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Expert Consensus on the Use of Diphenhydramine for Short-Term Insomnia: Efficacy, Safety and Clinical Applications

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Abstract: Insomnia is the most prevalent sleep disorder, estimated to affect at least one-third of the global population. There are a variety of treatment options available for both acute and chronic insomnia. Currently, the pharmacological arsenal for treating insomnia includes short- or intermediate-acting benzodiazepine hypnotics, non-benzodiazepine hypnotic sedatives, melatonin receptor agonists, and sedating antidepressants. Diphenhydramine, a first-generation antihistamine, is commonly used in the treatment of allergies and dermatitis. This review examines the preclinical and clinical efficacy and safety evidence of diphenhydramine in treating short-term insomnia. Additionally, it provides expert consensus on its implementation as an over-the-counter medication for this condition. The available evidence indicates that diphenhydramine is an effective treatment for acute insomnia in adults, offering a safe, and affordable option for most patients suffering from this condition. Experts concur that there is strong evidence supporting the recommendation of diphenhydramine for the treatment of acute insomnia in adults.

Keywords: Diphenhydramine; antihistamines; short-term insomnia; experts' consensus

1. Introduction

Insomnia is broadly understood as a disruption in sleep. It is defined by difficulties in overall sleep, little or no sleep when possible, and associated daytime dysfunction (1). Other features of insomnia are difficulty in initiating sleep, waking up during the night, and early awakenings. Insomnia is a prevalent sleep disorder worldwide (2). For instance, in the United States, a survey of 7,428 adults revealed that nearly half reported difficulty sleeping, with an estimated prevalence of insomnia at 23.2% (3). In Latin America, a study conducted in four major cities—Montevideo, Mexico City, Santiago, and Caracas—examined 4,533 participants and found a high prevalence of symptoms related to sleep disorders, including 34.7% diagnosed with insomnia (4). In Colombia, a study of 1,325 women from diverse ethnic backgrounds reported that nearly one-third experienced insomnia (5).

It is recognized as a disease in its own since it significantly impairs quality of life, daytime functioning, and overall health. Therefore, it should be promptly treated once detected. Cognitive

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behavioral therapy for insomnia (CBT-I) is widely recognized as the first-line therapy (6). Pharmacotherapy is also a helpful tool for treating insomnia, it has demonstrated to improve significantly latency to sleep and awakenings (7). The choice of medication is a critical aspect of insomnia management, as tailoring treatment to the individual can optimize outcomes and minimize risks. While widely approved medications for insomnia, such as benzodiazepines and Z-drugs, are commonly prescribed, other effective options, like antihistamines, are not as broadly endorsed despite their potential benefits.

This article provides a comprehensive review of insomnia, focusing on the available literature regarding diphenhydramine (DPH) for short-term management of insomnia. It includes an expert consensus from various medical specialties on the use of DPH, with particular emphasis on its safety, efficacy and special considerations in children and the elderly. Finally, it contrasts these findings with existing literature, offering a nuanced perspective on the role of DPH in the treatment of short-term insomnia.

1.1. Pathophysiological and Clinical Aspects of Insomnia

There is no definitive consensus on the biological basis of insomnia. Nonetheless, hyperarousal is widely accepted as a primary biological mechanism. From a biological perspective, hyperarousal results from overactivation of the ascending reticular activation systems and the hypothalamic-pituitary-adrenal (HPA) axis (8,9). It manifests as elevated heart rate, abnormal heart rate variability, altered core body temperature, and blunted reductions in metabolic rate typically associated with non–rapid eye movement (non-REM) sleep (10).

The Spielman model posits that insomnia is influenced by three factors: predisposing factors (genetic, personality, or environmental traits that increase vulnerability), precipitating factors (acute events, such as trauma), and perpetuating factors (behavioral and cognitive patterns that sustain insomnia and lead to chronic forms)(11).

Insomnia is diagnosed clinically based on various criteria, including those outlined in the International Classification of Sleep Disorders, Third Edition (ICSD-3), the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and the International Classification of Diseases, Tenth Revision (ICD-11). According to the ICSD-3, insomnia is defined as a persistent difficulty in initiating or maintaining sleep, or waking earlier than desired, accompanied by resistance to going to bed at an appropriate time or inability to sleep without external intervention, despite having adequate opportunities and conditions for sleep (12).

