

REVIEW

Liquid antipsychotics in the management of psychomotor agitation: a focus on promazine

Marta Matrone¹, Alessandro Cuomo², Sergio De Filippis³, Andrea Fagiolini⁴, Mario Amore^{5,6}

¹Von Siebenthal Neuropsychiatric Clinic and Hospital, Genzano di Roma, Rome, Italy; ²School of Medicine, Department of Molecular Medicine, University of Siena, Siena, Italy; ³Neuropsychiatric Clinic, Villa Von Siebenthal, Genzano di Roma, Rome, Italy; ⁴Department of Molecular and Developmental Medicina, University of Siena School of Medicine, Siena, Italy; ⁵Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Section of Psychiatry, University of Genoa, Genoa, Italy; ⁶Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Ospedale Policlinico San Martino, Genoa, Italy

Abstract

Psychomotor agitation (PMA) is a prominent clinical issue frequently observed in various psychiatric and neurological conditions, including schizophrenia, bipolar disorder, Parkinson disease, dementia and substance use disorder. Characterized by motor restlessness, anxiety and irritability, PMA can rapidly escalate into aggression and violence, necessitating prompt intervention to ensure patient and caregiver safety. The prevalence of PMA in psychiatric emergency settings ranges from 4.3% to 10%, imposing a substantial burden on healthcare systems. Despite the critical nature of PMA, there is a lack of standardized treatment protocols, particularly concerning the use of liquid formulations of antipsychotics such as liquid promazine, which may offer unique advantages in emergency care. This review aims to provide a comprehensive analysis of the existing literature on the efficacy, safety and tolerability of liquid antipsychotics, with a particular focus on promazine, in the management of PMA. An extensive literature search was conducted across publicly available databases with no time

limitations to ensure the inclusion of all relevant articles. The findings suggest that liquid promazine offers several benefits, including ease of administration, rapid onset of action and improved patient compliance, making it a valuable option in acute PMA management. However, the review also highlights the need for future research, particularly long-term studies and head-to-head comparisons with other antipsychotics, to better establish the clinical utility of liquid promazine. Future research should focus on expanding the evidence base for liquid antipsychotic formulations, which will contribute to improved clinical outcomes in the management of PMA.

Keywords: aggression, emergency, liquid antipsychotics, management, promazine, psychomotor agitation.

Citation

Matrone M, Cuomo A, De Filippis S, Fagiolini A, Amore M. Liquid antipsychotics in the management of psychomotor agitation: a focus on promazine. *Drugs Context*. 2024;13:2024-6-5. <https://doi.org/10.7573/dic.2024-6-5>

Introduction

Psychomotor agitation (PMA) is a challenging symptom observed in various psychiatric and medical conditions, often necessitating prompt intervention to ensure the safety and well-being of the individual. Characterized by motor restlessness, anxiety, irritability and increased psychomotor activity, PMA presents with emotional activation and heightened sensitivity to both internal and external stimuli, which may lead to impaired cognitive performance.^{1,2}

PMA is frequently observed in various neuropsychological conditions, such as schizophrenia and bipolar disorder, as well as in neurological disorders like Parkinson disease, Alzheimer-type dementia, other forms of dementia and instances of substance abuse.¹⁻³ The condition can manifest as restlessness, decreased attention, irritability, and inappropriate behaviour, which may progress to anxiety, impulsivity, aggression and violence if not managed promptly.¹ The prevalence of PMA in psychiatric emergency services ranges from 4.3% to 10%.^{1,4} Patients with schizophrenia, bipolar disorder or dementia with

PMA account for nearly 50% of psychiatric emergency service visits.¹ In the USA, agitation episodes contribute to approximately 1.7 million emergency medical service visits annually,⁵ with recent studies indicating that up to 10% of emergency room visits in the USA and Europe are due to a PMA episode.⁶ In Spain, about 15% of patients with bipolar disorder and 25% of patients with schizophrenia experience at least one episode of PMA annually.¹ Similarly, in Brazil, 24% of psychiatric emergencies are due to agitation episodes.⁶ The prevalence of psychotic and bipolar disorders in Europe is estimated to be 1.2% and 0.9% of the total population, respectively.^{7,8} Studies from Italy highlight the significant clinical attention required for patients with PMA. For instance, a study conducted by the University of Brescia reported that 62.6% of patients exhibited agitation that met the criteria for immediate medical intervention.⁴ Another study found that 10% of patients admitted to psychiatric facilities showed hostile behaviour, with 3% of patients physically assaulting others, including healthcare personnel.⁹ Additionally, a 7-year Italian study reported 11.6% cumulative incidence of aggression per admission.¹⁰

PMA also imposes a significant economic social burden due to the cost associated with its management, including prolonged hospital stays, readmissions and overall hospitalization expenses.^{6,11} The fluctuating course of PMA, which progresses from mild to severe episodes if left untreated, poses many challenges such as decreased patient co-operation, maintaining patient dignity and ensuring effective physician–patient interactions.⁶ There exists a considerable chance of PMA episodes arising from substance intoxication or withdrawal, particularly with opioids.¹² Identifying substance use as an exacerbating factor is essential for determining appropriate treatment and developing strategies for long-term management. Despite international expert consensus recommendations for managing PMA in patients with psychiatric conditions, such as bipolar disorders, depressive and stress disorders, and schizophrenia, the absence of standardized protocols and clinical tools hinders timely diagnosis and appropriate management.²

A key challenge in the management of psychotic disorders is the risk of dysphagia, particularly in older patients who may avoid medications due to cognitive difficulties, the complexity of the instructions for medication use and the side-effects of antipsychotic drugs, including xerostomia (dry mouth), impaired swallowing muscle function or oesophageal injury.^{13,14} This highlights the need for better and immediate treatment options for PMA, especially those that can improve treatment adherence during acute episodes.¹⁵

Liquid formulations of antipsychotic drugs have emerged as a preferred choice in managing PMA due

to their ease of administration, better bioavailability and lower production costs.¹⁶ In emergency care settings, an effective treatment strategy for acute PMA should include medications that are easy to administer, have quick onset of action, lead to minimal sedation and have predictable pharmacokinetics. However, the literature on liquid antipsychotic formulations, particularly promazine, remains limited. This review aims to present the available literature on the management of PMA with liquid antipsychotic drugs, with a special focus on promazine, and its therapeutic status.

