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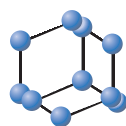


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REVIEW ARTICLE

BENTHAM
SCIENCE

Older and Newer Strategies for the Pharmacological Management of Agitation in Patients with Bipolar Disorder or Schizophrenia

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Abstract: Background: The management of acute agitation in patients with bipolar disorder or schizophrenia is a multifaceted and dynamic task, which presents unique and complex challenges to healthcare providers.

Objective: To ascertain and describe which medications are best to use in patients with agitation, affected by bipolar disorder or schizophrenia.

Method: Selective review of current literature and guidelines referred to the treatment of agitation in individuals affected with bipolar disorder or schizophrenia

Results: When possible, the pharmacologic management of agitation should be preceded by a in-depth evaluation of the possible causes of the agitation. The use for of first and second-generation antipsychotic medications, of benzodiazepines and of the newer inhaled antipsychotic loxapine, is reviewed and commented.

Conclusion: The mainstay of medication treatment of acute agitation should be based on a thorough assessment cause. If agitation is due to delirium or to another physical condition, an attempt to address the underlying causes should be always considered. When agitation is primarily due to schizophrenia or bipolar disorder, antipsychotics and/or benzodiazepines are usually the mainstay of treatment. Newer inhaled formulation of loxapine has shown ability to rapidly reduce the agitation in mild to moderate patients with schizophrenia or bipolar disorder, with a decrease in agitation that was evident since the first assessment, 10 minutes after the first dose.

Keywords: Agitation, bipolar, schizophrenia, antipsychotics, benzodiazepines, loxapine, intramuscular, oral, inhaled.

1. INTRODUCTION

Treatment of agitation represents a major clinical challenge [1]. In many circumstances, behavior control methods such as de-escalation, verbal intervention, offering food and/or beverages, letting patients smoke or offering nicotine substitutes (e.g. nicotine patches or gums), may be useful to begin with the initial management of agitation and to prevent its escalation into aggression or violence [2, 3]. However, when the above mentioned attempts fail to control agitation, the use of specific psychotropic drugs becomes crucial. Before starting medications, an attempt should be made to establish the cause for agitation, which can inform treatment choice. However, acute agitation is common and may occur

across a range of somatic, psychiatric, and substance abuse disorders, and a diagnosis is often still unclear when rapid intervention is necessary.

Nonetheless, the choice of medication for an agitated patient should be informed at least by a provisional diagnosis and by the presumed etiology underlying the observed symptoms. For instance, agitation that is deemed as likely to stem from organic causes (e.g. hypoglycemia, hypoxia, thyroid storm) should not be treated with an antipsychotic, whereby the prescription of an antipsychotic and/or benzodiazepine is appropriate for agitation that has a psychiatric etiology. It is believed that abnormalities in the biogenic amines - dopamine, norepinephrine, and serotonin - as well as adenosine [4], glutamate [5] and the inhibitory neurotransmitter γ -aminobutyric acid (GABA) are involved in the etiology of agitation due to psychiatric reasons [6-8]. Specifically, it is hypothesized that agitation associated with psychosis, mania,

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and substance abuse is mainly correlated with elevated dopaminergic neurotransmission, whereby decreased GABAergic transmission is the primary characteristic of agitation associated with dementia, depression, and anxiety [9].

In agitated patients affected by bipolar disorder or schizophrenia, benzodiazepines or second-generation antipsychotics (SGA) are usually preferred over first-generation antipsychotics (FGA) but there are instances in which older antipsychotics or newer medications represent a valid alternative.

2. TYPES OF MEDICATION

There is no medication or class of medications that has proven to be the “best” in all cases of patients with bipolar disorder or schizophrenia that present with agitation. However, the choice usually falls on antipsychotics (first or second generation) and benzodiazepines, which may be administered in oral, intramuscular or intravenous formulations. A recent addition to the armamentarium for the treatment of agitation is inhaled loxapine, which is approved by the FDA for the acute treatment of agitation in individuals with bipolar disorder or schizophrenia [10] and by the EMA for the quick control of mild to moderate agitation in adult patients with bipolar disorder or schizophrenia [11].

2.1. First Generation Antipsychotics

First Generation Antipsychotics (FGA) have been widely used for management of agitation in bipolar disorder and schizophrenia. The mechanism of action that is involved in FGA ability to control agitation is not known, but is likely related to their ability to antagonize dopamine receptors, which leads to a reduction of activation and psychomotor agitation while addressing the underlying psychotic symptoms. Also, some FGAs are structurally similar to gamma-amino-butyric acid (GABA) - an inhibitory neurotransmitter - and are hence able to directly act on the GABA receptor [12].

