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Efektivitas Kombinasi Haloperidol–Difrenhidramin dalam Penatalaksanaan Agitasi Akut pada Skizofrenia: Tinjauan Naratif

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Abstrak

Pada fase akut, orang dengan skizofrenia dapat mengalami agitasi yang dapat membahayakan diri sendiri dan orang sekitar. Haloperidol telah digunakan secara luas untuk penanganan agitasi akut karena efeknya yang cepat, namun prevalensi gejala ekstrapiramidal (EPS) cukup tinggi. Penggunaan agen dengan efek antikolinergik sebagai terapi EPS masih menjadi perdebatan dalam praktik psikiatri. Beberapa guideline tidak merekomendasikan penggunaan antikolinergik sebagai terapi untuk profilaksis EPS, namun pada prakteknya psikiatri memberikan kombinasi haloperidol-difenhidramin (HD) sebagai profilaksis EPS. Tinjauan ini bertujuan untuk mengkaji efektivitas penggunaan kombinasi HD dalam mengelola agitasi akut. Penelusuran artikel yang relevan secara sistematis melalui database *ScienceDirect*, *Scopus*, *Springer*, dan *Elsevier* dalam 10 tahun terakhir. Review artikel, laporan kasus, dan konferensi abstrak dieksklusi. Hasil review menemukan bahwa efektivitas kombinasi HD sebanding dengan monoterapi haloperidol dengan kejadian EPS yang lebih rendah. Namun efek sedasi berlebih dan hipotensi terjadi pada kelompok kombinasi HD. Kombinasi ini tidak direkomendasikan sebagai terapi lini pertama karena masih kurangnya bukti pendukung, risiko efek samping, dan terdapat alternatif pilihan terapi yang lebih aman. Pemilihan terapi agitasi akut harus berdasarkan pada profil klinis pasien dengan mempertimbangkan manfaat dan risikonya.

Keywords:
Schizophrenia, Antipsychotic, Haloperidol, Diphenhydramine, Agitation

Abstract

People with schizophrenia can experience agitation that can be dangerous to themselves and others in acute phase. Haloperidol has been widely used for the treatment of acute agitation because of its rapid effects, but the prevalence of extrapyramidal symptoms (EPS) is relatively high. The use of anticholinergics agent as EPS therapy is still a debate in psychiatric practice. Some guidelines do not recommend the use of anticholinergics as therapy for EPS prophylaxis, but in practice, psychiatry provides a combination of haloperidol-diphenhydramine (HD) as EPS prophylaxis. This review aims to examine the effectiveness of HD combination in managing acute agitation. A systematic search of relevant articles was conducted through the ScienceDirect, Scopus, Springer, and Elsevier databases in the last 10 years. Article reviews, case reports, and abstract conferences are excluded. The review found that the effectiveness of the HD combination was comparable to haloperidol monotherapy with a lower incidence of EPS. However, excessive sedation and hypotension occurred in the HD combination group. This combination is not recommended as first-line therapy due to the lack of supporting evidence, the risk of side effects, and the availability of safer alternative therapy options. The selection of acute agitation therapy should be based on the patient's clinical profile, considering the benefits and risks.

Introduction

Schizophrenia is a chronic psychiatric disorder characterized by psychotic symptoms such as delusions, hallucinations, and disorganized thinking and speech, which impair an individual's ability to differentiate between reality and fantasy. Globally, schizophrenia affects approximately 1% of the population, with a higher prevalence observed in urban areas and among individuals with a family history of mental illness. In the acute phase, patients are at significant risk of experiencing agitation, aggression, and self-harming behavior, which not only compromise patient safety but also burden caregivers and healthcare systems (Keepers et al., 2020; Mucci, 2024; Novianti et al., 2021). Therefore, rapid and effective pharmacological intervention is essential to stabilize the patient and prevent complications.