The diagnosis of insomnia can be achieved through a comprehensive clinical evaluation that includes a detailed sleep history, focusing on the onset, duration, and frequency of symptoms. Current sleep-wake patterns, along with environmental and social factors, should be assessed. A thorough medical and psychiatric history is essential, as well as an evaluation of substance use and medication intake (10).

In addition to clinical diagnosis, there are supportive diagnostic tools that, while not strictly necessary, can provide valuable information. Sleep diaries are recommended, as they offer insights into sleep efficiency and patterns (13). Polysomnography (PSG) is particularly useful when other sleep disorders are suspected, as it can reveal findings characteristic of insomnia, such as disrupted sleep continuity (14). Actigraphy can also be helpful, as it provides objective data on sleep state misperception and paradoxical insomnia (15,16). Furthermore, modern smart technologies, such as smartwatches, are increasingly used to monitor sleep patterns and can serve as practical tools to support the follow up of patients diagnosed with insomnia (17).

1.2. Treatment of Insomnia

Treatment includes both pharmacological and behavioral interventions (18). Behavioral interventions emphasize strict sleep hygiene and psychological approaches, such as CBT-i, and sleep restriction therapy (19). Although CBT-i has been demonstrated to improve sleep, it is not widely available in all regions. Therefore, it is crucial for the primary care physician to understand what to teach patients presenting with insomnia. Sleep hygiene, body-mind therapy, meditations,

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mindfulness and diaphragmatic breathing are also available interventions for managing insomnia (20). Primary care physicians should also be confident in the use of medications to manage insomnia.

Pharmacological options for treating insomnia include short- or intermediate-acting benzodiazepine (BDZ) hypnotics, non-benzodiazepine hypnotic sedatives (Z drugs), melatonin receptor agonists, orexin antagonists, and sedating antidepressants. The pharmacodynamics of these drugs can be categorized into GABAergic and non-GABAergic types. Most of them are detectable in plasma within 30 minutes of ingestion and have short to medium half-lives. As these drugs are hypnotic, they interact with other substances such as alcohol. Special populations, such as children and the elderly, must be considered when selecting a drug. Table 1 summarizes the main pharmacological features of currently used drugs for treating insomnia.

The use of diphenhydramine for short-term insomnia is a key focus of this consensus. The recent approval of diphenhydramine as an over-the-counter medication by the Food and Drug Administration, along with strong evidence supporting its effectiveness for short-term insomnia and the safety profile offered, has driven this research. Subsequent sections explore the available literature on the general pharmacological properties of diphenhydramine. To assess the accuracy and quality of the evidence, a consensus committee was assembled. Additionally, considerations are provided regarding its implementation as an over-the-counter treatment for short-term insomnia in Colombia.

2. Materials and Methods

2.1. Selection of Consensus Committee Members and Topics Being Assessed

A panel of five experts in sleep disorders was convened to participate in this consensus. CAC-O is a pharmacologist specializing in pharmacovigilance, with extensive experience in researching neurological disorders. MV and KJPG are neurologists specialized in sleep disorders, YSA is an otolaryngologist specializing in sleep disorders, and JEEC is a psychiatrist specializing in sleep disorders. Most of these experts are clinicians who regularly treat patients with various sleep disorders and have a deep understanding of central nervous system disorders, as well as high academic qualifications.

The objectives of this consensus were threefold: to gather the opinions of Latin American specialists on key issues related to the use of diphenhydramine in short-term insomnia, to thoroughly evaluate the available literature on the drug's efficacy and safety, and to delineate the clinical scenarios in which diphenhydramine is or is not an optimal choice.

Each expert was assigned to review selected literature, chosen through a quasi-systematic search. The reviewed studies were then carefully discussed, and a questionnaire was developed based on the most recent insomnia taxonomy. The key topics, selected in consultation with the committee, included drug effectiveness and safety, availability, patient age, treatment duration, and the level of evidence supporting each recommendation.

2.2. Literature Research

Literature search was carried out by scanning Medline for the Medical Subject Heading (MeSH) "Insomnia" AND " Diphenhydramine" via PubMed showed 115 results. There were no limitations in terms of the type and quality of studies, language, or provenance. The title and abstract of each article were screened for their relevance to the current approach by CA-O. The articles directly related to diphenhydramine and acute insomnia that were considered relevant were selected and reviewed. A total of 36 articles were chosen to provide the evidence support for this consensus.

