The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–11, 2018

0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2017.11.031

Pharmacology in Emergency Medicine

EVIDENCE-BASED REVIEW OF PHARMACOTHERAPY FOR ACUTE AGITATION. PART 2: SAFETY

Leslie S. Zun, MD, MBA

Chair, Department of Emergency Medicine, Chicago Medical School, Chicago, Illinois and Attending, Department of Emergency Medicine, Mount Sinai Hospital, Chicago, Illinois

Reprint Address: Leslie S. Zun, MD, MBA, Department of Emergency Medicine, Chicago Medical School, Department of Emergency Medicine, Mount Sinai Hospital, 1501 S California Ave, Chicago, IL 60608

☐ **Abstract—Background: The management of acute agitation in the emergency department often requires the administration of rapid-acting antipsychotic agents. However, there are few comparative studies and little guidance regarding the risks associated with use of such drugs in the acute setting. Objective: This structured evidence-based review compared the safety of antipsychotic pharmacotherapies for acute agitation using data from randomized controlled trials identified by a literature search of the PubMed database. Results: Based on findings from 34 blinded, randomized controlled trials, common acute adverse effects of second-generation antipsychotics and haloperidol were headache, dizziness, insomnia, and somnolence. There were some differences in incidence of extrapyramidal symptoms (EPS), degree of sedation, and acute QTc prolongations between agents. Conclusions: The results of this review demonstrate the improved safety (particularly regarding EPS and over-sedation) of certain newer-generation antipsychotic agents compared with haloperidol and benzodiazepines for the treatment of acutely agitated patients. The risk of prolonged QT interval and torsade de pointes needs to be considered with haloperidol and some of the second-generation antipsychotics.** © **2017 Elsevier Inc. All rights reserved.**

☐ **Keywords—acute agitation; treatment; management; safety; antipsychotics**

Conflict of interest: The author has received honoraria as a speaker for Teva Pharmaceuticals.

INTRODUCTION

There is frequently a need to manage patients presenting with agitation (excessive verbal or motor activity) in the emergency department (ED). Agitation may accompany psychiatric illnesses such as schizophrenia and bipolar disorder, or may be due to a range of other conditions such as substance abuse, head injury, or dementia. The immediate goal of management is to calm the patient so that agitation does not escalate to aggressive or violent behavior, which can lead to harm to the patient or ED staff. Current guidelines recommend that pharmacologic intervention is appropriate for patients when nonpharmacologic intervention has proven ineffective. The main aim of such intervention in the acute setting is the rapid induction of calm without oversedation, so that patients can participate in their own care (1,2). One of the challenges for the clinician is to administer appropriate fast-acting medication (often at a higher dose than in maintenance therapy) that will have a low risk of adverse effects. In this situation, the decision regarding which agent to administer may need to be made without the benefit of a complete diagnosis or medical history. As highlighted by Pacciardi and colleagues, current recommendations for pharmacological management of agitation in emergency settings give little guidance on safety issues (3).

The three classes of medication most frequently used to treat agitation are first-generation antipsychotics

(FGAs; e.g., haloperidol), second-generation antipsychotics (SGAs; aripiprazole, olanzapine, ziprasidone, asenapine, risperidone, and quetiapine), and benzodiazepines (such as lorazepam). Several antipsychotics are recognized to have the potential to cause serious adverse cardiovascular effects. Of the FGAs, haloperidol in particular is associated with arrhythmogenic effects, including the potentially fatal condition known as torsade de pointes. There is some evidence that several of the SGAs are also associated with an increased risk for torsade de pointes or with corrected QT (QTc) interval prolongation–a marker for increased risk of the condition. These include ziprasidone, olanzapine, quetiapine, risperidone, and aripiprazole–drugs commonly used in agitated patients (4,5). Best Practices in Evaluation and Treatment of Agitation (Project BETA) guidelines recommend that first-line use of quetiapine should be avoided in acute agitation due to an additional high risk of orthostatic hypotension in patients presenting in the ED, as they are often volume depleted (1). FGAs (in particular haloperidol) and some SGAs are also associated with the development of acute and long-term extrapyramidal symptoms (EPS) (4,6). Although benzodiazepines have a long history of effective use in treating agitation, they carry the risk of respiratory depression. Consequently, this class of drugs should not be administered in patients with respiratory conditions or in whom the use of a central nervous system depressant, such as alcohol, is known or suspected (1). Benzodiazepines, and to a lesser extent antipsychotics, have the potential for oversedation, which can compromise subsequent psychiatric evaluation and increase the resource use in caring for the patient (1,7).

In an accompanying article, the onset of efficacy of antipsychotic treatments for acute agitation was compared using data from randomized controlled trials (RCTs) (8). The aim of the present paper is to review evidence concerning the safety of such treatments in the same setting.

METHODS

Search Strategy

A search of the PubMed database (National Library of Medicine, includes MEDLINE) was conducted on March 20, 2017, to identify blinded RCTs, meta-analyses, and systematic reviews focusing on the use of antipsychotic agents in acute agitation. Search terms included the following free text terms: (*agitated*, *agitation*, *sedation*) combined with (*acute*, *acutely*, *24 h*, *rapid*, *emergency*, *short-term*) and (*treatment*, *management*). Only clinical studies conducted in humans and published in English since 1980 were included. Other sources of literature comprised the references lists of included studies, references of relevant reviews, and the author's personal files from related projects.

Inclusion and Exclusion Criteria

Abstracts identified by the search were reviewed subjectively for relevance by two independent reviewers (MJ, JP). Blinded (double- or rater-blinded) randomized, controlled (placebo or active controlled) studies that involved patients with acute agitation (regardless of setting) were included if adverse events were reported. Nonrandomized, uncontrolled, naturalistic, and open-label studies were excluded, as were those focusing on transitional or maintenance therapy, or agitation resulting from dementia-related psychosis in elderly patients.

Data Extraction

Full copies of potentially relevant articles identified by manual searching of abstracts were obtained for detailed review. Evidence tables were constructed, presenting data on medication, psychiatric condition, study design, population, sample size, study duration, and safety data (treatment-emergent adverse events [TEAEs], serious adverse events [as categorized in the original reports], EPS, and QT interval prolongation).

RESULTS

Evidence Base

The literature search retrieved 399 articles. In total, 34 relevant blinded RCTs of antipsychotic agents in acute agitation and five relevant systematic reviews/meta-analyses of pharmacologic treatment for agitation were identified (9–47). The 34 RCTs differed in patient setting, dosage, route of administration, choice of comparator, concomitant treatment, and industry support (Tables 1 and 2; Supplementary Tables 1 and 2).

Haloperidol was frequently used as the active comparator, but dose, route of administration, and combination with lorazepam varied between studies. Eleven studies were placebo controlled (12,13,16,17,19,20,28–32).

Most of the identified RCTs were conducted in agitated inpatients or patients presenting to psychiatric emergency services with psychotic disorders (Table 1). Twelve studies included patients presenting in the ED (Table 2). Of the seven studies conducted exclusively in the ED, one was conducted in patients with psychotic disorders and the remainder in patients with acute undifferentiated agitation, including patients with psychiatric or mood disorders, and alcohol and drug intoxication (33–36,38,41,42).