Methods

A comprehensive literature review was conducted across PubMed, Cochrane Library and Scopus to gather all the relevant information on promazine, with a particular focus on its efficacy, safety and tolerability in the management of PMA. The initial literature search was carried out in May 2022, and subsequent searches were conducted in August 2024. Specific keywords relevant to the research topic (e.g. “psychomotor agitation”, “promazine”, “first-generation antipsychotics”, “prevalence”, “liquid antipsychotics”, “psychomotor agitation management”) were employed to identify pertinent articles. The search was performed without time limitations, which allowed for the inclusion of all relevant studies, especially considering the limited data available on the subject. This approach facilitated a thorough review of the use of liquid antipsychotics, including promazine, in clinical settings. The selected studies were meticulously reviewed to extract and synthesize information. The search was restricted to studies published in English language and those that reported human clinical data. This approach ensured a robust and comprehensive overview of the existing knowledge on the subject. Given the focused nature of the search and the limited number of studies, a PRISMA diagram was not deemed necessary.

Ethical considerations

The authors declare that the review was conducted whilst paying attention to all perspectives of original studies and that they have conducted the review ethically. Institutional Review Board approval was not required as this is a review article with no original research data.

Review

Overview of PMA management

PMA is a complex and multifaceted condition that lacks a single, universally effective treatment approach.⁶ Ineffective management of PMA might lead to increased aggressive or violent behaviour and potentially serious

adverse events.¹⁶ Therefore, it is crucial to develop strategies to optimize the management of PMA, considering the severity of the condition and specific needs of the patient.¹⁶

Management strategies for PMA typically progress from non-pharmacological intervention to pharmacological treatment based on the severity of the symptoms.¹ Non-pharmacological approaches, which address the contextual or psychosocial aspects of agitation, include techniques such as music therapy, aromatherapy, sensory interventions, light therapy, and various forms of cognitive and behavioural therapies.^{17,18} These interventions have demonstrated efficacy in reducing agitation, and are often the first line of treatment, especially in the early stages of PMA.^{17,19}

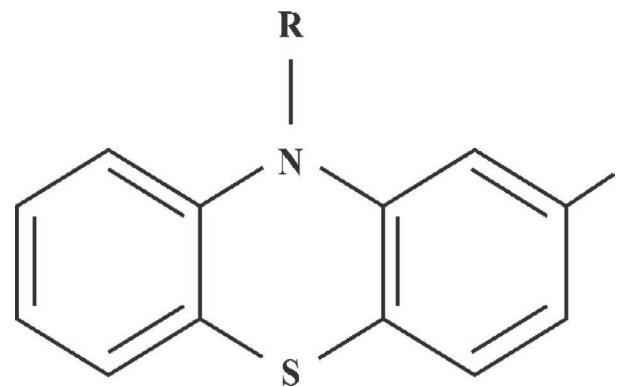
When non-pharmacological methods prove ineffective, pharmacological management becomes necessary.¹ Antipsychotics are the cornerstone of pharmacological treatment for PMA.²⁰ The choice of antipsychotics depends on factors such as the severity of PMA, patient characteristics, pharmacokinetics and pharmacodynamics of the drug, patient preferences regarding route of administration, and age.^{6,15,21} The goal is to achieve rapid and effective control of symptoms whilst minimizing adverse effects.

Available treatment options and classification of PMA drugs

Pharmacological treatment options for PMA are classified into three main categories: first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs) and benzodiazepines.¹ Each class of drugs has distinct mechanisms of action and is chosen based on the clinical presentation of the patient.

FGAs have been widely used in the management of PMA due to their potent dopamine receptor antagonism, which effectively reduces psychotic symptoms and agitation. Amongst the FGAs, phenothiazines represent a prominent sub-class. Phenothiazines, such as chlorpromazine and promazine, are characterized by their unique chemical structure, which consists of a three-ring system known as the phenothiazine ring. This tricyclic structure is composed of two benzene rings connected by a sulfur and nitrogen-containing central ring. The phenothiazine ring structure is crucial for the drug's pharmacological activity, particularly its ability to block dopamine D₂ receptors in the brain (Figure 1).²² This action helps alleviate symptoms of psychosis and reduces motor agitation, making phenothiazine effective in acute settings where rapid control is essential.¹ The central phenothiazine ring also allows for various chemical modifications, leading to the development of different phenothiazine derivatives

Figure 1. Chemical structure common to all phenothiazine rings.



Adapted from ref.²²

with varying potency and side-effect profiles. Despite their efficacy, their use is often limited due to the risk of extrapyramidal side-effects such as tardive dyskinesia, tremor, slurred speech, akathisia and dystonia.^{1,23} However, in acute situations, where rapid symptom control is necessary and oral administration is challenging, liquid formulations of these drugs further enhance their utility, offering ease of administration and faster absorption.²⁴

SGAs exert their effects by inhibiting both serotonergic and dopaminergic neurotransmission. This dual action often results in a better side-effect profile, particularly in terms of reduced extrapyramidal side-effects. Agents like aripiprazole, quetiapine, risperidone and ziprasidone have demonstrated efficacy in treating PMA, with oral olanzapine often preferred due to its favourable side-effect profile. The availability of intranasal olanzapine and evidence supporting its rapid tranquilization capabilities make it particularly suitable for emergency settings.^{25,26} However, risperidone carries a risk of hypotension in older patients, and whilst intramuscular aripiprazole is effective, oral SGAs remain underutilized despite their recommendation as first-line therapy for acute agitation.¹