2.3. Consensus Workflow and Methods To Achieve Consensus

Delphi methodology was followed to reach consensus among a panel of experts on the topic (21). This process included the selection of a group of qualified experts, who participated in several rounds of questionnaires designed to collect their opinions and judgments. After each round, anonymous and summarized feedback was provided to the group, allowing the experts to review and adjust their responses based on the input from the collective. This iterative process until a consensus was reached in most of the questions. Finally, the results were analyzed to obtain consensual conclusions that reflected the general agreement of the panel.

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Experts were assigned at least five articles each to review in preparation for an upcoming virtual meeting. During the meeting, different aspects of diphenhydramine were thoroughly assessed by all experts, considering the selected literature. A draft of the questionnaire was then reviewed and refined for proper taxonomy and syntax. A total of 12 questions were formulated (Box 1).

The questionnaire was divided into five sections. Section 1 focused on the evaluation of the use of diphenhydramine for insomnia, including its efficacy, safety, convenience, and cost in the management of insomnia. Section 2 addressed the types of insomnia in which diphenhydramine could be used. Section 3 examined the use of diphenhydramine as a hypnotic-sedative by age group. Section 4 considered the duration of diphenhydramine treatment for managing insomnia. Section 5 explored the evidence and levels of evidence on the use of diphenhydramine for managing insomnia.

All questions were quantified by a Likert Scale, being 1= total disagreement, 2 = partial disagreement, 3 = neutral, 4 = partial agreement, 5 = total agreement. An agreement of less than 60% of the votes was considered as no agreement, a supermajority between 60% and 74% was considered a weak agreement, a supermajority equal or greater than 75% as a strong agreement, and 100% as unanimous agreement. Consensus was defined as an interquartile range equal or less than 1. The interquartile range (IQR) was calculated by finding the difference between the third quartile (Q3) and the first quartile (Q1) (IQR = Q3 – Q1). All the answers were treated anonymously. Statistical analyses and figures were performed using MATLAB Online (MathWorks, Natick, MA, USA).

Table 1. Pharmacological characteristics and clinical indications of common drugs used in insomnia.

Drug	Pharmacological action/Group	Dose	T max	Vd	$t_{1/2}$	Metabolism/Elimination	Indication	Special population use
Diphenhydramine	H1RA	12.5 mg - 50 mg	2 - 3 hours	3.3 - 6.8 L/kg	2.4 - 9.3 hours	First-pass; CYP450 isoenzymes/urine	Insomnia, allergies, nausea	Chronic liver disease, QT prolongation
Hydroxyzine	H1RA	50 mg - 100 mg	2 hours	16.0 ± 3.0 L/kg	14 - 25 hours	Liver; CYP3A4, CYP3A5/urine	Anxiety, pruritus, insomnia, allergies	Elderly, renal and hepatic impairment
Quetiapine	D2/5-HT2A RA	25 mg - 100 mg	1.5 hours	10 ± 4 L/kg	6 - 7 hours	Liver; CYP3A4, CYP2D6/urine and feces	Psychiatric disorders, insomnia (low dose)	Young and elderly

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Levomepromazine	D2/H1/MRA	5 mg - 25 mg	1 - 2 hours (est.)	16 L/kg (est.)	~20 hours	Extensive first-pass; liver	Amnesia, nausea and vomiting, psychiatric disorders, insomnia (low doses)	Elderly
Temazepam	GABA-A PAM	7.5 mg - 30 mg	2 - 3 hours	1.3 - 1.5 L/kg	3.5 - 18 hours	Liver, conjugation/urine	Insomnia	Pregnancy (caution)
Triazolam	GABA-A PAM	0.125 mg - 0.5 mg	1 - 2 hours (est.)	~1 L/kg (est.)	1.5 - 5.5 hours	Liver, conjugation/urine	Insomnia	Elderly
Eszopiclone	GABA-A AG	1 mg - 3 mg	1 hour	89.9 L	6.1 hours	Liver, CYP3A, CYP2C8, CYP2E1/urine	Insomnia	Elderly
Zolpidem	GABA-A SA	5 mg - 10 mg	1.6 hours	0.54 - 0.68 L/kg	2.5 hours	Liver, CYP3A4, CYP1A2, CYP2C9/urine	Insomnia	Elderly, hepatic impairment
Amitriptyline	SERT/NETI	10 mg - 100 mg	2 - 12 hours	1221 ± 280 L	24.65 ± 6.31 hours	Liver, CYP2C19, CYP3A4, CYP2D6/urine	MDD, neuropathic pain, migraine, insomnia	Pregnancy, breastfeeding
Trazodone	SERTI/5-HT2A RA	25 mg - 200 mg	8 hours	0.84 ± 0.16 L/kg	7.3 ± 0.8 hours	Liver, CYP3A4/urine	MDD, insomnia, anxiety	QT prolongation

