TITLE: Use of Antipsychotics and/or Benzodiazepines as Rapid Tranquilization in Inpatients of Mental Facilities and Emergency Departments: A Review of the Clinical Effectiveness and Guidelines

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CONTEXT AND POLICY ISSUES:

Rapid tranquilization involves the assertive use of medication to calm severely agitated patients quickly, decrease dangerous behaviour, and allow treatment of a possible underlying condition. At present, there is no globally accepted agreement on which drugs should be used as first line for rapid tranquilization. As a result, there is a wide variation in the type of medications used in rapid tranquilization, which has been compounded by recent changes in the aims of rapid tranquilization – that is to calm patients rather than to sedate. Behavioural emergencies from acute psychotic disturbances, manic episodes, major depression, bipolar disorder, and substance abuse are responsible for approximately 6% of emergency department (ED) visits in the United States. Intramuscular (IM) injections of typical antipsychotics and benzodiazepines, given alone or in combination have been the first-line of treatment over the past few decades. IM administration results in a higher maximum plasma concentration in a shorter period of time than oral administration. These pharmacokinetic properties result in an earlier onset of action which is highly desirable in acutely agitated and aggressive patients. Treatment with typical antipsychotics has been associated with the development of extrapyramidal symptoms (EPS), including acute dystonia and akathisia, while benzodiazepine treatment can result in excessive sedation. More recently, IM formulations of atypical antipsychotics (ziprasidone, olanzapine, risperidone, aripiprazole) have offered a more favourable treatment option for acute agitation and aggression since these agents have a much lower propensity to cause EPS. These new formulations of atypical antipsychotics also provide the opportunity for seamless transition to oral dosing of the same agent, removing the need to switch from IM typical to oral atypical which is usually the drug of choice for long-term oral treatment.

The increased need for rapid tranquilization in mental facilities and EDs validates the need for assessment of the efficacy of current treatment options, and a survey of the evidence-based guidelines currently available. This report will review the clinical effectiveness of IM
antipsychotics and benzodiazepines for inpatients in mental facilities or EDs, and discerning the current guidelines available for this topic.

RESEARCH QUESTIONS:

1. What is the clinical effectiveness of using intramuscular antipsychotics and/or intramuscular benzodiazepines as rapid tranquilization for inpatients in mental facilities or emergency departments?

2. What are the evidence-based guidelines for using intramuscular antipsychotics and/or intramuscular benzodiazepines as rapid tranquilization for inpatients in mental facilities or emergency departments?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID Medline, OVID PsycInfo, The Cochrane Library (Issue 2, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between 2005 and March 2010. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs) and evidence-based guidelines.

SUMMARY OF FINDINGS:

The search identified six systematic reviews,8-13 one meta-analysis,14 three RCTs,4,15,16 one major guideline,2 and five supplementary guideline sources.3,17-20

Systematic reviews and meta-analyses

Kynoch et al. conducted a systematic review (2009) examining the effectiveness of interventions in the prevention and management of aggressive behaviours in patients admitted to an acute hospital setting.13 This review considered any RCT that examined best practice in the prevention and management of aggressive behaviours in an acute hospital setting. In the absence of RCTs, other research designs such as non-randomized controlled trials were considered for the narrative summary. Twelve studies and one dissertation met the inclusion criteria. After examining the included studies, it was evident that no two studies were directly comparable and therefore were not suitable for meta-analysis. The review presented several recommendations for clinical practice to prevent and manage aggressive behaviours including administration of medications, training programs for staff, physical restraints, and other non-pharmacological approaches. The findings presented in the review indicated that the combination treatment of IM lorazepam plus haloperidol is ideal. The review also indicated that “midazolam has a significantly shorter time to onset of sedation and a more rapid time of arousal than lorazepam or haloperidol.”13 Kynoch et al. identified the lack of high quality studies in the area as a limitation.
Four separate Cochrane reviews were identified that examined pharmacological treatments for psychosis-induced aggression or agitation,\textsuperscript{8,9,11,12} and one Cochrane review that specifically addressed acute schizophrenia and similar serious mental illnesses.\textsuperscript{10}

