown superiority of the combination to either agent alone, with few disadvantages. The combination treatments have shown faster reduction in agitation, less time in seclusion or restraint, fewer injections required, less total antipsychotic medication required and lower incidence of EPS.[76-79] The lower EPS witnessed with combination treatment is probably a result of benzodiazepine prophylaxis or treatment of antipsychotic-induced neuroleptic effects, as well as a consequence of the lower doses of antipsychotic medication required.

Although several benzodiazepine plus typical antipsychotic regimens have been studied, the majority of published research has examined the haloperidol plus lorazepam combination that reflects the most common clinical practice. Case reports, retrospective reviews, open-label trials, double-blind studies and a large, randomised, double-blind, multicentre emergency department study have all reported the superiority of the haloperidol plus lorazepam combination over either treatment alone for acute agitation.[67,70,80-82] The most frequently used dose is haloperidol 5mg intramuscularly combined with lorazepam 2mg intramuscularly, and both are stable for several hours at least when mixed in the same syringe (thus, the patient only needs one injection for the combination).

Most adverse events associated with combination treatment are less than those associated with single-agent typical antipsychotic treatment. Sedation can sometimes persist beyond a desirable endpoint with the haloperidol plus lorazepam combination, although most studies have shown that the sedation appears comparable to that with lorazepam treat-

ment alone. Several case studies have examined extremely large doses of haloperidol (up to 480mg intravenously) combined with lorazepam (up to 480mg intravenously) in medically compromised intensive care unit patients with good results.[83]

For a period of time the '9-1-1' intramuscular cocktail of haloperidol 9mg plus lorazepam 1mg plus benzatropine 1mg was popular in some regions of the US. Although this acronym has intrinsic allure in the emergency department, there is no published evidence to support such a combination of medications. The addition of benzatropine confers no therapeutic benefit as the incidence of EPS is extremely low when lorazepam is added to haloperidol, and benzatropine can worsen agitation when it is caused by delirium or intoxicants with anticholinergic effects. The combination of loxapine with lorazepam was reported to cause respiratory distress, hypotension and stupor in a few case studies.[84,85]

6. Atypical Antipsychotics

The development of 'serotonin/dopamine antagonists' or atypical antipsychotic agents has been a quantum advance in the treatment of psychotic illnesses, and has changed the prescribing landscape of psychiatry worldwide. Until recently these agents were available only in oral formulations and, thus, their use in the emergency treatment of acute agitation was limited. Although intramuscular formulations of typical antipsychotic agents are clearly effective in the treatment of acute agitation, most patients with needs for ongoing medication treatment beyond the episode of agitation will be switched to atypical oral agents because of the fewer adverse effects, better compliance and potentially superior treatment outcomes.[86,87] The transition period involved in switching from typical intramuscular to atypical oral antipsychotic medication may impose a risk of the emergence of adverse effects, breakthrough symptoms and loss of therapeutic advantage.[88]

Agitation is by definition a dysphoric state, and rapid tranquillisation with typical antipsychotics may cause some dysphoria as a treatment emergent effect (e.g. through akathisia or 'neuroleptic dysphoria').[89] Some patients experience symptoms of post-traumatic stress after treatment of an acute psychotic episode.[90] Conversely, a number of experienced emergency psychiatrists have observed that a small percentage of agitated patients treated with intramuscular atypical antipsychotics have voluntarily requested another dose during the acute phase of treatment (Preval H, Schneider J, Zeller S, personal communications). Intramuscular atypical antipsychotics would offer a tremendous advantage if patients experience a lessening of dysphoria during a treatment episode (as a separate but related medication effect from reduced agitation).

The majority of the published trials of intramuscular atypical antipsychotics used in the emergency treatment of agitation have involved medically stable, non-intoxicated patients who were able to consent to treatment and adhere to a research protocol. By design, such patients have moderate, not severe, levels of agitation. There are no controlled studies examining the efficacy of atypical antipsychotic medications in medically complicated patients, intoxicated patients or those with severe agitation. Thus far, clinical experience and one naturalistic study with intramuscular ziprasidone indicate its efficacy and tolerability in such complicated populations. The recent availability of rapid-acting, intramuscular formulations of atypical antipsychotic medications may represent an historical advance in the emergency treatment of acute agitation.