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Gabapentin	VGCC AI	100 mg - 600 mg	2 - 3 hours	58 ± 6 L	5 - 7 hours	Unchanged	Antiseizure, neuropathic pain, insomnia	Renal impairment
Melatonin	MT1/MT2 AG	1 mg - 5 mg	Variable	~1.2 - 1.5 L/kg (est.)	35 - 50 minutes	Liver, various	Insomnia, circadian rhythm disorders	Elderly, pregnancy (caution)

D2/5-HT2A RA: Antagonist of the D2 dopamine receptors and the 5-HT2A serotonin receptors; D2/H1/MRA: Antagonist of the D2 dopamine receptors, H1 histamine receptors, and muscarinic receptors (M); GABA-A AG: Agonist of the GABA-A receptors; GABA-A PAM: Positive allosteric modulator of the GABA-A receptors; GABA-A SA: Selective agonist of the GABA-A receptors; H1RA: Antagonist of the H1 histamine receptors; MT1/MT2 AG: Agonist of the MT1 and MT2 melatonin receptors; SERT/NETI: Inhibitor of the serotonin (SERT) and norepinephrine (NET) transporters; SERTI/5-HT2A RA: Inhibitor of the serotonin transporter (SERT) and antagonist of the 5-HT2A serotonin receptor; Vd: Volume of distribution; VGCC AI: Inhibitor of voltage-gated calcium channels. This table was generated mostly using DrugBank Open Data.

3. Results and Discussion

In this section, we present the results of the literature review on various aspects of diphenhydramine use for short-term insomnia. Additionally, we provide an analysis of the frequency and agreement among experts regarding each question within the same dimensions explored in the literature.

3.1. Diphenhydramine Pharmacodynamics and Efficacy in Insomnia

Diphenhydramine is a first-generation antihistamine discovered in the 1940s (22). Since its introduction to the market, it has been widely used for the treatment of various allergic conditions, including allergic rhinitis, urticaria, and dermatitis (23). Diphenhydramine antagonizes H1 histamine receptor. Histamine receptors have distinct roles and locations: H1 and H2 receptors are postsynaptic and excitatory, with H1 linked to phospholipase C and found in the hypothalamus and limbic regions, while H2 is coupled to adenylate cyclase and concentrated in the hippocampus, amygdala, and basal ganglia. In contrast, H3 receptors are presynaptic, inhibitory, and primarily located in the basal ganglia, regulating histamine and neurotransmitter release by inhibiting calcium channels (24).

H1 receptors are G-protein-coupled receptors (GPCRs) linked to the Gq pathway, which activates phospholipase C, leading to the inositol triphosphate (IP3) and diacylglycerol (DAG) signaling cascade, ultimately enhancing neural activity. These receptors exhibit high basal activity and induce cortical desynchronization, a state associated with heightened brain activity and wakefulness (25,26). Diphenhydramine acts as a negative allosteric modulator and inverse agonist of H1 receptors, blocking histamine's action at these sites. By inhibiting histamine binding, it reduces neuronal excitation mediated by H1 receptors, decreasing cortical activity and inducing sleepiness (27).

Box 1. Questionnaire regarding the use of diphenhydramine in short-term insomnia.

Section 1: Evaluation of the use of diphenhydramine for insomnia: Efficacy, safety, convenience, and cost of diphenhydramine in the management of insomnia:

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Diphenhydramine is an effective medication for the management of short-term insomnia.
Diphenhydramine is a safe medication for the management of short-term insomnia.
If diphenhydramine were available in the Colombian market, do you consider this medication could be an accessible option for managing short-term insomnia?
Diphenhydramine is a convenient medication for most patients with acute insomnia, regardless of their comorbidities or clinical situations, and therefore has the potential to be marketed as an over-the-counter (OTC) medication for managing short-term insomnia.