The review by Gilles et al. (2009) estimated the effects of IM benzodiazepines, alone or in combination with antipsychotics, when compared to placebo or antipsychotics, to control disturbed behaviour and reduce psychotic symptoms.\textsuperscript{11} The search identified eleven studies with a total of 648 participants. The review included all RCTs comparing benzodiazepines, alone or in combination with antipsychotics, with placebo or sole use of antipsychotics, for people with acute psychotic illnesses. The results from one RCT showed that when comparing IM lorazepam with placebo, sedation was similar, however, fewer people on lorazepam remained excited at 24 hours compared with placebo. The lorazepam and placebo group experienced similar non-significant, low levels of adverse effects. In the comparison of IM benzodiazepines (lorazepam, clonazepam, diazepam, flunitrazepam) versus use of IM antipsychotics without use of anticholinergics or antihistamines, people on benzodiazepines did not require additional medication compared to those given antipsychotics. Numbers sedated were also equivalent between groups as were mental state ratings. EPS were significantly higher in the antipsychotic treatment group. When the IM benzodiazepine plus antipsychotic combination was compared with antipsychotics alone there was no difference between groups in the need for additional medications or for mental state measures. EPS were significantly lower for people receiving both benzodiazepines and antipsychotics compared with those receiving antipsychotics alone. Overall, the authors concluded that:

- there is insufficient data from these studies to support or refute the use of benzodiazepines with or without antipsychotics where emergency drugs are needed. The sole use of older antipsychotics unaccompanied by anticholinergic drugs may be problematic, but studies in this review are not large enough to identify any serious adverse effects of benzodiazepines such as respiratory depression. Larger, more informative studies are needed before definite conclusions can be drawn as to the efficacy of benzodiazepines. (p.2)\textsuperscript{11}

Another Cochrane review considered IM haloperidol plus promethazine for psychosis-induced aggression.\textsuperscript{12} Using similar search strategy and selection criteria to the Gilles et al. systematic review, the authors identified four relevant high quality RCTs. One compared haloperidol plus promethazine with IM midazolam, one with IM lorazepam, one with haloperidol alone, and one with IM olanzapine. The review included people who were within an aggressive episode thought to be due to psychotic illness. IM haloperidol plus promethazine was an effective means of tranquilization with over two thirds of people being tranquil or sedated by 30 minutes, but midazolam was more rapid. The authors reported a considerable degree of statistical heterogeneity within the haloperidol plus promethazine versus benzodiazepines (both midazolam and lorazepam) comparison.\textsuperscript{12} Olanzapine was just as rapid in terms of tranquilization as the haloperidol/promethazine combination, but its effects were not as long lasting. Conclusions from the authors were:

- all treatments evaluated within the included studies were effective. Benzodiazepines, however, have the potential to cause respiratory depression, probably midazolam more so than lorazepam, and use of this group of drugs outside of services fully confident of observing for and managing the consequences of respiratory distress is difficult to justify. Haloperidol used on its own is at such risk of generating preventable adverse effects that unless it is the only choice, this evidence directs that this sole treatment should be avoided. IM olanzapine is valuable when compared with
A separate Cochrane review tried to estimate the effects of intramuscular, oral-velotab, or standard oral olanzapine compared with other treatments for controlling aggressive behaviour or agitation thought to be due to severe mental illness. The authors searched for RCTs, and identified 8 comparing oral-velotab or IM, or standard oral olanzapine to any treatment, for agitated or aggressive people with severe mental illnesses. Four trials compared IM olanzapine with placebo. The results showed that fewer people given olanzapine had 'no important response' by 2 hours compared with placebo and olanzapine was as acceptable as placebo. When compared with placebo, people given olanzapine required substantially fewer additional injections following the initial dose. Olanzapine did not seem to be associated with EPS. Two trials compared IM olanzapine with IM haloperidol, and found no differences by 2 hours for the outcome of 'no important clinical response'. Also, there was no difference in the need for further injections. Fewer people using IM olanzapine experienced akathisia in comparison to IM haloperidol, and fewer people allocated to olanzapine required anticholinergic medication by 24 hours compared with those given haloperidol. Two trials compared IM olanzapine with IM lorazepam, and found no difference between groups for the outcome of 'no important clinical response'. Fewer people on olanzapine required additional injections by 24 hours compared with those on lorazepam. Those receiving olanzapine were less likely to experience any treatment emergent adverse events, than those on lorazepam and over the same time period there were no obvious differences in the use of anticholinergic medication between groups. Overall, the authors suggested that IM olanzapine may be a useful option for treatment of patients with acute aggression or agitation.

