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COMPARISON BETWEEN OLANZAPINE AND HALOPERIDOL AS TREATMENT OF ACUTE AGITATION

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REVIEW **OPEN ACCESS**

ABSTRACT

Introduction – Antipsychotics have been used as a treatment of choice in acute agitation, with haloperidol being the most widely used from the first generation, and olanzapine from the second generation. Therefore, there is a need to understand these drugs, particularly in their efficacy and safety as a treatment of acute agitation.
Methods – This review uses several works of literature between 2011 to 2021 that discuss olanzapine and haloperidol as treatments for acute agitation.
Results – Atypical antipsychotic agents are equally effective when compared to typical antipsychotics in treating acute agitation
Discuss – On several head-to-head comparisons, olanzapine showed superiority to haloperidol based on the onset of efficacy.
Conclusion – Agitated patients interfere with the diagnostic and treatment process. First-line treatment involves verbal de-escalation for patients and if failed, a physician could use pharmacological intervention in the form of rapid tranquillization to continue the therapeutic process. When determining which drug to use, a physician must consider both efficacy and safety. Due to the heterogeneity of study results, it is difficult to conclude that a certain agent is the best treatment for acute agitation. Olanzapine and haloperidol are equally effective antipsychotic agents in treating agitated symptoms. Olanzapine has numerous advantageous properties, including a lesser risk of causing extrapyramidal side effects that in turn can aggravate agitation, but the downside of olanzapine is that it is expensive and has limited availability compared to haloperidol. On the other hand, haloperidol, as a monotherapy or combination therapy either with an antihistamine-anticholinergic or benzodiazepine is a good alternative. Therefore, determining which agent to use should consider the comprehensive state of the patient, as is almost always the case when psychotropic medications are prescribed.

Keywords: olanzapine, haloperidol, agitation.

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INTRODUCTION

Agitation is a typical case presentation in the medical and psychiatric emergency departments.[1] The degree of agitation can escalate to aggressive and violent behavior, posing a risk of harm to the patient, health care providers, and others, necessitating prompt treatment.[2,3] An attempt at de-escalation should be done first and if failed, a rapid tranquilizer could be administered.[2]

The main goal for rapid tranquilizers is to immediately produce calm without oversedation, allowing patients to engage in their therapeutic process. Antipsychotics are preferred as the first-line treatment for acute agitation, particularly in the case of psychiatric psychosis.[3] First-generation (typical) antipsychotics have long been used to treat, with intramuscular haloperidol as the most frequently used in the emergency department for acute agitation.[4] Its prominence stems from several appealing characteristics, including long-term safety records, no impact on hemodynamic status such as blood pressure or heart rate, and no respiratory depression.[5] However, haloperidol carries a risk of inducing acute extrapyramidal side effects (EPS) such as dystonia, pseudoparkinsonism, and akathisia.[6] More recently, expert guidelines suggest newer atypical antipsychotics as first-line medications in many cases over the typical one, particularly because they have fewer side effects.[5] Compared with typical antipsychotics, atypical antipsychotics are associated with a substantially lower risk of extrapyramidal syndrome such as dystonia or akathisia, with incidence rates of less than 1%. Among atypical antipsychotics, olanzapine is one of the preferred treatments.[4]

In Indonesia, both intramuscular olanzapine 10 mg and haloperidol 5 mg are among the recommended treatments for acute agitation.[7] Aside from their therapeutic profile, availability and cost also differ between these two drugs. Therefore, there is a need to have a better understanding of olanzapine and haloperidol as treatment of acute agitation, especially about their efficacy and safety.

METHOD

The approach used in this article is a review. A search of *ScienceDirect, ProQuest, Wiley Online Library, PubMed, Cochrane, Cambridge Core,* and *Google Scholar* databases was performed on September 5, 2021, to identify publications that discuss olanzapine and haloperidol as treatment of acute agitation using "olanzapine", "haloperidol", and "acute agitation" as search terms. Publication types included are RCTs, systematic reviews, evidence-based reviews, and retrospective and prospective observational studies that were published between 2011 to 2021.