Benzodiazepines are sedative drugs that modulate the inhibitory effects of GABA on the central nervous system, making them effective for rapid tranquilization in acute agitation.^{1,27,28} Lorazepam is a commonly used benzodiazepine, often in combination with antipsychotics for the management of acute PMA.²⁹

Promazine as a treatment option for PMA

Promazine, a member of the phenothiazines class of the FGAs, is primarily used for the management of PMA, aggressive behaviour, schizophrenia and other psychotic disorders.¹ It was first approved in the USA for the management of PMA in 2005. In the European Union, it

was approved as a short-term treatment for moderate to severe PMA as well as for addressing agitation and restlessness in older individuals. In the European Union, promazine is approved in both tablet and syrup formulations, with the syrup being formulated at a concentration of 25 mg/5 mL.³⁰

Promazine acts as an antagonist to dopamine D₂ receptors, inhibiting dopaminergic neurotransmission in a dosage-dependent manner. This action helps reduce the severity of psychotic-related symptoms, although it is also associated with extrapyramidal side-effects at higher doses.¹²¹ Unlike some other antipsychotics, promazine has lower propensity to induce hyperprolactinaemia, making it a preferred option in certain clinical scenarios.

Promazine's pharmacokinetic profile also contributes to its clinical utility. The drug is efficiently absorbed from the gastrointestinal tract, with peak plasma concentrations occurring within 2–4 h after oral administration. Its effects are typically noticeable within 20 min, making it a valuable option for rapid symptom control. The drug's half-life of approximately 6 h allows for sustained therapeutic effects, although multiple daily doses may be required in some patients to maintain symptom control.^{31–33} Promazine undergoes extensive hepatic metabolism, producing several metabolites that are excreted in the urine.^{31–33}

In clinical practice, promazine has been shown to be effective in managing psychotic agitation. Several studies have highlighted its efficacy in both short-term and long-term treatment scenarios. In a study conducted by Azima and Durost on 259 patients with acute psychiatric syndromes, promazine was effective in reducing symptoms of agitation with minimal extrapyramidal side-effects when compared to chlorpromazine.³⁴ Another study by Robertson²⁴ explored the use of liquid promazine in hospitalized patients with psychotic agitation. The results showed that 74% of patients treated with liquid promazine experienced marked improvement, and the study emphasized the benefits of the liquid formulation, noting its rapid onset of action and ease of administration, which are particularly advantageous in managing highly agitated patients.²⁴ Further evidence of promazine's efficacy comes from a study conducted by Graffeo³⁵ over a 3-year period. This study involved 180 patients with chronic psychosis who were hospitalized and treated with different formulations of promazine, including tablets, liquid form and intramuscular injections. The study demonstrated marked improvement in 26% of patients and moderate improvement in 48%, indicating that promazine was effective in modifying disturbed behaviour patterns. This allowed for successful psychotherapy, which ultimately led to the discharge of 26 patients from the hospital.³⁵

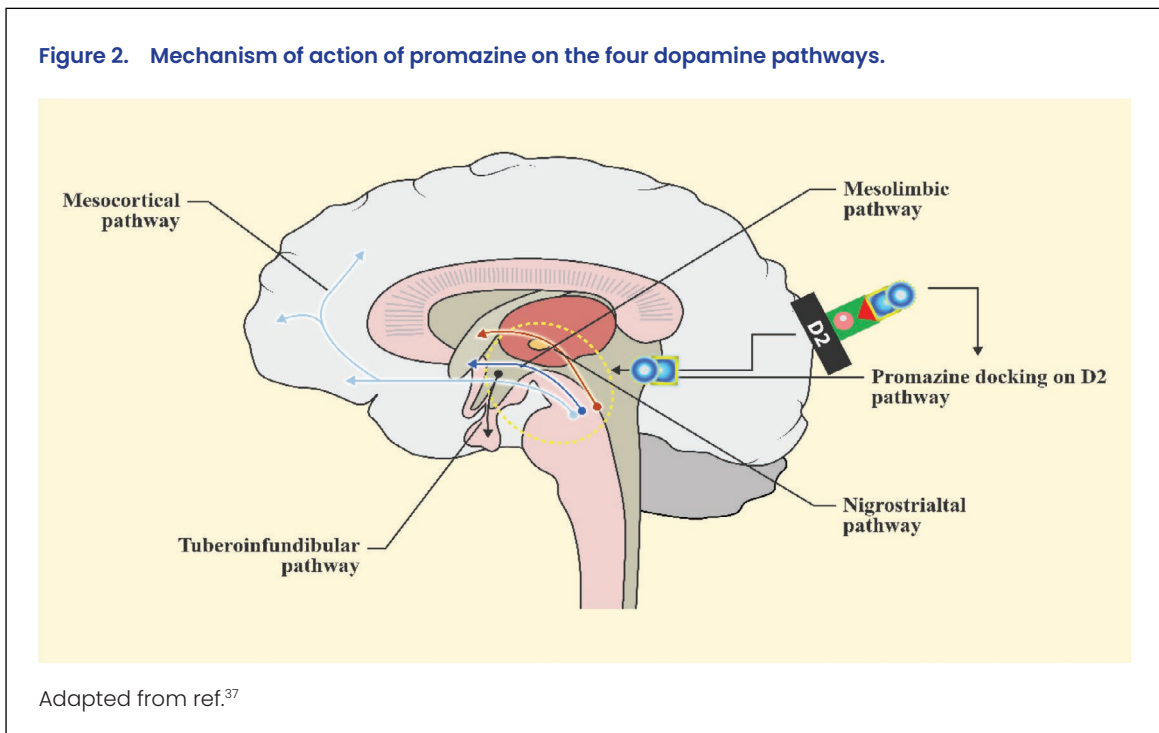
Lastly, an 18-month prospective, observational study by Nobili et al. provided additional evidence for the efficacy of promazine.³⁶ This study included 349 older patients (aged ≥65 years) with dementia residing in 35 Alzheimer disease special care units in Italy. The study focused on the use of antipsychotics, including promazine, to manage behavioural and psychological symptoms of dementia. The results showed that promazine was frequently prescribed by healthcare professionals for managing agitation in patients with Alzheimer disease, with a significant reduction in agitation symptoms observed amongst the treated patients. It is important to highlight that promazine has also been associated with withdrawal symptoms when abruptly discontinued, necessitating a gradual tapering over 3–4 weeks.³⁶