Section 2: Type(s) of insomnia where diphenhydramine could be used:

Diphenhydramine is a useful medication for short-term (less than 3 months in duration).
Diphenhydramine is a useful medication for chronic insomnia (more than 3 months in duration).

Section 3: Use of diphenhydramine as a hypnotic-sedative by age group:

Diphenhydramine is an effective and safe medication for children aged 7 and older.
Diphenhydramine is an effective and safe medication for young adults (18 to 65 years) for managing short-term insomnia.
Diphenhydramine is an effective and safe medication for elderly individuals (65 years and older) for managing short-term insomnia.

Section 4: Duration of diphenhydramine treatment for managing insomnia:

The maximum recommended duration for using diphenhydramine as a hypnotic/sedative for short-term insomnia should be around four weeks.

Section 5: Evidence and levels of evidence on the use of diphenhydramine for managing short-term insomnia:

There is a sufficient body of clinical evidence to recommend the use of diphenhydramine in patients with short-term insomnia.
There is a sufficient level of clinical evidence to recommend the use of diphenhydramine in patients with short-term insomnia.

Diphenhydramine can easily cross the blood-brain barrier due to its lipophilic nature. Once in the brain, its sedative effect is enhanced by its ability to interact with other neurotransmitter systems other than the histaminergic. Although its affinity is lower to H1, diphenhydramine can also affect muscarinic acetylcholine receptors, which also play a role in regulating the sleep-wake cycle. Blockade of these receptors contributes to secondary sedative (28). Please refer to Table 2 for a summary of the most important clinical studies evaluating the use of diphenhydramine in the management of insomnia.

Deepening in diphenhydramine evidence for insomnia, Rickels et al. conducted a double-blind, crossover study to evaluate the effect of diphenhydramine on insomnia in adults. They compared 50 mg of diphenhydramine with a placebo in 111 patients with mild to moderate insomnia. Significant improvements were observed in sleep latency and restfulness with diphenhydramine. Furthermore,

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the authors recommended diphenhydramine as an over the counter (OTC) sleep aid in the treatment of temporary mild to moderate insomnia (29).

Similarly, Roth et al. compared the effects of diphenhydramine (50 mg TID) and loratadine (10 mg and 40 mg) in 16 healthy adults. Diphenhydramine significantly reduced sleep latency but was associated with impaired daytime performance. However, it is worth noting that diphenhydramine was used at high doses in this study and the patients took the medication every 8 hours (including two daytime doses) instead of taking the medication at night, before going to sleep (30). Moreover, Boberly et al. recruited healthy young adult volunteers who received 50 to 75 mg of diphenhydramine. Self-reported sleep latency showed mild hypnotic effects, with no significant differences in subjective sleep parameters, and no deterioration in psychomotor performance or rebound insomnia (31).

Schweitzer et al. compared drowsiness and performance levels between two antihistamines, diphenhydramine and cetirizine. The study administered 50 mg of diphenhydramine, 10 mg/day of cetirizine, or a placebo three times daily for three days. Twelve atopic subjects received each treatment in a double-blind Latin square design. The main findings indicated that diphenhydramine, unlike cetirizine, caused acute decreases in alertness and performance. However, tolerance to its sedative effects developed by day three, suggesting that diphenhydramine may be useful for short-term insomnia (32).

Regarding diphenhydramine for insomnia in the elderly, Teutsch et al. compared the hypnotic effects of diphenhydramine and methapyrilene with those of pentobarbital in hospitalized veterans. The main findings indicated that 50 mg or 150 mg of diphenhydramine were no more effective than 60 mg of pentobarbital in treating insomnia, meaning diphenhydramine was no different to pentobarbital to induce sleep (33). Similar findings were obtained by Glass et al. (34). Furthermore, Stewart et al. conducted a randomized, double-blind, crossover clinical trial to test 50 mg of diphenhydramine and 15 mg of temazepam. The main results showed that diphenhydramine reduced sleep latency more effectively than placebo, provided longer sleep duration than temazepam on the fifth night, and both temazepam and diphenhydramine were associated with residual daytime drowsiness (35).