RESULT

Acute Agitation

As described by The Diagnostic and Statistical Manual of Mental Disorders V (DSM-V), agitation is an excessive motor activity associated with a feeling of inner tension.[8] Its distinctive traits include motor restlessness, irritability, inappropriate or purposeless psychomotor activity, and increased sensitivity to stimuli which can progress to aggressive and even to violent behavior.[2,3,9] A variety of underlying factors can induce agitation, including psychiatric disorders, alcohol or drug intoxication/withdrawal, neurological conditions, and other general medical conditions.[3] Acute agitation is a frequent occurrence in psychiatric treatment settings, with an estimated prevalence of 10%. According to reports, agitation is a "common symptom" among patients seeking psychiatric emergency care for schizophrenia, bipolar disorder, or dementia, around 1.7 million visits each year in the US are likely to include patients who are agitated.[4]

When non-pharmacological methods fail to relieve agitation, a physician considers a pharmacological treatment commonly referred to as rapid tranquilization. The main objective of the intervention is to calm the patient to decrease the risk of injury to the patient as well as others. Currently, the objective is to attain tranquilization without oversedation. Rapid tranquilization using antipsychotics and sedative medications has typically been used to achieve this goal.[3]

First-Generation (Typical) Antipsychotics: Haloperidol

Typical or first-generation antipsychotics have an extensive track record of being used for the treatment of agitation. The precise mechanism of reducing agitation with typical antipsychotics remains uncertain although it is thought to be related to its blockade of dopamine transmission in the brain, particularly at the D2 receptor, which might act to reduce motor agitation. In addition, some typical antipsychotics have structural similarities to the human inhibitory neurotransmitter gamma-aminobutyric acid (GABA) and bind with the human GABA receptor at high concentrations.[1,2]

Haloperidol is a both highly potent and selective antagonist of the dopamine-2 (D2) receptor that belongs to the butyrophenone class of typical antipsychotics. It has a strong track record of effective and safe usage in the acute setting for the treatment of agitation. This drug has been the most frequently prescribed antipsychotic for the treatment of acute agitation.[1]

Haloperidol has little to no effect on vital signs, has minimal anticholinergic activity, and has few interactions with non-psychiatric medication. However, it is associated with unpleasant, potentially dangerous side effects, that is extrapyramidal effects, such as tremors, slurred speech, akathisia, dystonia, and neuroleptic malignant syndrome.[2,4] It is also associated with QTc prolongation despite much research has reported that clinically adverse cardiac effects are uncommon.[1] Furthermore, because the majority of atypical antipsychotics are equally effective in the treatment of agitation and have low rates of extrapyramidal side effects, current guidelines consider typical antipsychotics to be less preferred than their atypical counterparts.[1,2,4]

Second-Generation (Atypical) Antipsychotics: Olanzapine

Atypical antipsychotic agents are equally effective when compared to typical antipsychotics in treating acute agitation.[10] Atypical antipsychotic drugs theoretically have a characteristic of higher affinity for serotonin 5-HT2 receptors and relatively lower affinity for D2 receptors which differentiate them from haloperidol and other typical agents. That characteristic is theoretically allowing them to normalize rather than suppress dopaminergic transmission. Thus, they may exert a therapeutic action for agitated patients while posing a relatively lower risk of extrapyramidal side effects, owing to their lesser effect on the nigrostriatal pathway of dopamine in the brain. The characteristic is shared by several atypical antipsychotics with only olanzapine, aripiprazole, and ziprasidone available in the form of intramuscular and intravenous injection, although the latter is not advised, and used as rapid tranquilization.[1,11]

Olanzapine is a dopamine/serotonin antagonist that belongs to the thienobenzodiazepine class and has relatively higher affinities for the histamine receptor making sedation its notable side effect.[1,6,11] Due to the possibility of respiratory depression and symptomatic hypotension, combining olanzapine with benzodiazepines is not recommended.[1,11,12] The development of extrapyramidal syndrome following olanzapine treatment is rare. As mentioned before, when compared to typical antipsychotics, atypical antipsychotics have a reduced risk of near-term extrapyramidal adverse effects such as dystonia or akathisia, with reported rates of less than 1%.[1,11] However, atypical antipsychotics are considerably more expensive than their typical counterparts.[11]