In addition to clinical studies, an in vitro study provided further insights into the efficacy of promazine in managing PMA.³⁷ This study focused on promazine's interaction with dopamine receptors, which is central to its antipsychotic effects. This investigation revealed that promazine can reversibly block dopamine-mediated responses at medium concentrations <5 μM (Figure 2),^{37,38} suggesting its potential to effectively inhibit dopamine activity, a key factor in controlling agitation and psychotic symptoms. This in vitro study supports the clinical findings by elucidating the mechanism through which promazine exerts its therapeutic effects, reinforcing its role as an effective treatment option for PMA. The ability of promazine to modulate dopaminergic neurotransmission in a dose-dependent manner aligns with its observed clinical benefits in reducing the severity of agitation and psychotic symptoms. This combination of in vitro and clinical evidence underscores the efficacy of promazine, particularly in situations where controlling excessive dopamine activity is essential.

In terms of safety, promazine is generally well tolerated, with a lower incidence of extrapyramidal side-effects (chlorpromazine: 4%; promazine: 0%)³⁴ and hyperprolactinaemia compared to other FGAs.^{121,34} This is partly due to its weaker anticholinergic and α-adrenergic blocking effects, which reduces the likelihood of side-effects such as dry mouth, constipation and hyperprolactinaemia. However, it is important to note that promazine, like all antipsychotics, can cause drowsiness and has the potential for drug interactions, particularly in older patients with comorbid conditions.

Overview of available liquid formulations of antipsychotic drugs

Liquid formulations of antipsychotics, including promazine, have been developed to improve clinical outcomes and treatment adherence, particularly in populations with swallowing difficulties, cognitive impairment or

Figure 2. Mechanism of action of promazine on the four dopamine pathways.

those requiring supervised administration.¹⁵ Liquid antipsychotics offer several advantages over traditional tablets and capsules, including easier administration, faster absorption and potentially higher bioavailability, which can lead to quicker therapeutic effects. Currently marketed FGAs available in liquid formulation are presented in Table 1.^{30,39–41} Licensed liquid antipsychotics include both FGAs, such as chlorpromazine, promazine, haloperidol, sulpride and trifluoperazine, and SGAs, like amisulpride, aripiprazole, clozapine, risperidone and quetiapine.^{29,15} These liquid formulations are available in various forms, including solutions, emulsions, microsuspensions and nanosuspensions, with the latter offering enhanced solubility and bioavailability due to the smaller particle sizes.

The availability of liquid formulations is particularly beneficial in emergency settings, where rapid control of symptoms is required, and in long-term care settings, where patients may have difficulty swallowing or may be uncooperative. By providing a more manageable and less invasive option, liquid formulations help ensure that patients receive timely and effective treatment, thereby reducing the need for more coercive measures such as physical restraint or involuntary medication administration.³¹

Summary

This review presents a comprehensive overview of the existing literature on liquid promazine in the management of PMA. Promazine, particularly in its liquid form, has demonstrated efficacy in managing PMA, offering advantages such as ease of administration and rapid

onset of action, which are crucial in emergency settings. Despite the number of studies specially focusing on oral promazine, existing research supports its utility in reducing symptoms of agitation with a generally favourable safety profile.^{42,43}

The studies reviewed, including those by Robertson²⁴ and Azima and Durost³⁴ highlight promazine's effectiveness in treating acute psychiatric conditions with minimal extrapyramidal side-effects compared to other antipsychotics like chlorpromazine. These findings are particularly relevant given the challenges associated with the management of PMA, where rapid control of symptoms is often necessary to prevent escalation to more severe behaviours such as aggression or violence.

Recent evidence also suggests that oral promazine is frequently preferred (57.8%) over injections (50.6%) in agitated patients with psychiatric disorders.⁴⁴ This preference underscores the importance of considering patient comfort and ease of administration in the management of agitation. Oral formulations reduce the need for invasive procedures, which can be particularly beneficial in de-escalating situations and maintaining a therapeutic alliance with the patient.

Table 2 outlines the practical applications and recommendations for integrating liquid promazine into clinical practice, highlighting its effectiveness and safety in managing psychomotor agitation. A significant advantage of liquid antipsychotics is their enhanced bioavailability compared to tablets.⁴³ Liquid antipsychotics have demonstrated better bioavailability due to their

Table 1. First-generation liquid antipsychotics available for treatment of psychomotor agitation.