In the case of diphenhydramine use in children with sleep disorders, Russo et al. conducted a double-blind, placebo-controlled trial of diphenhydramine at 10 mg/kg. The main findings showed that diphenhydramine produced a significant reduction in sleep latency and night awakenings, with a marginal increase in sleep duration. Additionally, global weekly evaluations of daytime performance favored diphenhydramine over placebo (36). The pharmacokinetics of diphenhydramine in children (2–17 years) were studied using a weight and age-based dosing schedule (6.25–50 mg). Cmax and AUC increased by 90% to 140% across age groups, with a tmax of 1.5 hours. Oral clearance increased with age, but no maturation effect was seen after allometric scaling. Mild somnolence was the most common side effect (95%) (37).

Sunshine et al,. evaluated the sedative effect of diphenhydramine in a group of 1,295 postpartum women with sleep problems through a controlled, double-blind study. The patients were assigned to receive an oral dose of diphenhydramine hydrochloride (12.5, 25, or 50 mg), mepirizole fumarate (36, 72, or 144 mg), or a placebo. The hypnotic activity was clinically evaluated using both subjective and objective techniques. It was found that both mepirizole and diphenhydramine, at all doses, were effective hypnotics compared to the placebo, based on sleep latency, sleep duration, nighttime awakenings, global assessment, and morning alertness. Although a dose-response relationship was documented, it was also concluded that increasing the dose of these medications within the studied range produced only a minimal increase in efficacy (38).

3.2. Pharmacokinetics of Diphenhydramine

Simons et al. investigated the pharmacokinetics of diphenhydramine in 21 subjects categorized into three groups: children, young adults, and elderly individuals. Participants were administered a diphenhydramine syrup at a dose of 1.25 mg/kg, and blood samples were collected over a 72-hour period. The study revealed that half-life ($t_{½}$), area under the curve (AUC), and mean residence time (MRT) increased with age, whereas clearance and volume of distribution decreased. In contrast, no

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significant differences were observed in maximal plasma concentration (Cmax) or time to maximal concentration (Tmax) across age groups. The authors noted significant variations in t½ and clearance rates between age groups (39). These findings suggest that elderly individuals experience prolonged drug exposure, highlighting the potential need for dose adjustments to achieve an effective and safe therapeutic steady state. The data are summarized in Table 3.

Table 2. Summary of the most important clinical studies evaluating the use of diphenhydramine in the management of insomnia.

Reference	Population	Design	Doses	Efficacy	Safety
Barbone et al. (1998)	200 adults over 65 years old	Double blind, crossover	50 mg	Increased sleep duration, reduced awakenings	Increased daytime sleepiness
Borbély et al. (1988)	10 young and healthy adults	Double blind, crossover	50 mg and 75 mg	No significant differences in subjective sleep parameters compared to placebo	DPH did not cause deterioration in psychomotor performance or rebound insomnia.
Carruthers et al. (1978)	Hospitalized patients with insomnia	Double blind	25 mg, 50 mg and 100 mg	Efficacy in sleep induction at doses of 50 mg and 100 mg	No specific adverse effects are detailed.
Glass et al. (2008)	Elderly with insomnia	Cross-over, randomized	50 mg	Improvement only in the number of awakenings compared to placebo	Similar number of adverse events, one fall reported with temazepam
Kudo y Kurihara (1990)	Adults with insomnia	Not specified	50 mg	Significant reduction in sleep latency	Increased daytime sleepiness
Meuleman et al. (1987)	17 nursing home residents	Double blind, crossover	50 mg	Shorter sleep latency and longer sleep duration than temazepam	Worse performance on neurological tests compared to placebo
Morin et al. (2005)	184 patients with mild insomnia	Multicenter, randomized, placebo-controlled	50 mg (2 times a day)	Improvements in subjective sleep parameters, increased sleep efficiency in the first 14 days	There were no significant residual effects or serious adverse events.