Rathbone et al. (2009) updated a previous report by searching the Cochrane Schizophrenia Group Register (September 2003) to estimate the effects of droperidol compared to other treatments for controlling disturbed behaviour and reducing psychotic symptoms for people with suspected acute psychotic illnesses. The review included RCTs comparing droperidol to any other treatment for people with suspected acute psychotic illnesses, including schizophrenia, schizoaffective disorder, mixed affective disorders, the manic phase of bipolar disorder, or a brief psychotic episode. The search identified two relevant trials, one of which looked at IM administration. When IM droperidol was compared to IM haloperidol, those given droperidol were less likely to need additional injections by 30 minutes than those administered haloperidol, but was not statistically significant. The authors indicated that the obvious lack of quality research in this area limits what conclusions can be made. Currently, use of droperidol for ED situations has been justified by experience rather than evidence from well conducted and reported RCTs trials.

The last identified Cochrane systematic review updated an existing version which estimated the clinical effects of oral and IM zuclopenthixol acetate for the management of acute aggression or violence thought to be due to serious mental illnesses, in comparison to other drugs used to treat similar conditions. The updated search identified RCTs involving people thought to have serious mental illnesses comparing zuclopenthixol acetate with other drugs. The review was unable to identify any data for the primary outcome of tranquilization, and found no data on more episodes of aggression or harm to self or others. One trial reported no significant difference in adverse effects for people receiving zuclopenthixol acetate compared with those using haloperidol at one, three, and six days.
The authors conclude that recommendations on the use of zuclopenthixol acetate for the management of psychiatric emergencies in preference to 'standard' treatment have to be viewed with caution due to the lack of evidence. This review did not find any suggestion that zuclopenthixol acetate is more or less effective in controlling aggressive acute psychosis, or in preventing adverse effects than IM haloperidol, and neither seemed to have a rapid onset of action. (p.2)

A meta-analysis by Battaglia et al. (2005) used a post-hoc analysis to assess the relationship between 24-hour IM and transitional oral dosages of olanzapine and haloperidol. The study used data from a multinational, double-blind RCT comparing the efficacy of olanzapine, haloperidol, and placebo in acutely agitated inpatients aged 18 years or older with schizophrenia. Patients received IM olanzapine or haloperidol over 24 hours, followed by 4 days of oral treatment with either antipsychotic. The results showed that for both treatments, IM administration lowered agitation as measured by PANSS-EC (excited component of the positive and negative syndrome scale). Upon completion of the IM haloperidol phase, the rate of transition to lower oral doses was significantly higher in the single-injection subgroup compared with the multiple-injection subgroup. This trend was not maintained in the group receiving olanzapine. The author’s conclusions were primarily on transitioning to oral treatment and not on the comparative efficacy of each agent.

Randomized controlled trials

Veser et al. (2006) conducted a prospective, randomized, placebo-controlled, double-blind study of 30 patients presented to the ED with acute agitation and/or psychosis. Three groups of 10 patients received either oral risperidone and IM lorazepam, oral haloperidol and IM lorazepam, or oral placebo and IM lorazepam. Patients were evaluated using the BPRS (brief psychiatric rating scale) and PANSS (positive and negative syndrome scale). The results showed that IM lorazepam alone was as effective as lorazepam plus haloperidol or lorazepam plus risperidone in this small trial. The authors stated that “while not statistically significant, a trend toward better outcomes with combined treatment warrants further study.”

An additional prospective RCT from Martel et al. (2005) compared the efficacy of sedation, need for rescue sedation, rates of respiratory depression, and complications of IM drperidol, ziprasidone, and midazolam when used for the treatment of ED patients requiring sedation for acute undifferentiated agitation. A total of 144 patients were enrolled; 50 patients received droperidol, 46 received ziprasidone, and 48 received midazolam. Each of the medications was successful at managing acute agitation; however more ziprasidone patients were still agitated at 15 minutes in comparison to droperidol and midazolam. Only a limited number of EPS were seen in this study. The authors stated that patients who received midazolam required rescue medication more often than patients who were given droperidol or ziprasidone.

One RCT was identified that examined rapid tranquilization in ethnic subpopulations. Raveendran et al. (2007) compared the effect of IM olanzapine with IM haloperidol plus promethazine on rapid tranquilization of agitated or violent people with mental illness in India. Both treatments resulted in similar proportions of people being tranquil or asleep at 15 minutes. However, more patients that were given olanzapine required additional drugs over four hours than those given haloperidol plus promethazine. Adverse effects were uncommon with both treatments. The results showed that IM olanzapine and IM haloperidol plus promethazine were effective at rapidly tranquilizing or sedating agitated or violent patients with mental illness but
the combination resulted in fewer additional medical interventions within four hours of intervention.