Drugs	Formulation	Approved dosage (mg)	Approved indications
Haloperidol	Oral solution	2 mg/mL and 10 mg/mL	In adult patients, it is indicated for treatment of schizophrenia and schizoaffective disorder. Also indicated for the treatment of moderate-to-severe manic episodes associated with bipolar I disorder, persistent aggression and psychotic symptoms in patients with moderate-to-severe Alzheimer dementia and vascular dementia when non-pharmacological treatments have failed and when there is a risk of harm to self or others
Chlorpromazine	Oral syrup	100 mg/5 mL and 25 mg/5 mL	Schizophrenia along with different psychoses (especially paranoid), mania and hypomania, severe anxiety, psychomotor agitation, excitement and violent or dangerously impulsive behaviour. Used as an adjunct in the short-term management of these conditions
Promazine	Oral syrup	25 mg/5 mL and 50 mg/5 mL	As an adjunct to short-term management of moderate-to-severe psychomotor agitation; agitation and restlessness in older patients
Trifluoperazine	Oral solution	5 mg/5 mL	Given in low doses, it can be used as an adjunct in the short-term management of anxiety states, depressive symptoms that are secondary to anxiety as well as agitation It is recommended in high doses for the treatment of symptoms and prevention of relapse in schizophrenia and in other psychoses, especially paranoid type. However, it is not indicated for depressive psychoses. Additionally, it may also be used as an adjunct in the short-term management of severe psychomotor agitation and dangerously impulsive behaviour, for example, mental sub-normality

favourable dissolution profiles, which not only improve therapeutic outcomes but also increase treatment adherence due to the ease of administration.¹⁸ The rapid absorption of liquid antipsychotics, coupled with their quick onset of action, makes them valuable options in the emergency and long-term care settings. This aligns with the broader literature on the benefits of liquid antipsychotic formulations, which are increasingly recognized as essential tools in the management of PMA, particularly in older patients with swallowing difficulties or cognitive impairments, and situations where supervised administration is needed.^{18,21,35,45}

Timely recognition and treatment of PMA are crucial for ensuring the safety of both patients and caregivers.¹⁶ Early identification and appropriate management of PMA can reduce the need for coercive measures such as involuntary medication, physical restraint and seclusion, which can be distressing and potentially traumatic for the patient.^{6,16} Regular follow-ups, adherence to PMA treatment protocols and awareness regarding agitation, along with appropriate use therapeutic pharmacological alternatives, including suitable formulations, are essential in reducing the disease burden associated with PMA for both patients and caregivers.²

When compared to other FGAs, the α -adrenergic blocking and weak anticholinergic effects of promazine may be responsible for causing relatively less dryness of mouth and constipation. Additionally, promazine-HCl does not block dopamine within the tuberoinfundibular tract, which may explain its lower incidence of hyperprolactinaemia compared to other antipsychotic agents or risperidone (Figure 3).⁴⁶ These characteristics further underscore the potential benefits of promazine in specific patient populations, particularly where minimizing side-effects is a priority.

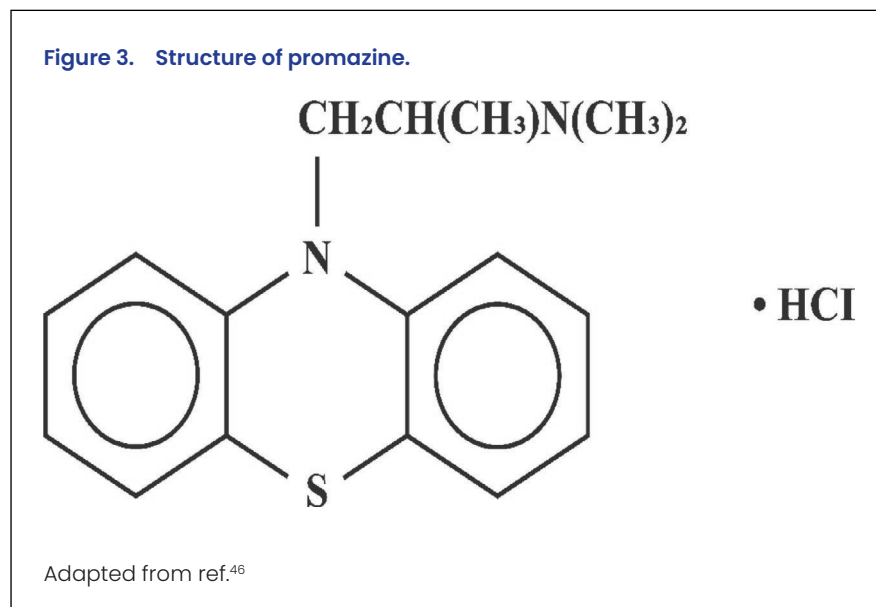
Limitations, implications for clinical practice and future directions

Whilst the reviewed studies provide evidence supporting the use of promazine, particularly in liquid form, it is important to recognize several limitations that warrant further investigation. Many of the studies focus on short-term outcomes, with limited data on the long-term effects of promazine use, particularly regarding chronic side-effects such as metabolic disorder. There is also notable absence of recent randomized controlled trials examining the effect of promazine, which limits the current understanding of its efficacy and safety in contemporary clinical practice. Future research should aim

Table 2. Integrating liquid promazine into clinical practice: practical applications and recommendations for liquid promazine.