6.1 Risperidone

Risperidone is a benzisoxazole derivative with high affinity for dopamine/serotonin receptors, and is available in oral (tablet/oral disintegrating tablet [ODT]/liquid) and depot injection preparations. Two studies, one non-randomised and one randomised, have compared the combination of risperidone liquid concentrate 2mg plus oral lorazepam 2mg with the combination of intramuscular haloperidol 5mg plus intramuscular lorazepam 2mg for treatment of psychotic agitation.[91,92] Both studies were limited by the absence of double-blind procedures, and indicated that the two interventions were equally effective in reducing agitation measured at

30, 60 and 120 minutes. Both treatments were well tolerated. For agitated patients willing to take medication and comply with treatment protocols, the combination of oral risperidone and lorazepam appears to be an acceptable regimen.

6.2 Ziprasidone

Ziprasidone is a benzisothiazol piperazine, dopamine/serotonin antagonist with low propensity for causing EPS, and became the first atypical antipsychotic available in a fast-acting intramuscular preparation. Intramuscular ziprasidone reaches peak plasma concentrations in 30–45 minutes, has an elimination half-life of 2–4 hours and duration of effect of at least 4 hours.[93]

Two pivotal double-blind, randomised studies of intramuscular ziprasidone at doses of 2mg versus 10mg (117 patients) and 2mg versus 20mg (79 patients) showed that ziprasidone 10 or 20mg intramuscularly was superior to 2mg in the treatment of agitated psychotic patients.[94,95] Significant reduction in behavioural activity was observed as early as 15 minutes (10mg) and 30 minutes (20mg) in these two studies. Further analyses comparing treatment effects between these studies demonstrated a statistically significant dose-related effect (20mg greater than 10mg). Most patients receiving ziprasidone 20mg intramuscularly received one (42%) or two injections (37%).

No patients in either study discontinued as a result of adverse effects. The following treatment emergent adverse effects were recorded for the 20mg dose (41 patients) and rated as 'mild to moderate': somnolence (20%), nausea (12%), dizziness (10%), injection site pain (7%) and headache (5%). One patient in the intramuscular ziprasidone 10mg group experienced moderate akathisia, and one patient in the intramuscular 2mg group experienced mild, unspecified EPS.

The US FDA has advised caution with ziprasidone because of its propensity to increase the QTc interval, especially when used with other QTc-prolonging drugs or illness predisposing to increased QTc. Ziprasidone prolongs the QTc interval to a greater degree than haloperidol, olanzapine or risperidone, but less than thioridazine.[27] In the previously mentioned pivotal ziprasidone intramuscular studies, ECGs were obtained at baseline and end of study, and those with clinically relevant ECG abnormalities at baseline were excluded. Treatment-emergent minor changes in QTc interval were reported; however, none were clinically significant and no QTc interval was reported to be >500ms. In the intramuscular ziprasidone 20mg group, three and four patients had clinically relevant increase in heart rate (sitting and standing, respectively). In the intramuscular 10mg group, clinically significant changes in blood pressure and pulse were reported as <5% of patients, with no apparent pattern of change noted.

To date, there have been no prospective, controlled trials examining intramuscular ziprasidone versus an active comparator, such as haloperidol or lorazepam, in the emergency phase (<24 hours) of treatment for acute agitation. Two studies have compared intramuscular ziprasidone with intramuscular haloperidol over a 7-day trial, where hospitalised patients were transitioned to oral ziprasidone or oral haloperidol after 3 days of intramuscular treatment.[96,97] These studies have shown that intramuscular ziprasidone is better tolerated than intramuscular haloperidol (significantly less EPS), and that intramuscular ziprasidone can be transitioned to oral ziprasidone with relatively few adverse consequences. One non-randomised, nonblind observational study of 110 patients in a psychiatric emergency service found that ziprasidone 20mg intramuscularly was effective in calming highly agitated patients (non-consenting), with significant tranquillising effects shown as early as 15 minutes after administration.[98] Most notably, this study included agitated patients with nonspecific psychoses (72 patients), alcohol intoxication (10 patients, median blood alcohol level = 285 mg/dL) and substance-induced psychosis (28 patients). There are no published trials examining intramuscular ziprasidone use in patients exclusively with bipolar mania. In clinical practice many psychiatric emergency services in the US are now using intramuscular

ziprasidone at a 20mg dose as a first-line treatment for severe agitation.