Guidelines and recommendations

The National Institute for Health and Clinical Excellence (NICE) commissioned the National Collaborating Centre for Nursing and Supportive Care (NCC-NSC) to develop guidelines on the short-term management of disturbed or violent behaviour in adult psychiatric inpatient settings and emergency departments for mental health assessments. The guidelines were produced by a multidisciplinary Guideline Development Group (GDG) and the development process was undertaken by the NCC-NSC. Recommendations were based on the best available evidence of clinical and cost-effectiveness, and were arrived at by the GDG using formal consensus methods. Evidence for rapid tranquilization published up to 2003 was considered. The guideline states “that where rapid tranquilization through oral therapy is refused, is not indicated by previous clinical response, is not a proportionate response, or is ineffective, a combination of an IM antipsychotic (haloperidol) and an IM benzodiazepine (lorazepam) are recommended.” The guideline also reports that IM olanzapine may be considered, while zuclopenthixol acetate injection is not recommended for rapid tranquilization due to long onset and duration of action. IM chlorpromazine or diazepam were also not recommended. The NICE guideline presents a chart of pharmacological agents suited for rapid tranquilization, and a supplementary treatment algorithm in a separate quick reference guide. Similar treatment algorithms for rapid tranquilization of acutely disturbed patients were also produced by other groups, also recommending that IM haloperidol and/or lorazepam and olanzapine be used in this patient group.

The American College of Emergency Physicians (ACEP) presented a report on clinical policy which focused on four critical issues concerning the medical assessment and management of ED patients who present with psychiatric symptoms. From these critical issues, one which was raised which was pertinent to the current topic asked, "What is the most effective pharmacologic treatment for the acutely agitated patient in the ED?" The authors found no Class I data (based on RCTs) and therefore the recommendations are based on observational and descriptive studies. These studies used both oral and IM administration. The clinical report recommends use of a benzodiazepine (lorazepam or midazolam) or a conventional antipsychotic (haloperidol or droperidol) as effective monotherapy for the initial drug treatment of acutely agitated undifferentiated patients in the ED. If rapid sedation is required, droperidol should be considered instead of haloperidol. The authors stated that the combination of IM benzodiazepine and haloperidol may produce more rapid sedation than monotherapy in the acutely agitated psychiatric patient in the ED.

Limitations

Few studies have been conducted to evaluate the clinical efficacy of antipsychotics and benzodiazepines for rapid tranquilization of inpatients of mental facilities and ED. The studies available enrolled low numbers of patients (n = 10-150 for each arm), and had methodological issues (i.e. study design – naturalistic, case studies, observational). In some studies, route of administration was not clearly stated or delivery across and between groups was mixed (i.e. oral, IV, IM). Another very important factor to consider was the rate of withdrawal in these studies. Also, there is variety of primary outcome measures reported across studies (i.e.}
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sedation, discharge, time to treatment discontinuation, BPRS and PANSS-EC scores) making direct comparisons challenging. Furthermore, there does not seem to be any formalized agreement on which drugs should be used as first line for rapid tranquilization. As a result, there is a wide variation in the type of medications used in rapid tranquilization.

Additional well conducted RCTs on this topic are needed, but this is complicated by its own limitations. RCTs investigating potential agents to control acute agitation are not able to enroll severely agitated patients (as measured by PANSS-EC scores), because these individuals are unable to provided informed consent prior to receiving study medication.6,22 As a result, the efficacy of agents reported to reduce agitation in RCTs may represent the response of patients who are less severely ill than hospitalized inpatients or patients who arrive at the ED. Observational or naturalistic studies typically have fewer inclusion and exclusion criteria than RCTs, and thus may more closely represent treatment effectiveness in usual clinical practice.6 However, observational and naturalistic studies do not always share the same level of rigor as RCTs. The present review identified several possibly relevant observational and naturalistic studies.6,22-26

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

There is a lack of primary studies evaluating the clinical efficacy of antipsychotics and benzodiazepines for rapid tranquilization of inpatients of mental facilities and ED. In the available literature, both benzodiazepines and antipsychotics seem to be effective in mediating the symptoms of agitation and/or aggression. Guidelines and clinical practice vary on the choice of drugs used for rapid tranquilization in mental facilities and the ED, with some recommendations largely based on consensus statements and observational data. From the literature, it seems that where rapid tranquilization is needed, a combination of an IM antipsychotic (haloperidol) and an IM benzodiazepine (lorazepam) are recommended. Consideration of other agents such as olanzapine and risperidone were also reported. The limited available data on the use of antipsychotics and/or benzodiazepines for rapid tranquilization may be a consideration for decision-making.

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