DISCUSS

Efficacy Comparison

On several head-to-head comparisons, olanzapine showed superiority to haloperidol based on the onset of efficacy.[13,14] In the observational study conducted by Lauren *et al* (2018) with an Altered Mental Status Scale score at 15 minutes from baseline as a primary parameter of adequate sedation, olanzapine 10 mg showed 20% more adequately sedated patients than haloperidol 5 mg, with the median time to adequate sedation 14 and 20 minutes for olanzapine and haloperidol respectively.[13] Similarly, in the observational study conducted by Suzuki *et al* (2014) olanzapine showed more rapid anti-agitation effects than haloperidol. The efficacy parameters used were PANSS-EC, PANSS, and ACES scales in which olanzapine mean reduction scores from baseline are significantly greater than those of haloperidol.[14]

Olanzapine also showed superiority to haloperidol in terms of the requirement of additional rescue sedation in several other studies.[13-17] In a retrospective observational study conducted by Klein *et al* (2019), olanzapine showed fewer rescue sedation rates than haloperidol both at the 1-hour mark and in the entire ED stay duration. Rescue rates for olanzapine at 1 hour and the entire ED duration were 11% and 19% respectively whereas rescue rates for haloperidol were 18% and 26%.[15] Another retrospective study by MacDonald *et al* (2012) also found a similar result. The study found that the rates of additional medication were 26% for haloperidol 5 mg and 4.5% for olanzapine 10 mg respectively, which were the most frequently prescribed doses of both drugs.[16] These results also concur with a randomized trial study by Baldacara *et al* (2011). In this study, both olanzapine and haloperidol reduced OAS and OASS scores to fewer than 10 within one hour of administration, but within 12 hours, olanzapine mean value of additional medication is only 0,37 compared to 1,53 in haloperidol, indicating that a greater number of patients receiving olanzapine did not require additional medications.[17]

However, other studies show contrasting results. In a study conducted by Wilson *et al* (2012), the adequacy of agitation reduction was similar between olanzapine and haloperidol, as evaluated indirectly by the total of patients who needed rescue medications within 3 hours.[18] Moreover, according to the percentage of patients in that study who require additional doses of antipsychotic drugs to manage agitation, haloperidol showed better efficacy than olanzapine with lesser, even though both drugs showed similar efficacy by repeated doses needed to control agitation in a study conducted by Freeman *et al*.[19] Chan *et al* (2014) conducted a multicenter, double-blind, randomized, parallel study and reported that the efficacy between the trial groups, which was intramuscular olanzapine 10 mg/d against intramuscular haloperidol 7.5 mg/d, did not produce statistically different result. The parameter used to measure efficacy was the changes in PANSS-EC Scale score from baseline to the 2-hour mark after the first injection.[20]

Another interesting result to point out is that combination therapy of haloperidol has similar efficacy to olanzapine. A study by Huang *et al* (2015) measuring the efficacy in treating acute agitation with PANSS-EC scores from the first injection until and at 2 hours mark showed that a combination of 5 mg intramuscular haloperidol with 2 mg lorazepam has comparable efficacy to intramuscular lorazepam. Other parameters used in this study were the number of additional injections administered and CGI-S score changes after the first injection in 24 hours. Both parameters showed similar efficacy between the treatment regimens.[21] Similar results were also reported in a study by MacDonnald *et al* (2012) where haloperidol plus a benzodiazepine efficacy is comparable to olanzapine monotherapy based on rescue medication needed.[16]