Clinical evidence	Implications for practice	Suggested improvements for clinical practice
Effectiveness of liquid promazine in managing PMA	Liquid promazine has demonstrated efficacy in managing PMA in patients with psychiatric disorders, particularly in those with swallowing difficulties or those requiring rapid symptom control	Incorporate liquid promazine as a first-line option for PMA management in patients with swallowing difficulties or those needing immediate effect
Favourable safety profile of liquid promazine	Despite some mild adverse effects, such as drowsiness, dry mouth and constipation, liquid promazine is generally well tolerated and safe for use in diverse patient population, including older patients	Enhance patient education on managing side-effects, and monitor older patients closely for any adverse reactions to optimize safety
Patient preference for oral over parenteral antipsychotics	Oral formulations, especially liquids, are preferred by patients due to their non-invasive nature and administration, making them a suitable alternative to injections	Increase the availability and prescribing of oral liquid antipsychotics in settings where patient preferences and comfort are prioritized
Improved bioavailability of liquid formulations	Liquid antipsychotics provide better bioavailability compared to tablets, leading to more effective symptom control and quicker therapeutic effects	Encourage the use of liquid formulations in cases where rapid onset of action is necessary, such as in acute agitation or emergency settings
Challenges in administration of tablets/capsules	Patients with cognitive impairments, memory problems or physical difficulties may struggle with tablets or capsule administration, leading to non-adherence	Transition such patients to liquid formulations to improve adherence and therapeutic outcomes; train caregivers on the proper administration of liquid medications
Suitability of liquid antipsychotics in emergency situations	Liquid antipsychotics reach the bloodstream relatively quickly, making them effective for use in emergencies to calm patients rapidly	Prioritize liquid formulations in emergency protocols for managing acute agitation and distress, especially in settings where quick action is critical
Potential for reducing coercive measures	Effective use of liquid antipsychotics could decrease the need for physical restraints, seclusion and involuntary medication, reducing patient trauma	Educate clinical staff on the benefits of liquid formulations in managing agitation and integrate these into protocols as alternatives to coercive methods
Role of multidisciplinary teams	A collaborative approach involving various healthcare professionals can enhance the management of PMA and ensure comprehensive patient management	Promote multidisciplinary team involvement in PMA management, including regular case reviews and treatment plan adjustments based on patient progress
Timely recognition and treatment of PMA	Early intervention in PMA can prevent the escalation of agitation and reduce the need for coercive measures, improving overall patient outcomes	Implement regular screening protocols for early detection of PMA and develop standard treatment pathways that include liquid promazine as an option
Use of liquid antipsychotics in older patients and those with cognitive impairment	Liquid formulations have proven effective and safe in older patients with swallowing difficulties and in those with cognitive impairments	Tailor antipsychotic treatment to individual patient needs by using liquid formulations in populations where swallowing difficulties or cognitive impairments are present

PMA, psychomotor agitation.



to address these gaps by conducting long-term studies that monitor patients over extended periods.

Additionally, whilst the studies reviewed provide valuable insights into the efficacy and safety of promazine, there is a need for more head-to-head comparisons with other antipsychotics, particularly in liquid form. Such studies would provide clearer guidance on the relative advantages and disadvantages of promazine compared to other options, helping clinicians make better-informed decisions.

Given the diverse populations that experience PMA, future research should explore the differential effects of promazine across these groups. For example, studies could investigate whether certain sub-groups, such as patients with specific psychiatric diagnoses or those with comorbid medical conditions, respond differently to promazine. This would help further refine the use of promazine and ensure it is used most effectively across different patient populations.

The findings from this review highlight the importance of tailoring management of PMA strategies to individual patient needs, with a particular focus on selecting appropriate drug formulations. The use of liquid formulations, such as liquid promazine, offers a valuable option for patients who do not tolerate or respond well to solid oral dosage forms. These formulations should be considered part of comprehensive approach to PMA management, particularly in settings where rapid symptom control is required. Further research is needed to expand the evidence base for liquid formulations of antipsychotics especially concerning long-term outcomes and patient

preferences. Additionally, more studies are needed for comparing the efficacy and safety of liquid formulations with other drug delivery methods, such as intramuscular injections and orally disintegrating tablets, to better inform clinical decision-making.

Conclusion

The management of PMA requires a multifaceted approach that includes both non-pharmacological and pharmacological interventions. Antipsychotics, including FGAs like promazine, remain a cornerstone of pharmacological treatment, particularly in cases where non-pharmacological methods are insufficient. The drug's rapid onset of action and ease of administration, especially in its liquid form, make it a valuable treatment option for patients who require prompt symptom relief, including those with swallowing difficulties or in emergency settings. The favourable safety profile of promazine further supports its use, particularly in older patients and those with complex health needs. However, despite these promising findings, there remains a need for further research to establish promazine's position in the therapeutic landscape. Future studies should focus on larger, more diverse populations to confirm these results, explore the long-term efficacy and safety of promazine, and investigate its potential benefits in combination with other treatments. Additionally, research into optimizing dosage and administration routes and in understanding the molecular mechanisms underlying promazine's effect would provide deeper insights and enhance its clinical utility in managing PMA and other related disorders.

Contributions: This paper is based on the collective experience and expertise of all authors. Every author assisted with the data assessment, development, and review of the present article and they acknowledge that they understand the journal on issues involved in ethical publication and affirm that this report complies with those guidelines. This manuscript was also subjected to a formal review by the sponsor. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Availability of data: The authors confirm that the data supporting the findings of this study are available within the article.

Disclosure and potential conflicts of interest: MM and MA have no conflicts of interest to declare. AC has been a consultant for Angelini, Janssen, Lundbeck, Otsuka, Recordati, Pfizer and Viatri; a speaker for Angelini, Aspen, Biogen, Boehringer Ingelheim, GSK, Janssen, Lundbeck, Neuraxpharma, Otsuka, Recordati, Pfizer and Viatri. SDF has received consultation fees from Angelini, Janssen, Lundbeck, Otsuka, Viatri and Janssen; and has been a speaker for Angelini, Janssen, Lundbeck, Otsuka, Viatri and Neuraxpharma. AF has been a consultant for Angelini, Janssen, Lundbeck, Otsuka, Recordati, Pfizer and Viatri; a speaker for Angelini, Aspen, Biogen, Boehringer Ingelheim, Janssen, Lundbeck, Neuraxpharma, Otsuka, Recordati, Pfizer and Viatri; and has received research grants from Janssen, Boehringer Ingelheim, Otsuka, Angelini and Lundbeck. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: <https://www.drugsincontext.com/wp-content/uploads/2024/10/dic.2024-6-5-COI.pdf>

Acknowledgements: Publication writing support was provided by Dr Palash Kumar Das (PhD) and Uma Dasam, and additional editorial assistance was provided by Dr Shazia Khanam (PhD, all three employed with Tata Consultancy Services, India). The authors would also like to acknowledge the invaluable support of Dr Shivam Srivastava, MD, Dr Sanjay Hadigal, MD, and Dr Andrea Guarino (all three employed with Viatri Inc.) in the development of this article. The study was funded by Viatri.