Antipsychotics are the cornerstone of schizophrenia management. In acute episodes, intramuscular (IM) administration of antipsychotics is preferred due to its rapid onset of action, which is critical for controlling severe agitation (Ceraso et al., 2020; Grover et al., 2017; Sabe et al., 2021). Haloperidol, a first-generation antipsychotic (FGA), is commonly used in this setting because of its proven efficacy and availability in short-acting IM formulations that begin to act within 20–30 minutes (Keepers et al., 2020; Sadock et al., 2015; Trevor et al., 2015). Despite its effectiveness, haloperidol is associated with a high risk of extrapyramidal symptoms (EPS), which can negatively impact treatment adherence and clinical outcomes. A systematic review stated that haloperidol increased the risk of akathisia and extrapyramidal, and increased the use of anticholinergics (Gao et al., 2008). Some RCTs have found that haloperidol is associated with the effects of parkinsonism and akathisia (Haddad et al., 2012).

The use of anticholinergics agent to prevent EPS is still a matter of debate in psychiatric practice. Current treatment guidelines recommend the use of anticholinergic agents when EPS symptoms occur (Haddad et al., 2012; Karthickeyan & Nadu, 2018; Ohno et al., 2019). The American Psychiatric Association (APA) recommends starting with the lowest dose and for the shortest duration. The World Federation of Societies of Biological Psychiatry (WFSBP) suggests lowering the dose of antipsychotics if parkinsonism occurs. The British Association of Psychopharmacology (BAP) and the Indian Psychiatric Society (IPS) do not allow anticholinergics for EPS prophylaxis (Chatterjee et al., 2022). In clinical practice, however, some psychiatrists administer diphenhydramine prophylactically alongside haloperidol to prevent EPS.

Diphenhydramine possesses strong anticholinergic and sedative properties, and several studies suggest that it may reduce the incidence of EPS when used as a prophylactic agent (Miller, 2021). One study mentioned that EPS was significantly reduced in the diphenhydramine group compared to placebo (p= 0.01) (D'Souza et al., 2018). The National Guidelines for Psychiatric Services state that diphenhydramine can be given if the patient experiences side effects of EPS (KEMENKES, 2015). Diphenhydramin can be combined with haloperidol as an EPS prophylaxis (Curry et al., 2023; Gerson et al., 2019). Nonetheless, the use of the haloperidol-

diphenhydramine (HD) combination also raises concerns, including the potential for drug interactions, excessive sedation, and possible long-term cognitive effects. These considerations highlight the need for a balanced approach when selecting pharmacological interventions in acute psychiatric emergencies.

This review aims to examine the pharmacological rationale behind the use of the haloperidol-diphenhydramine combination in managing acute agitation in schizophrenia, evaluate its clinical benefits and limitations, and explore alternative therapeutic options that may offer improved efficacy with a reduced side effect profile. A better understanding of these factors is expected to guide clinicians in optimizing treatment strategies for patients experiencing acute agitation episodes.

Method

This narrative review was conducted by systematically searching relevant articles in the ScienceDirect, Scopus, Springer, and Elsevier databases. The search strategy employed the following keywords: “Effectiveness”, “Haloperidol”, “Diphenhydramine”, “Acute Agitation”, and “Schizophrenia”, using Boolean operators to refine the results. Inclusion criteria included articles published in English within the last 10 years involving human subjects and focusing on the use of haloperidol and diphenhydramine in managing acute agitation in schizophrenia. Articles that were not peer-reviewed, case reports, conference abstracts, and studies irrelevant to the analysis topic were excluded. The selection process was carried out in stages, starting with a review of the title and abstract, followed by a thorough review of the full text to assess its uniformity and quality. Data from eligible studies were described narratively to identify recurring patterns, compare results, and formulate conclusions that can be applied in clinical practice.

Results and Discussion

Pathophysiology and Clinical Manifestations of Acute Schizophrenia

The pathophysiology of schizophrenia is multifactorial and varies from person to person. Several theories about the cause of schizophrenia have been proposed, such as neurotransmitter disorders, genetic factors, and psychosocial factors (Sadock et al., 2015). Based on the neurotransmitter disorder theory, the leading cause involves dysregulation of the dopaminergic system. Hyperactivity of dopamine in the mesolimbic pathway contributes to positive symptoms such as hallucinations and delusions, while dopamine deficits in the mesocortical pathway are associated with cognitive impairment and negative symptoms (Adamu et al., 2023; Brisch et al., 2016). Another theory is that dysfunction of the NMDA glutamate receptor causes an imbalance of neurotransmitters that worsens cognitive impairment and social deficits. Brain imaging studies have shown structural changes such as reduced volume of the prefrontal cortex and hippocampus, which play a role in cognitive and emotional dysfunction in schizophrenia (Adell, 2020; Cohen et al., 2015; Hu et al., 2017).