Systematic reviews about the treatment of acute agitation which include olanzapine and haloperidol also offer different conclusions. The difficulty in reaching conclusions is because while there is plenty of data and an abundance of high-quality randomized control trials, the data available are very heterogeneous, differing in interventions, populations being studied, outcome measures, and even in findings, that preclude more than simple description.[22-26] Some conclusions from several systematic reviews, ranging from in favor of olanzapine, neutral, to in favor of haloperidol, albeit not firmly are: pair-wise analyses indicate that olanzapine is superior to haloperidol after 60 minutes, although there is no clear pattern of superiority of one medication over another[22]; intramuscular administration of olanzapine has rapid onset of efficacy, observed at 15-30 minutes and is faster than intramuscular haloperidol which is at 30-60 minutes even when combined with lorazepam[23]; confirmation that short-acting intramuscular atypical antipsychotic has similar efficacy compared to haloperidol and its proven effectiveness when compared to placebo in treating agitation symptoms in schizophrenia patients[24]; there is no established first-line treatment to use as a rapid tranquilizer when comparing the efficacy, safety, or dosage among chemical restraints, but haloperidol monotherapy or in combination with benzodiazepines (i.e midazolam or lorazepam) administered via intravenous, oral, or intramuscular could be recommended to front-line physicians to effectively reduce agitated symptoms, even when progressed to aggressive and violent behaviours[25]; and that first-choice medications as a rapid tranquilizer are haloperidol combined with promethazine or olanzapine and are considered suitable for usage in hospital or even outpatient settings.[26]

Safety Comparison

In numerous research about acute agitation treatment side effects were not analyzed or often analyzed only as secondary outcomes, making information about the profile of intramuscular antipsychotic side effects scarce. This situation could also possibly be due to the acute nature of agitation, the need for immediate efficacy, that side effects, particularly those that take time to emerge, are less relevant (e.g. weight gain). Therefore, it is suggested that a physician should consider their decisions on the side-effect profiles obtained from standard six-week oral formulation studies, as there is no reason to anticipate that side-effect profiles will change depending on the formulation in which a medication is delivered. Atypical antipsychotics, whether oral or intramuscular, have dizziness, headache, sleeplessness, and somnolence documented as their common acute side effects. One study of intramuscular olanzapine reported clinically significant increases in QTc interval in 7.9% of patients that received intramuscular olanzapine 10mg but is still lower than those that received intramuscular haloperidol (14.9%), although many studies of intramuscular olanzapine have not reported such occurrence. It is also found that a greater incidence of extrapyramidal syndrome occurred in the

treatment with haloperidol during the acute period compared to other antipsychotic agents, which is as expected. Moreover, the incidence of the extrapyramidal syndrome was reported significantly lower in patients treated with intramuscular olanzapine compared to other intramuscular agitation agents such as typical antipsychotics and benzodiazepines. The incidence of acute dystonia treated with intramuscular olanzapine was 1.1% compared to 2.9% when treated with other agents. Similarly, lower occurrence of akathisia and parkinsonism was also found, with 2.3% and 2.9% occurrence in intramuscular olanzapine respectively, and 5.5% and 7.8% in other agents respectively.[28]

Cost Comparison

In a retrospective study by Freeman *et al* comparing the costs of regimens for the treatment of acute episodes of agitation, it is found that the costs of haloperidol monotherapy or even in combination with intramuscular lorazepam and/or diphenhydramine are significantly less than the cost of olanzapine therapy. With similar efficacy, haloperidol monotherapy or combination therapy costs less than one-sixth the cost of olanzapine therapy.[19] In Indonesia, the cost of a box of haloperidol 5 mg injection is less than a quarter of the cost of a box of olanzapine 10 mg injection.[29]

CONCLUSION

Agitated patients interfere with the diagnostic and treatment process. First-line treatment involves verbal de-escalation for patients and if failed, a physician could use pharmacological intervention in the form of rapid tranquillization to continue the therapeutic process. When determining which drug to use, a physician must consider both efficacy and safety. Due to the heterogeneity of study results, it is difficult to conclude that a certain agent is the best treatment for acute agitation. Olanzapine and haloperidol are equally effective antipsychotic agents in treating agitated symptoms. Olanzapine has numerous advantageous properties, including a lesser risk of causing extrapyramidal side effects that in turn can aggravate agitation, but the downside of olanzapine is that it is expensive and has limited availability compared to haloperidol. On the other hand, haloperidol, as a monotherapy or combination therapy either with an antihistamine-anticholinergic or benzodiazepine is a good alternative. Therefore, determining which agent to use should consider the comprehensive state of the patient, as is almost always the case when psychotropic medications are prescribed.

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