6.3 Olanzapine

Olanzapine is a dopamine/serotonin antagonist in the thienobenzodiazepine class, and has recently been approved for intramuscular administration. Intramuscular olanzapine reaches maximum concentration in 15–45 minutes, has an elimination half-life of 30 hours and duration of action up to 24 hours.[99]

Four, double-blind, randomised, placebo- and active-comparator studies were pivotal in showing that intramuscular olanzapine was efficacious in treating acute agitation in patients with schizophrenia, bipolar mania and dementia. In the first study in 285 patients with schizophrenia, intramuscular olanzapine 10mg reduced agitation to a greater degree than intramuscular haloperidol 7.5mg or intramuscular placebo at 15, 30 and 45 minutes after injection.[100] In the second study in 270 patients with schizophrenia, patients received from one to three injections of intramuscular olanzapine (2.5, 5, 7.5 or 10mg), intramuscular haloperidol 7.5mg or intramuscular placebo. Intramuscular olanzapine exhibited a dose-response relationship for reduction in agitation, and was superior to haloperidol on some measures of agitation at the higher dose range (7.5–10mg).[101] In the bipolar mania study of 201 patients, intramuscular olanzapine 10mg was superior to intramuscular lorazepam 2mg and intramuscular placebo at 30, 60 and 90 minutes on measures of impulsivity, tension, hostility, uncooperativeness and excitement, and across all measures of agitation at 2 hours post-dose.[102] A significantly greater percentage of patients required only one intramuscular olanzapine dose over 24 hours in the bipolar mania study (74%) compared with intramuscular lorazepam (47%). In the study of agitation associated with Alzheimer's disease and/or vascular dementia in 272 patients, intramuscular olanzapine 5mg showed statistically significant lowering of agitation at 30 minutes, whereas intramuscular lorazepam 1mg required 60 minutes to separate from placebo.[103] In each of these studies, intramuscular olanzapine maintained therapeutic effects 24 hours after the initial injection.

Collectively, these studies recorded no adverse events that were significantly different from placebo. The following were adverse events recorded for >5% of patients treated with intramuscular olanzapine: somnolence (13%) [6% placebo] and dizziness (9%) [2% placebo]. One patient treated with intramuscular olanzapine 10mg experienced an unspecified EPS.

Minor changes in the QTc interval (from baseline ECG to 24-hour endpoint) were reported and none were judged to be clinically significant, although three olanzapine-treated patients in the dementia study met criteria for an abnormal QTc interval change (as well as three patients in the lorazepam treatment group and three patients in the placebo treatment group). A pooled analysis of the QTc data from these trials showed a small (3ms), statistically significant decrease in QTc interval with intramuscular olanzapine treatment.[104] At 2 hours post injection patients receiving intramuscular olanzapine showed greater orthostatic change in pulse rate (7 beats per minute), supine systolic blood pressure (−7mm Hg) and standing systolic blood pressure (−5mm Hg). These changes were not present at 24 hours post dose and were considered clinically insignificant.

Since the introduction of intramuscular olanzapine to the European market a total of 49 adverse events have been reported, of which eight were fatal.[105] Cardiorespiratory depression, hypotension and bradycardia were noted in these case reports. A review of the fatalities indicated that excessive dosages had been used and concomitant administration of benzodiazepines and/or other antipsychotics had occurred. Significant comorbidities were also present in these patients, making it difficult to attribute the deaths solely to intramuscular olanzapine. Regardless, intramuscular olanzapine should not be coadministered with other medications, especially benzodiazepines (or other CNS depressants) in view of these reports. These findings also highlight the need for further study on the safety of intramuscular

