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EVIDENCE-BASED REVIEW OF PHARMACOTHERAPY FOR ACUTE AGITATION. PART 1: ONSET OF EFFICACY

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☐ **Abstract—Background: The main goal of antipsychotic medication in the management of acute agitation in the emergency department is to rapidly induce calm without oversedation, enabling patients to participate in their own care. However, there is a paucity of comparative studies, particularly with newer fast-acting second-generation antipsychotic agents. Objective of the Review: This structured evidence-based review compared the onset of efficacy of antipsychotic treatments for acute agitation using data from randomized controlled trials identified by a literature search of the PubMed database. Results: Based on findings from 28 blinded randomized controlled trials, onset of efficacy was rapid and generally observed at the first time point after intramuscular administration of ziprasidone (15–30 min) or olanzapine (15–30 min), but was more likely to be delayed with intramuscular haloperidol, even when combined with lorazepam (30–60 min), and intramuscular aripiprazole (45–90 min). When administered orally, rapid onset of efficacy was also consistently observed at the first assessment time point with olanzapine (15–120 min), risperidone (30–120 min), and sublingual asenapine (15 min). Significant effects were apparent for inhaled loxapine within 10–20 min. Effects were apparent within approximately 5–10 min with i.v. droperidol. Onset of efficacy was typically more rapid with second-generation antipsychotic agents than benzodiazepines, but data are limited. Conclusions: Although the patient populations of trials included in this review do not truly reflect that of the emergency department, the results provide useful information to emergency physicians on the rapid efficacy of certain newer-generation antipsychotic agents for the treatment of acutely agitated patients.** © 2017 Elsevier Inc. All rights reserved.

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

INTRODUCTION

Agitated patients presenting to the emergency department (ED) with increased verbal and motor activity can rapidly become hyperactive, aggressive, and violent, which can lead to self-harm or assault. Agitation can result from a number of underlying causes, including psychiatric illness, alcohol or drug intoxication/withdrawal, neurologic problems (either head injury or neurologic disease), and other general medical conditions. Determining safety and developing the most appropriate management plan according to the severity of agitation should be the initial tactic in the acute setting and is more important than establishing a definitive diagnosis (1).

Several scales are commonly used to determine agitation severity and guide treatment decisions in the ED (Supplementary Table 1) (2–10). These include the Agitated Behavior Scale, the Behavioral Activity Rating Scale (BARS), the Overt Aggression Scale, the Richmond

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Agitation-Sedation Scale, and the Positive and Negative Syndrome Scale (PANSS), of which the excitation component (PANSS-EC) is commonly used in clinical trials to assess agitation (2,4,7–9). The American Association of Emergency Psychiatry does not consider any particular scale to be best, but does recognize that BARS is both reliable and easy to administer (even for nonspecialists) and has included it in the 2012 Best Practices in the Evaluation and Treatment of Agitation in the Emergency Setting (Project BETA) treatment algorithms (11). Notably, few of the available scales predict progression to violence/aggression or the need for medication in agitated patients (12).

The main goal of medication for the management of agitation in the acute setting is to induce calm quickly but without oversedation, thus enabling patients to participate in their own care (13). Rapid onset of drug action is key to facilitating patient assessment, permitting diagnosis, and allowing emergency physicians to begin the therapeutic process. In the ED, clinically useful medications should also be effective even when only a provisional diagnosis is possible, and offer ease of preparation; nontraumatic administration; consistent pharmacokinetics/pharmacodynamics; sustained duration of effect; and low risk of adverse events/drug interactions, which can complicate the management process and affect the willingness of patients to comply with future treatment (12,14).

Three classes of medication are used frequently to treat agitation: first-generation antipsychotics (e.g., haloperidol and droperidol); second-generation antipsychotics (e.g., aripiprazole, olanzapine, ziprasidone, asenapine, risperidone, and quetiapine); and benzodiazepines (e.g., lorazepam). Before the introduction of second-generation antipsychotics, intramuscular (i.m.) haloperidol and lorazepam were the most widely used agents for acute agitation, demonstrating efficacy across multiple diagnoses and in medically compromised patients (15). Both agents, however, are associated with worrisome side effects (16,17). Fast-acting i.m., oral, and oral dispersing tablet (ODT) formulations of second-generation antipsychotics are now available. Loxapine, a first-generation antipsychotic, has also been reformulated into an inhaled powder for rapid absorption. Although the pharmacokinetics of these agents can be compared, the time taken to reach peak plasma concentration does not correlate with onset of clinical activity (18). Unfortunately, only a few well-controlled head-to-head clinical studies have been performed with second-generation antipsychotic agents, thus their comparative efficacy can only be speculated upon from indirect comparisons (19,20).

The aim of this evidence-based review is to compare the onset of efficacy of antipsychotic treatments for acute agitation using data from randomized controlled trials (RCTs) identified by a structured literature search. The accompanying article examines the comparative safety of these agents in the acute setting (21).

METHODS

Search Strategy

A search of the PubMed database (National Library of Medicine, includes MEDLINE) was performed on March 20, 2017, to identify blinded RCTs 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*). Publication types included RCTs, meta-analyses, systematic reviews, and phase 3 and 4 clinical trials. Only studies conducted in humans and published in English since 1980 were included. Other sources of literature comprised the reference 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. Blinded (double- or rater-blinded) randomized, controlled (placebo- or active-controlled) studies that involved patients with acute agitation (regardless of setting) were included if a clearly defined onset of efficacy (quantified using an assessment scale) was reported within a time frame of 2 h after study drug administration. 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, summarizing data on medication, psychiatric condition, study design, population, sample size, study duration, onset of efficacy, and first time point assessed.

Definitions

Onset of efficacy was defined as the first time at which the intervention showed a statistical benefit over control (either placebo or active); first time at which there was a statistical benefit over baseline scores in the treated group; or median and mean time to sedation, dependent on study design.