Compared to haloperidol, chlorpromazine, a low-potency phenothiazine, has a higher propensity to cause hypotension, particularly in the elderly, causes more pain at the site of injection, has more anticholinergic side effects, and a higher likelihood to lower the seizure threshold [13-15]. Also, when used intravenously chlorpromazine may cause prolonged unconsciousness [16]. Moreover the use at high doses may be associated with sudden death [17]. As a result, intramuscular chlorpromazine is not recommended [18] and the phenothiazines in general are seldom considered as a first choice for the management of agitation.

Haloperidol is a highly potent and selective dopamine-2 (D2) receptor antagonist and has a long track record of effective use for the management of acute agitation [19, 20]. For a relatively long time, haloperidol used to be considered as a safe and effective medication when administered intramuscularly or intravenously. However, serious adverse events have been described, including neuroleptic malignant syndrome [21], dystonia and other extrapyramidal side-effects, which may even worsen agitation [18]. In addition, it has been reported that FGAs sometimes cause dysphoria after use [22, 23].

Although the exact incidence of EPS adverse events is unclear, one study reported that EPS symptoms were observed in up to 20% of agitated individuals that received haloperidol monotherapy versus a percentage of only 6% of subjects that were treated with haloperidol combined with lorazepam [24]. Also, the combination of haloperidol-lorazepam was related to a faster reduction in agitation [25]. Other studies have reported that a combination of haloperidol with promethazine or diphenhydramine may lower EPS incidence [26, 27].

For these reasons, haloperidol is often administered together with other medications, such as lorazepam, promethazine, or diphenhydramine [19]. Yet, the use of multiple medications to control agitation may rise the risks of cardiovascular side effects, excessive sedation and pharmacokinetic or pharmacodynamics interactions.

Other worrisome adverse events that have been described for haloperidol, include torsade de pointes [28, 29], cardiac arrest and sudden death [30, 17].

For the reasons above, haloperidol carries a label warning that specifies that “higher doses and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation and TdP”. [31]. The updated FDA warning notes that high doses and intravenous use of haloperidol increase the risk of QT prolongation and TdP and that particular caution necessary when treating patients with any dose or formulation of haloperidol have other conditions that have been correlated to higher risk to prolong QT trait, such as electrolyte imbalance (*i.e.*, hypokalemia and hypomagnesemia). Also, particular caution is warranted when patients are affected by cardiac abnormalities, low thyroid function, familial long QT syndrome, or are receiving medications that are able to increase the QT interval.

Because of the risk of QT increase and TdP, ECG monitoring is necessary if haloperidol is administered intravenously. However, haloperidol intravenous administration is not endorsed by any regulatory agency, including the USA Food and Drug Administration [31].

Of interest, agitation itself may prolong QTc trait. For instance, compared to psychiatric out-patients, acutely agitated patients have been described to have a 50 ms longer QTc trait [32].

Also, patients with agitation may be at higher risk of death when QTc prolongation occurs, given that adrenaline may sensitize the heart and increase the risk of arrhythmias [18, 29].

The short-acting depot medication zuclopenthixol acetate has been longly used for rapid tranquillization [33]. However, injecting patient that has never been treated before with a long half-life drug may be dangerous and the Royal College of Psychiatrists' consensus advocates that such use in naïve patients only in ‘exceptional circumstances’. Also, zuclopenthixol use in agitated patients is discouraged because of the delayed onset (about 8 hours) of its benefits [34] limited and by the fact that the highest plasma concentrations are reached after a relatively long period of time of 36 hours [35]. Also, fatal cardiac events and sudden deaths have been reported [18].

2.2. Second Generation Antipsychotics

Second-generation antipsychotics (SGA), also called typical antipsychotics, are frequently used for the pharmacological management of acute agitation. Aripiprazole, olanzapine and ziprasidone, come in both intramuscular and oral formulations.

Compared with FGA, SGAs carry a lower risk of side effects such as dystonia or akathisia, with rates that have usually reported as lower than 1% [36-38]. Most studies in bipolar disorder or schizophrenia have indicated that SGA are more effective than placebo, and similar to haloperidol, in reducing agitation [39-45].

Oral olanzapine is one of the best-studied SGAs for psychiatric agitation. Yet, a number of studies have also demonstrated that medications such as aripiprazole, quetiapine, risperidone, or ziprasidone are efficacious as well [46, 47]. Usually, oral medicines should be preferred over intramuscular agents when a patient is cooperative and has no contraindications to oral use. However, many agitated patients are not cooperative and oral medication may have too slow an onset in patients with severe agitation.