Funding declaration: The authors received no funding in this research. The writing support was funded by Viatri.

Copyright: Copyright © 2024 Matrone M, Cuomo A, De Filippis S, Fagiolini A, Amore M. Published by *Drugs in Context* under Creative Commons License Deed CC BY NC ND 4.0, which allows anyone to copy, distribute, and transmit the article provided it is properly attributed in the manner specified below. No commercial use without permission.

Correct attribution: Copyright © 2024 Matrone M, Cuomo A, De Filippis S, Fagiolini A, Amore M. <https://doi.org/10.7573/dic.2024-6-5>. Published by *Drugs in Context* under Creative Commons License Deed CC BY NC ND 4.0.

Article URL: <https://www.drugsincontext.com/liquid-antipsychotics-in-the-management-of-psychomotor-agitation-a-focus-on-promazine>

Correspondence: Alessandro Cuomo; Assistant Professor in Psychiatry, Division of Psychiatry, School of Medicine, Department of Molecular Medicine, University of Siena, Siena, Italy. Email: alessandrocuomo86@gmail.com

Provenance: Submitted; externally peer reviewed.

Submitted: 21 June 2024; **Accepted:** 18 September 2024; **Published:** 21 November 2024.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

For all manuscript and submissions enquiries, contact the Editorial office editorial@drugsincontext.com

For all permissions, rights, and reprints, contact David Hughes david.hughes@bioexcelpublishing.com

References

1. Pompili M, Ducci G, Galluzzo A, et al. The management of psychomotor agitation associated with schizophrenia or bipolar disorder: a brief review. *Int J Environ Res Public Health*. 2021;18:4368. <http://doi.org/10.3390/ijerph18084368>
2. Vieta E, Garriga M, Cardete L, et al. Protocol for the management of psychiatric patients with psychomotor agitation. *BMC Psychiatry*. 2017;17:328. <http://doi.org/10.1186/s12888-017-1490-0>
3. de Berardis D, Fornaro M, Orsolini L, et al. The role of inhaled loxapine in the treatment of acute agitation in patients with psychiatric disorders: a clinical review. *Int J Mol Sci*. 2017;18:349. <http://doi.org/10.3390/ijms18020349>
4. Sacchetti E. Psychomotor agitation in psychiatry: an Italian Expert Consensus. *Evid Based Psychiatr Care*. 2017;3:1–24.
5. Holloman GH Jr, Zeller SL. Overview of project BETA: best practices in evaluation and treatment of agitation. *West J Emerg Med*. 2012;13:1–2. <http://doi.org/10.5811/westjem.2011.9.6865>
6. Cavalcante DA, Gadelha A, Noto C. How challenging is to manage agitated patients? *Braz J Psychiatry*. 2019;41:277–278. <http://doi.org/10.1590/1516-4446-2019-4105>
7. Kovács G, Almási T, Millier A, et al. Direct healthcare cost of schizophrenia – European overview. *Eur Psychiatry*. 2018;48:79–92. <http://doi.org/10.1016/j.eurpsy.2017.10.008>
8. Pini S, de Queiroz V, Pagnin D, et al. Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol*. 2005;15:425–434. <http://doi.org/10.1016/j.euroneuro.2005.04.011>
9. Biancosino B, Delmonte S, Grassi L, et al. Violent behavior in acute psychiatric inpatient facilities: a national survey in Italy. *J Nerv Ment Dis*. 2009;197:772–782. <http://doi.org/10.1097/NMD.0b013e3181bb0d6b>
10. Grassi L, Biancosino B, Marmai L, et al. Violence in psychiatric units: a 7-year Italian study of persistently assaultive patients. *Soc Psychiatry Psychiatr Epidemiol*. 2006;41:698–703. <http://doi.org/10.1007/s00127-006-0088-5>
11. Martínez-Raga J, Amore M, Di Sciascio G, et al. 1st International experts' meeting on agitation: conclusions regarding the current and ideal management paradigm of agitation. *Front Psychiatry*. 2018;9:54. <http://doi.org/10.3389/fpsy.2018.00054>
12. Shah M, Huecker MR. Opioid withdrawal. StatPearls. Treasure Island, FL: StatPearls Publishing; 2024. <https://www.ncbi.nlm.nih.gov/books/NBK526012/>. Accessed July 21, 2023.
13. Fusco S, Cariati D, Schepisi R, et al. Management of oral drug therapy in elderly patients with dysphagia. *J Gerontol Geriatr*. 2016;64:9–20.
14. Rodgers JE, Thudium EM, Beyhaghi H, et al. Predictors of medication adherence in the elderly: the role of mental health. *Med Care Res Rev*. 2018;75:746–761. <http://doi.org/10.1177/1077558717696992>
15. Papazisis G, Siafis S. The added value of liquid antipsychotics: the case of quetiapine. *Curr Clin Pharmacol*. 2019;14:101–107. <http://doi.org/10.2174/1574884713666181102145236>
16. Mutsatsa S, Bressington D. Oral liquid antipsychotic formulation in the treatment of psychosis. *Br J Mental Health Nurs*. 2013;2:126–127. <http://doi.org/10.12968/bjmh.2013.2.3.126>
17. Millán-Calenti JC, Lorenzo-López L, Alonso-Búa B, et al. Optimal nonpharmacological management of agitation in Alzheimer's disease: challenges and solutions. *Clin Interv Aging*. 2016;11:175–184. <http://doi.org/10.2147/CIA.S69484>
18. Livingston G, Kelly L, Lewis-Holmes E, et al. Non-pharmacological interventions for agitation in dementia: systematic review of randomised controlled trials. *Br J Psychiatry*. 2014;205:436–442. <http://doi.org/10.1192/bjp.bp.113.141119>
19. Carrarini C, Russo M, Dono F, et al. Agitation and dementia: prevention and treatment strategies in acute and chronic conditions. *Front Neurol*. 2021;12:644317. <http://doi.org/10.3389/fneur.2021.644317>
20. Bjarke J, Gjerde HN, Jørgensen HA, et al. Akathisia and atypical antipsychotics: relation to suicidality, agitation and depression in a clinical trial. *Acta Neuropsychiatr*. 2022;34:282–288. <http://doi.org/10.1017/neu.2022.9>
21. Gareri P, De Fazio P, Stilo M, et al. Conventional and atypical antipsychotics in the elderly: a review. *Clin Drug Investig*. 2003;23:287–322. <http://doi.org/10.2165/00044011-200323050-00001>
22. Ayano G. First generation antipsychotics: pharmacokinetics, pharmacodynamics, therapeutic effects and side effects: a review. *Res Rev J Chem*. 2016;5:53–63.
23. Mathews M, Gratz S, Adetunji B, et al. Antipsychotic-induced movement disorders: evaluation and treatment. *Psychiatry*. 2005;2:36–41.
24. Robertson RB. Control of symptoms in the chronic psychoses with concentrated liquid promazine. *Mil Med*. 1958;123:108–112.
25. Shrewsbury SB, Hocevar-Trnka J, Satterly KH, et al. The SNAP 101 double-blind, placebo/active-controlled, safety, pharmacokinetic, and pharmacodynamic study of INP105 (nasal olanzapine) in healthy adults. *J Clin Psychiatry*. 2020;81:19m13086. <http://doi.org/10.4088/JCP.19m13086>