Clinical manifestations in the acute phase, patients experience significant hallucinations, delusions, confusion in thinking, and agitation. Auditory hallucinations such as voices giving orders and paranoid delusions cause patients to feel watched or threatened without a clear basis. Catatonic behavior, such as rigid body postures, repetitive movements, or inappropriate emotional responses, may appear. Psychomotor agitation, such as restlessness and aggression, can also occur. In some cases, this behavior can be dangerous to oneself or others (Farah, 2018; McCutcheon et al., 2023). Schizophrenia patients require intensive care to stabilize their condition in acute agitation. Rapid intervention with pharmacological therapy is essential to control symptoms and prevent long-term impacts on the patient's quality of life.

Haloperidol Mechanism of Action

Haloperidol is a typical antipsychotic from the butyrophenone group that works as a dopamine D2 receptor antagonist in the central nervous system. This mechanism plays a role in reducing positive and negative symptoms that commonly occur in schizophrenia patients. Blockade of dopamine D2 receptors occurs mainly in the mesolimbic and mesocortical pathways, which contributes to its therapeutic effects in reducing positive and negative symptoms. Haloperidol has a high potential to stabilize the condition of patients with severe agitation and disturbances in the perception of reality in the acute phase of schizophrenia. It has a sedative effect that is useful in controlling aggressive behavior. Research on the efficacy of haloperidol in treating acute agitation shows that this drug has high effectiveness in relieving symptoms of agitation in patients with psychotic disorders. This effect is related to the faster onset of action of haloperidol compared to several other antipsychotics, so it is often the leading choice in the management of the acute phase of schizophrenia (Amato et al., 2018; EMA, 2017; Li et al., 2016).

Several clinical studies support the use of haloperidol in severe agitation in schizophrenia. The rapid therapeutic effect is associated with the high affinity of haloperidol for dopamine D2 receptors, which allows for short-term inhibition of dopaminergic transmission. In addition, compared with atypical antipsychotics, haloperidol shows a faster response in reducing motor hyperactivity and aggression, so it is often used in the form of intramuscular injection for the treatment of acute conditions in psychiatric emergency units. The antagonistic effects of haloperidol on the nigrostriatal, tuberoinfundibular, and medulla oblongata may cause various side effects, such as extrapyramidal symptoms (EPS). Haloperidol can also cause parkinsonism, such as tremors, muscle rigidity, and bradykinesia, as well as tardive dyskinesia (Leucht et al., 2008; Marshall, 1953; Rybakowski, 2023). Almost all antipsychotics are associated with dose-dependent EPS to varying degrees, and haloperidol has the highest OR (OR= 7.56) at a dose of 30 mg/day (Grover et al., 2017; Siafis et al., 2023). Therefore, administration of drugs that have anticholinergic effects is known to provide benefits in overcoming EPS side effects.

Diphenhydramine Mechanism of Action

Diphenhydramine is commonly used to treat extrapyramidal events (EPS). Research on the effectiveness of diphenhydramine shows that antagonism of histamine H1 receptors and muscarinic receptors can reduce symptoms of acute dystonia and parkinsonism due to the use of typical antipsychotics such as haloperidol. Several studies have compared diphenhydramine with other anticholinergic agents, such as benzatropine, and found its effectiveness in treating EPS is relatively equivalent. However, diphenhydramine tends to have a more substantial sedative effect. However, the use of diphenhydramine as EPS prophylaxis in the long term is not recommended due to potential side effects such as excessive sedation, cognitive impairment, and the risk of tolerance and dependence (Hanafi et al., 2017; Huf et al., 2016; Jeffers et al., 2022; Natarelli et al., 2023).