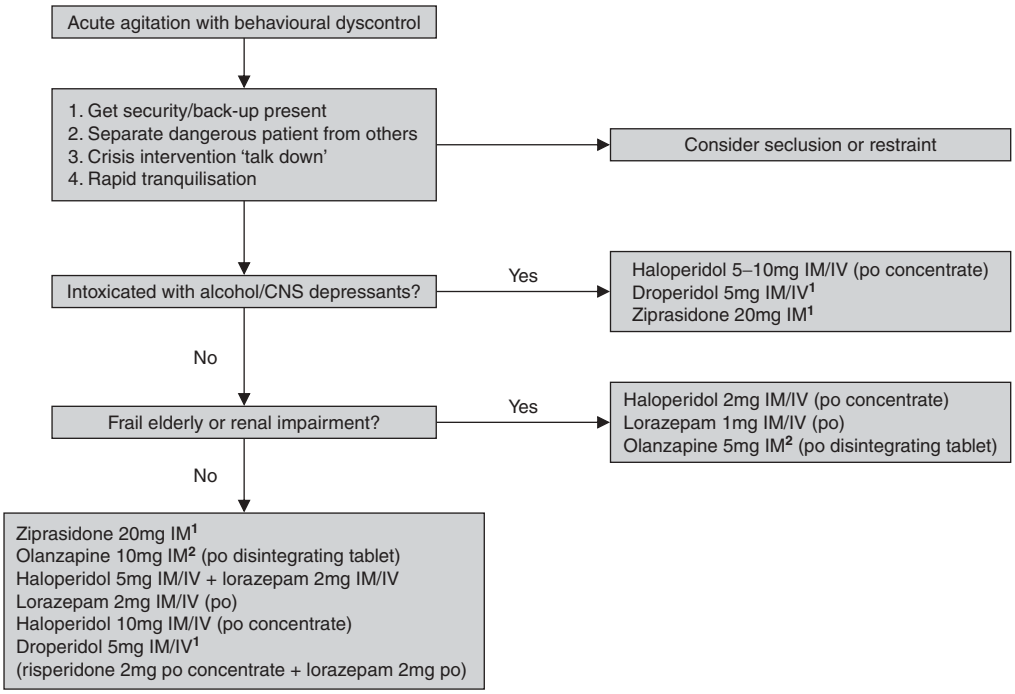

Fig. 1. Acute agitation with behavioural dyscontrol: clinical management guideline. **1** Do not use with increased corrected QT interval. **2** Do not give simultaneous intramuscular (IM)/intravenous (IV) CNS depressants (e.g. benzodiazepines). **po** = oral.

olanzapine in patients with alcohol or other sedative intoxication.

One study has shown that the alleviation of agitation was sustained following transition from intramuscular to oral olanzapine, where 91% of patients completed the intramuscular phase (24 hours) and 86% completed the 4 days of oral treatment.[106] Intramuscular olanzapine has been shown to have distinct calming versus nonspecific sedative effects.[12] To date, no studies are published on the use of intramuscular olanzapine in patients with severe agitation (non-consenting patients) or significant medical morbidity, or in those with alcohol or drug intoxication states.

In addition to intramuscular and oral tablet preparations of olanzapine, an ODT is also available. Olanzapine ODT dissolves in less than a minute and has identical bioequivalence to standard oral tablets; however, one non-peer reviewed poster presentation showed that the onset of absorption was faster.[107] Although the differences in plasma concentration are minimal, and less than one would expect for a significant difference in therapeutic effect, the olanzapine ODT preparation has become a commonly used therapy for moderately agitated patients in emergency departments or inpatient settings who are willing to take medication. In another non-peer reviewed poster presentation, an open-case, unblinded study found that olanzapine 20mg ODT was effective in reducing acute agitation within 60 minutes, and sedation was noted to be "shallower than traditional medication regimens".[108]

7. Pharmacological Treatment of Acute Agitation: Clinical Management Guideline

A clinical pathway algorithm for treating acutely agitated patients with behavioural dyscontrol is shown in figure 1. The assumption is made that psychological and environmental methods have been insufficient to control agitation and that the patient will require assertive medication manage-

ment. The treatment team should immediately notify the security or back-up clinical staff and separate the agitated patient from others, while simultaneously attempting 'talk down' techniques for the patient.[109] Seclusion and restraint options should also be considered during this time, and may be employed concurrently with the rapid tranquillisation. Rapid tranquillisation options are shown in order of preference, with oral agents in parentheses for those patients with less severe agitation, able to comply with treatment and willing to take oral medication. The goals of rapid tranquillisation are to calm the patient quickly, decrease the likelihood of harm to self or others, allow diagnostic tests or procedures, attenuate psychosis (if present) and decrease use of seclusion and restraint.

If the patient is obviously intoxicated with alcohol or other sedatives, haloperidol or droperidol should be used and benzodiazepines avoided. These butyrophenones have the largest accumulated efficacy and safety record in treating such patients, who are at great risk for medical comorbidity.[39,83] Preliminary research findings and current clinical practice support the use of ziprasidone in this population, although further research is needed to confirm efficacy and safety.