26. Kolli P, Kelley G, Rosales M, et al. Olanzapine pharmacokinetics: a clinical review of current insights and remaining questions. *Pharmgenomics Pers Med*. 2023;16:1097–1108. <http://doi.org/10.2147/PGPM.S391401>
27. Bak M, Weltens I, Bervoets C, et al. The pharmacological management of agitated and aggressive behaviour: a systematic review and meta-analysis. *Eur Psychiatry*. 2019;57:78–100. <https://doi.org/10.1016/j.eurpsy.2019.01.014>
28. Ward K, Citrome L. The treatment of acute agitation associated with schizophrenia or bipolar disorder: investigational drugs in early stages of their clinical development, and their clinical context and potential place in therapy. *Expert Opin Investig Drugs*. 2020;29:245–257. <https://doi.org/10.1080/13543784.2020.1727884>
29. Amore M, D'Andrea M, Fagiolini A. Treatment of agitation with lorazepam in clinical practice: a systematic review. *Front Psychiatry*. 2021;12:628965. <http://doi.org/10.3389/fpsy.2021.628965>
30. SmPC. Promazine hydrochloride 25mg/5ml oral syrup, 2020. <https://www.medicines.org.uk/emc/product/6697/smpc/print>. Accessed August 27, 2024.
31. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. *CMAJ*. 2005;172:1703–1711. <https://doi.org/10.1503/cmaj.1041064>
32. Hu OY, Curry SH. Stability, human blood distribution and rat tissue localization of promazine and desmonomethylpromazine. *Biopharm Drug Dispos*. 1989;10:537–548. <https://doi.org/10.1002/bdd.2510100603>
33. Dollery C. *Therapeutic Drugs*; vol 1. 3rd ed. Edinburgh: Churchill Livingstone; 1999:236–238.
34. Azima H, Durost H. Comparison of the effects of promazine and chlorpromazine in mental syndromes. *Can Med Assoc J*. 1957;77:671–675.
35. Graffeo AJ. Three years of treatment of chronic hospitalized psychotic individuals with promazine (Sparine). *Am J Psychiatry*. 1960;116:842. <https://doi.org/10.1176/ajp.116.9.842>
36. Nobili A, Pasina L, Trevisan S, et al. Use and misuse of antipsychotic drugs in patients with dementia in Alzheimer special care units. *Int Clin Psychopharmacol*. 2009;24:97–104. <https://doi.org/10.1097/yic.0b013e328323aaf0>
37. Myers PR, Livengood DR, Shain W. Characterization of a depolarizing dopamine response in a vertebrate neuronal somatic cell hybrid. *J Cell Physiol*. 1977;91:103–118. <https://doi.org/10.1002/jcp.1040910111>
38. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th ed. Cambridge: Cambridge University Press; 2008.
39. FDA. Haloperidol – haloperidol solution, 2022. <https://www.medicines.org.uk/emc/product/15252/smpc/print>. Accessed August 27, 2024.
40. SmPC. Chlorpromazine 25 mg/5 ml solution, 2017. <https://www.medicines.org.uk/emc/product/4558/smpc/print>. Accessed August 27, 2024.
41. SmPC. Trifluoperazine 5 mg/5 ml oral solution. <https://www.medicines.org.uk/emc/product/9496/smpc/print>. Accessed August 27, 2024.
42. Talofen. Patient information leaflet. <https://www.pharmacompass.com/chemistry-chemical-name/talofen>. Accessed November 25, 2023.
43. Lesse S. An evaluation of promazine hydrochloride in psychiatric practice. *Am J Psychiatry*. 1957;113:984–987. <https://doi.org/10.1176/ajp.113.11.984>
44. Cipriani N, Baldini I, Costolini G. Agitation and aggression in the elderly: pharmacological strategies in a court of Tuscany physicians. *Evid Based Psychiatr Care*. 2017;3:35–37.
45. Miller J. Managing acute agitation and aggression in the world of drug shortages. *Ment Health Clin*. 2021;11:334–346. <https://doi.org/10.9740/mhc.2021.11.334>
46. Kiningham KK. Promethazine. xPharm: The Comprehensive Pharmacology Reference. 2007. <https://doi.org/10.1016/B978-008055232-3.62473-0>