Effectiveness of Haloperidol-Diphenhydramine Combination

The goal of pharmacological therapy for acute agitation is to calm the patient with low risk of side effect. Several factors influencing drug selection are side effect profiles, tolerability, onset, and duration of therapy. Haloperidol is a typical antipsychotic in oral or IM form that the FDA has approved as an acute agitation therapy. Studies on the effectiveness and safety of haloperidol for acute agitation have been widely conducted. Haloperidol has minimal side effects on vital signs and minimal interactions with other drugs, but the risk of EPS induction is higher. In many cases, haloperidol may be the only appropriate therapeutic option for acute agitation (Schleifer, 2011; Wilson et al., 2012; Zareifopoulos & Panayiotakopoulos, 2019).

As far as the author knows, this is the first review article discussing the effectiveness of the haloperidol-diphenhydramine (HD) combination in the management of acute agitation in schizophrenia patients. As many as two articles stated that the HD combination helps overcome acute agitation (Gamcsik & Adams, 2024; Jeffers et al., 2022). The group of patients who received the HD combination had fewer need for additional doses (Gamcsik & Adams, 2024). The incidence of EPS in the group receiving diphenhydramine was lower when compared to the group without diphenhydramine. However, the group that did not receive diphenhydramine had a shorter hospital stay and a lower risk of hypotension (Jeffers et al., 2022). These results indicate that the HD combination produces symptom improvement comparable to Haloperidol monotherapy but with a lower incidence of EPS side effects.

Table 1. Summary of article analysis

Author (year)	Method	Intervetion	Result
Jeffers et al., (2022)	Retrospective cohort study	Haloperidol-lorazepam-diphenhydramine combination (B52) vs Haloperidol-lorazepam combination (52)	Patients receiving 52 were more likely to require antimuscarinic drugs within 2 days ($p= 0.04$). No EPS was experienced in the B52 group. Group 52 had shorter hospital stay ($p= 0.03$), lower incidence of hypotension ($p < 0.001$), and less physical restraint ($p= 0.001$) compared to group B52.
Gamcsik & Adams, (2024)	Retrospective medical record review	Haloperidol versus other antipsychotics	Within 24 hours of antipsychotic dose initiation, 28% of patients in

Author (year)	Method	Intervetion	Result
		(ziprasidone, olanzapine, chlorpromazine) IM diphenhydramine was given to 55% (n=41) of patients in the haloperidol group versus 9% (n=3) in the other antipsychotic group.	the haloperidol group versus 55% of patients in the other antipsychotic groups required additional doses or physical restraints. Four people in the haloperidol group experienced EPS.

IM = Intramuscular

Certain guidelines advise against using anticholinergics for EPS prevention and suggest their use only when the patient develops EPS symptoms, such as acute dystonia or parkinsonism. (Table 2). The Mental Health Clinician study (2024) found that the combination of haloperidol-diphenhydramine was used in 55% of agitation cases in a psychiatric ward. This reflects common clinical practice, but the retrospective study did not directly compare effectiveness with other options (Gamcsik & Adams, 2024). The combination of HD is effective in treating acute agitation, especially for EPS prophylaxis. However, this combination may not be ideal as first-line therapy. The risk of side effects such as excessive sedation and hypotension, as well as more extended hospital stays, occurred in patients using the combination of HD (Jeffers et al., 2022). Several case reports also show that diphenhydramine in high doses can cause delirium (Hoffmann et al., 2021; Huf et al., 2016). Other findings mention that effects such as excessive sedation, dry mouth, hypotension, and potential cognitive impairment in elderly patients still need to be monitored (Oktasari et al., 2025). Therefore, the combination of HD in long-term use needs to be closely monitored to avoid more serious side effects (Liviskie et al., 2023).