If the patient is a frail elderly person, has known renal impairment or appears to be medically compromised, consider smaller doses of a single agent. Haloperidol, lorazepam and olanzapine all have established efficacy and safety in such clinical populations. Ziprasidone has generally been avoided in the elderly because of concerns about QTc prolongation.[110]

For all other severely agitated patients, intramuscular olanzapine and intramuscular ziprasidone deserve strong consideration as first-line agents. Intramuscular olanzapine has more robust research evidence and has shown superiority (faster onset of action, greater efficacy, fewer adverse effects) over haloperidol and lorazepam in clinical trials. The recent reports of adverse events (including eight fatalities) associated with intramuscular olanzapine underscores the need to follow strict prescribing guidelines, specifically that intramuscular olanzapine should only be given as a single agent using recommended doses, with close observation for 2–4 hours following administration. Until additional safety data become available, intramuscular olanzapine should be avoided in patients with alcohol or sedative intoxication. Intramuscular ziprasidone has weaker research support; however, it has been widely used since its introduction into clinical practice (2002) with empirically good results. One naturalistic study has shown intramuscular ziprasidone to be effective in severely agitated patients, including those with alcohol and substance intoxication. Although some clinical evidence suggests that QTc interval concerns with ziprasidone may be exaggerated, it should not be used in patients with known QTc interval-associated conditions.[111] The haloperidol plus lorazepam combination remains a clinical standard with strong research and empirical support in a variety of clinical populations (including in severely medically compromised patients). Either agent alone remains an adequate, although generally not first-line, therapeutic option for severe agitation. Droperidol is efficacious; however, it has some associated medico-legal risk and is no longer available in some hospital formularies.

For oral therapy, haloperidol concentrate, lorazepam (oral/sublingual), olanzapine ODT and risperidone concentrate combined with lorazepam have all displayed efficacy in the treatment of agitation. Haloperidol should be considered as a first choice for patients with alcohol or other sedative intoxication (lorazepam should be avoided because of CNS depressant effects, and olanzapine or risperidone have not yet been adequately studied in this population). In non-intoxicated patients with a history of significant EPS from antipsychotics, haloperidol should only be used in combination with lorazepam or with a prophylactic anticholinergic medication. Other than olanzapine or risperidone being better tolerated than haloperidol, there are no clear indications from the available data for preference among these oral treatments.

8. Conclusion

Decades of empirical evidence and a substantial body of research has shown that typical antipsychotics and benzodiazepines (haloperidol and lorazepam as prototypes), alone or in combination, are effective agents for use in rapid tranquillisation. Each has significant risks and adverse effects. Typical antipsychotics may cause EPS or akathisia and, less commonly, neuroleptic malignant syndrome or cardiac arrhythmias. Benzodiazepine use may result in excessive sedation, CNS depression, ataxia or respiratory compromise.

Two atypical antipsychotic agents are now available as fast-acting intramuscular injections for treatment of acute agitation. Intramuscular ziprasidone has gained widespread use in the US since its introduction in 2002, and is indicated for treatment of agitation associated with schizophrenia and other nonspecific psychotic conditions. One naturalistic study showed intramuscular ziprasidone to be safely used and effective in highly agitated patients with alcohol intoxication and drug-induced psychotic states. Ziprasidone has a relatively greater propensity to increase the QTc interval than other atypical antipsychotic agents and, thus, the US FDA has advised caution when used with medications or illnesses predisposing to increased QTc. Intramuscular olanzapine has robust research evidence showing rapid efficacy in agitation associated with schizophrenia, schizoaffective disorder, bipolar mania and dementia. Since the introduction of intramuscular olanzapine to clinical practice, a significant amount of adverse events have occurred in which cardiorespiratory depression, hypotension and bradycardia were observed (including eight fatalities). A review of these cases indicated that excessive dosages and concomitant use of CNS depressant medications had occurred.

The availability of fast-acting intramuscular antipsychotics for rapid tranquillisation represents a significant advance in emergency psychiatry. More than 2 years of empirical evidence with intramuscular ziprasidone in the absence of reported serious adverse events may indicate that QTc interval concerns are clinically insignificant. Further research aimed specifically at examining the cardiac effects in naturalistic conditions (medically compromised, agitated patients) may allow clarification of this issue. The cardiorespiratory concerns that have surfaced with intramuscular olanzapine strongly suggest further study to elucidate the contraindications for this agent (e.g. in patients with known or suspected alcohol or other CNS depressant intoxication). Finally, a 'head-to-head' prospective, randomised trial of intramuscular ziprasidone, olanzapine or haloperidol plus lorazepam in highly agitated, psychotic patients would allow direct comparison of the speed of onset, efficacy, tolerability and safety of these newer agents with each other as well as with an accepted standard.

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