Intramuscular preparations of the SGA ziprasidone [48], olanzapine [49] and aripiprazole [50] show a better extrapyramidal side-effect profiles than intramuscular haloperidol, while providing similar effect sizes in terms of controlling agitation [41, 25].

These intramuscular medications are indicated by the FDA for treatment of acute agitation associated with schizophrenia [48-50] and - limited to olanzapine and aripiprazole - bipolar mania. Also, these medications have been recommended over the first-generation antipsychotics [25].

However, since the approval of intramuscular olanzapine, several adverse events have been described, some of which were fatal [51]. Hypotension, bradycardia and cardiorespiratory depression were noted and excessively high doses and/or concomitant prescription of benzodiazepines and/or of other antipsychotics seemed a likely contributor to death [46]. Hence, intramuscular olanzapine should not be administered together with other medications, such as benzodiazepines, antipsychotics or other CNS depressants. Careful post-injection monitoring of the patient is recommended. In the case of a severe adverse event an intensive care unit should be easily accessible.

An open-label study that compared ziprasidone with haloperidol in a sample of 132 individuals reported that intramuscular ziprasidone prescribed at 5-20 mg was equivalent or better than haloperidol prescribed at 2.5-10 mg in reducing agitation [40]. Compared with haloperidol, ziprasidone was associated with significantly less extrapyramidal side-effects. The efficacy of intramuscular ziprasidone was tested in subjects with acute psychotic agitation in two similarly designed 24-hour, multisite, randomized, double-blind trials [52, 53], which both demonstrated significant superiority to placebo.

Intramuscular aripiprazole has been approved in the EU and US for the management of agitation in subjects with schizophrenia or bipolar I disorder. In several trials, intramuscular aripiprazole has proven better than placebo and

well tolerated in the control of agitation in individuals with bipolar I disorder, schizophrenia and schizoaffective disorder [54-58]. Aripiprazole carries a relatively low risk of extrapyramidal symptoms, *e.g.* akathisia [59], cardiovascular effects, weight gain, hyperprolactinaemia and other metabolic issues [60-62].

Orally disintegrating formulations of aripiprazole, olanzapine, and risperidone, and have been developed but this method of administration does not improve time to onset and these medications are bioequivalent to the regular oral tablets and provide similar efficacy and safety at the same dose [49, 50, 63, 64].

Sublingual asenapine, is approved by the FDA for the treatment of patients with schizophrenia or patients with bipolar disorder and a manic or mixed episode. Differently from the orally disintegrating tablets of aripiprazole, olanzapine, and risperidone sublingual asenapine might partially be absorbed in the oral mucosa and peak plasma concentration is reached in 30-60 minutes [65]. Hence, this medication might have the advantage of at least partially avoiding first-pass metabolism; however, even more than with all oral medications, treatment requires patient cooperation [66].

In a double-blind, randomized, placebo-controlled trial for acute agitation, sublingual asenapine showed an effect size comparable to that observed for intramuscular SGA [67]. However, sublingual asenapine is not approved for acute agitation. Hence, its use for this condition would be considered off label.

2.3. Benzodiazepines and Other Anticonvulsants

Benzodiazepines (BDZ) are frequently prescribed for rapid control of agitation owing to their anxiolytic and sedative effects. Also, BDZ enhance gamma-amino-butyric acid activity, which may provide an direct antipsychotic effect *via* inhibition of dopamine mediated transmission [68]. However, the main effects of benzodiazepines for the treatment of agitation is mainly linked with their capacity to decrease arousal [69].

A relatively large number of studies have evaluated benzodiazepines and typical antipsychotics in the treatment of acute agitation. Most studies found similar efficacy, less EPS and increased sedation [69]. The most serious risks of benzodiazepines include respiratory depression, which is more frequent when high doses are prescribed. However, this adverse event can be quickly reversed with the partial agonist flumazenil. Also, case reports of behavioral disinhibition with benzodiazepines have been reported [70].

This risk seems heightened when high doses of benzodiazepines are prescribed [71] and in patients showing symptoms such as hostility or difficulty controlling impulse [70, 72].

Lorazepam is the only benzodiazepine with complete, rapid and consistent intramuscular absorption. Peak plasma concentrations are reached 60-90 minutes after dose when intramuscular or sublingual lorazepam are administered. The elimination half-life is 12-15 hours and duration of effect is at least 8-10 hours [73, 74].