Table 2. Important factors from the guidelines regarding the use of anticholinergics with antipsychotics

	Guidelines	Recommendation
KEMENKES, (2015)	National Guidelines For Psychological Services Indonesia	1. Prophylactic use NOT mentioned 2. If side effects occur, such as extrapyramidal syndrome (acute dystonia or parkinsonism), the initial approach is to reduce the dose of antipsychotics. If symptoms persist, anticholinergic agents, such as trihexyphenidyl, benztropine, atropine sulfate, or diphenhydramine IM or IV injection, should be given.
Barnes et al., (2020)	British Association of Psychopharmacology (BAP)	1. Anticholinergics should NOT be generally prescribed 2. Anticholinergic medications should be used only for acute symptoms that respond to them—such as acute dystonia or drug-induced Parkinsonism—and their use should be assessed individually for each patient.
Keepers et al., (2020)	American Psychiatric Association (APA)	1. Anticholinergics should be prescribed for Acute Dystonia in lowest dose and for shortest possible duration

Guidelines		Recommendation
		2. Prophylactic use may be appropriate for individuals at high risk of developing drug-induced parkinsonism 3. For long-term use, the risk of anticholinergics outweigh their potential benefits
Grover et al., (2017)	Indian Psychiatric Society (IPS)	1. Prophylactic use NOT mentioned 2. Anticholinergics are recommended for treatment of emergent Acute Dystonias 3. In cases of acute drug-induced parkinsonism, anticholinergics should be considered only after attempts to reduce the dose or switch the antipsychotic have been made.

In addition, there are other therapy options that can be an alternative in the treatment of acute agitation. Generally, the drug classes that can be used for acute agitation therapy in schizophrenia patients are typical antipsychotics, atypical antipsychotics, and benzodiazepines. Atypical antipsychotics or second-generation antipsychotics (SGAs) such as olanzapine, ziprasidone, and aripiprazole are available in oral and intramuscular forms and can be used as an option for acute agitation therapy (Gale et al., 2021; Mühlbauer et al., 2019; Zareifopoulos & Panayiotakopoulos, 2019). SGAs not only work on dopamine receptors but also serotonin and histamine receptors, so they have the advantage of reducing depression and providing sedation in schizophrenia patients (Keepers et al., 2020). In addition, the side effects of EPS when using SGAs are minor than those of haloperidol. Therefore, alternative atypical antipsychotics are increasingly being considered, especially in long-term therapy. QT interval prolongation is common in the use of aripiprazole and ziprasidone, so regular monitoring is needed (Zareifopoulos & Panayiotakopoulos, 2019).

Benzodiazepines such as diazepam, lorazepam, and clonazepam are known to be efficacious for the treatment of agitation. However, in cases of agitation due to psychosis, benzodiazepines only provide a sedative effect without addressing the cause of agitation. In addition, the use of benzodiazepines can cause excessive sedation, hypotension, and respiratory depression when given in parenteral form. In some cases, benzodiazepines are combined with haloperidol to increase the sedative effect and reduce psychotic symptoms (Wilson et al., 2012).

Although still a matter of debate, the use of HD combination is an option in acute agitation therapy in schizophrenia patients. The high cost of SGA and limited accessibility in some health facilities make the HD combination a more cost-effective alternative for reducing psychotic symptoms with minimal EPS (Calver et al., 2015; Liviskie et al., 2023). The combination of haloperidol and diphenhydramine is an effective and practical regimen for controlling acute agitation in patients with schizophrenia, especially when IM administration is required, and the risk of EPS is high. The choice of therapy should consider the benefit-risk ratio and be tailored to the patient's clinical condition.

Limitation of the study

The limitation of this research is that it only reviews the available articles. Research on the effectiveness and risk of side effects of the haloperidol-diphenhydramine combination is still limited, so it lacks sufficient evidence for psychiatric practice. Further research may be needed to support the selection of rational acute agitation therapy in schizophrenic patients. Research on every aspect of therapy, including effectiveness, safety profile, and long-term impact of HD combinations, is needed to determine the optimal acute agitation therapy with minimal risk of side effects.

Conclusion

The combination of Haloperidol-Diphenhydramine is effective in managing acute schizophrenia by reducing psychotic symptoms and agitation with minimal risk of EPS. Clinically, this combination accelerates patient stabilization, although the risk of excessive sedation and cognitive impairment requires close monitoring to ensure long-term safety.

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