Drug interactions are limited given that lorazepam is quickly metabolized *via* a conjugation to an inactive glucu-

ronide, with no involvement of the oxidative cytochrome P450 system. Several studies have demonstrated that lorazepam has comparable efficacy to haloperidol in the management of psychotic or manic agitation, and some trials have even indicated superiority [75-78]. Lorazepam can be administered intravenously, which may be helpful for the rapid control of severe agitation [61, 62].

Diazepam is effective when administered intravenously [79], but is not recommended for intramuscular administration due to its erratic absorption [80]. As a result, intramuscular lorazepam, which is better and more reliably absorbed [73], is the BDZ of choice [81, 82].

Several reports, including one placebo-controlled double-blind trial involving patients with chronic schizophrenia, have suggested that clonazepam may escalate psychosis or agitation in some individuals [83-85]. Hence, clonazepam has a very limited, if any, role for the treatment of acute agitation.

Midazolam -a fast-acting benzodiazepine- is not FDA approved for acute agitation. Yet, there has been interest in the potential use of this formulation for this indication [86]. Intranasal midazolam avoids first-pass metabolism since it is absorbed by the nasal mucosa. Intranasal midazolam induced calming within 15 to 20 minutes in children [87]. The use of intravenous midazolam is limited because of the risk of respiratory depression and respiratory arrest. Hence, it should be used only in settings where a continuous monitoring of respiratory and cardiac functions is possible. Specifically, an immediate availability of equipment for ventilation, intubation and resuscitative drugs should be present [61].

In some cases other anticonvulsive agents have been associated with the successful control of agitation particularly in manic episodes [88]. Oral gabapentin [89] and intravenous valproate [90, 61] might be interesting off-label alternatives to the use of benzodiazepines.

2.4. Newer Treatments for Agitation

Loxapine has been available for many years as an oral formulation of a FGA and has shown an established safety and efficacy profile [91]. Recently, loxapine was reformulated as an inhaled powder that can be directly administered to the lungs, at a lower dose. This results in a quick dissemination into the systemic circulation with peak plasma levels that are reached within two minutes of administration [10]. The safety and efficacy of inhaled loxapine for acute agitation have been demonstrated in two Phase III clinical trials, in schizophrenia and bipolar disorder [92, 93]. The effect sizes were comparable to those observed in similar studies of antipsychotics or lorazepam administered intramuscularly [94]. However, clinical effects were observed as early as 10 minutes after inhalation, which was the first time point that this was measured [92, 93]. Loxapine resulted superior to placebo throughout the remaining periods of the study, at all-time points that were measured. In the schizophrenia trial, the effect size (ES) difference from placebo on the Positive and Negative Syndrome Scale Excited Component (PEC) at the 2 h assessment point resulted 0.45 for loxapine 5 mg and 0.60 for loxapine 10 mg (Cohen's d) [95].

Inhaled loxapine was generally well tolerated. Extrapyramidal adverse events and akathisia were relatively un-

common and the most frequently reported adverse effect was dysgeusia. However, spirometry studies suggested risk of bronchospasm, with the potential to lead to respiratory distress and respiratory arrest. For this reason, the use of inhaled loxapine is restricted to the hospital setting [66]. Rapid treatment of bronchospasms can be achieved with bronchodilators such as short-acting β -agonists (e.g. inhalatory salbutamol).

Interestingly, inhalatory loxapine has been approved by the EMA for the control of agitation in adult patients with schizophrenia or bipolar disorder, these last, both during manic and depressive episodes with or without mixed features. In clinical practice the successful use of inhalatory loxapine in agitated depression has been reported [96].

CONCLUSION

The most common strategies for the pharmacological treatment of acute agitation in schizophrenia and bipolar disorder include FGA, SGA and benzodiazepines.

Given the concerns over tolerability and risks of FGA, SGA medications are usually preferred. However, SGA are not void of risks, such as hypotension and bradycardia. Cardiorespiratory depression has been observed in patients treated with intramuscular olanzapine, especially when this medication is associated with parenteral benzodiazepines. Benzodiazepines, particularly intravenous lorazepam, are a valid alternative. However, caution needs to be exercised with these drugs as well, owing to the presence of risks of severe adverse events such as respiratory depression, which however can usually be readily reversed with appropriate treatment (e.g. flumazenil). Hence, flumazenil and resuscitation equipment should be readily accessible, especially when benzodiazepines are used at high doses and in the intravenous route. Recently developed inhaled formulation of loxapine has shown the ability to rapidly reduce the agitation in individuals with schizophrenia or bipolar disorder, with a decrease in symptoms that was evident since the first assessment, 10 minutes after the first dose. Inhaled loxapine may be an important new tool for the treatment of mild to moderate agitation.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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