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Moulin et al. (2022)	27 participants	Randomized, double-blind, placebo-controlled, crossover	50 mg	Improvements in sleep debt, no significant improvements in other sleep quality parameters	Significant improvement only in sleep debt, no serious adverse effects
Richardson et al. (2002)	15 healthy volunteers aged 18-50 years	Randomized, double-blind, crossover	50 mg (2 times a day)	Increased drowsiness on day 1, tolerance developed by day 4	Performance decline reversed on day 4
Rickels et al. (1983)	111 patients with mild to moderate insomnia	Double blind, crossover	50 mg	Improved several sleep parameters, patients reported feeling more rested	More side effects reported with DPH
Roehrs et al. (1993)	12 young and healthy men	Double blind, Latin square	50 mg	Significant sedative effects for 6.5 hours, similar to triazolam	Residual sedation for ethanol but not for DPH and triazolam
Roth et al. (2001)	30 subjects with transient insomnia	Randomized, double-blind	50 mg	Reduced sleep latency, improved sleep quality	Daytime sedation reported
Russo et al. (1976)	50 children with sleep disorders	Placebo controlled	10 mg/kg	Significantly reduced sleep latency and night awakenings	Significantly reduced sleep latency and night awakenings
Schweitzer et al. (1994)	12 atopic subjects	Double blind, crossover	50 mg (3 times a day)	Decreased alertness and performance on day 1, tolerance developed by day 3	CNS depression only on the first day
Stone et al. (2000)	27 healthy adults	Double blind, crossover	25 mg and 50 mg	Improvements in sleep latency and total sleep time compared to placebo	Daytime drowsiness and psychomotor effects at some doses
Sunshine et al. (1978)	1295 postpartum women with insomnia	Not specified	Not specified	No specific results are detailed.	No specific results are detailed.
Teutsch et al. (1975)	More than 100 patients in VA hospitals	Comparative with placebo	50 mg y 150 mg	It was not significantly different from pentobarbital for control of insomnia	No significant differences in adverse effects

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Table 3. Pharmacokinetics parameters between age group.

Parameter	Children (8.9 ± 1.7 y.o.)	Young Adults (31.5 ± 10.4 y.o.)	Elderly (69.4 ± 4.3 y.o.)
Weight (kg)	31.6 ± 6.8	70.3 ± 9.9	71.0 ± 11.4
Dose (mg)	39.5 ± 8.4	87.9 ± 12.4	86.0 ± 7.3
Cmax (ng/mL)	81.8 ± 30.2	133.2 ± 37.6	188.4 ± 54.5
Tmax (h)	1.3 ± 0.5	1.7 ± 1.0	1.7 ± 0.8
t½ (h)	5.4 ± 1.8	9.2 ± 2.5	13.5 ± 4.2
Cl (mL/min/kg)	49.2 ± 22.8	23.3 ± 9.4	11.7 ± 3.1
Vdss (L/kg)	17.9 ± 5.9	14.6 ± 4.0	10.2 ± 3.0
Vd (L/kg)	21.7 ± 6.6	17.4 ± 4.8	13.6 ± 6.3
AUC (ng/mL/h)	475 ± 137	1031 ± 437	1902 ± 572
MRT (h)	6.4 ± 1.6	11.3 ± 3.1	14.8 ± 2.8

Cmax: Maximum plasma concentration; tmax: Time to reach maximum plasma concentration; t1/2: Elimination half-life; Cl: Clearance (mL/min/kg); Vdss: Volume of distribution at steady state (L/kg); Vd: Volume of distribution (L/kg); AUC: Area under the concentration-time curve (ng/mL/h); c. Table adapted from: (39).

3.3. Toxic Effects of Diphenhydramine

Diphenhydramine overdose can have toxic effects, such as increased sedation and antimuscarinic effects. Clinical signs and symptoms include drowsiness, hyperpyrexia, mydriasis, fever, flushing, agitation, tremor, dystonic reactions, hallucinations, and electrocardiographic changes on the EKG, such as prolonged QRS complexes and QT intervals, as well as the appearance of a Brugada-like syndrome. High doses, particularly in children, may result in delirium, psychosis, arrhythmias, coma, or cardiovascular collapse. Differential diagnoses for diphenhydramine intoxication include tricyclic antidepressant overdose, acetaminophen overdose, hypoglycemia, and serotonin syndrome (28,40).

Together, there are many studies showing diphenhydramine improves key parameters related to sleep including sleep onset latency and overall sleep quality. In addition, the rapid pharmacokinetic action of diphenhydramine allows for rapid sleep onset, which may be beneficial for patients with insomnia who need immediate intervention to promote rest. Unlike other sedative hypnotics, diphenhydramine has minimal abuse potential and a low risk of residual sedation as a side effect. These characteristics make diphenhydramine an attractive option for the short-term treatment of insomnia, especially in vulnerable populations such as the elderly, provided that the dose and duration of treatment are carefully selected to minimize potential risks.

3.4. Consensus Results

The following are the results of the consensus for each dimension analyzed, results on interquartile range across the rounds are showed in figure 1. In Section 1, "Evaluation of the Use of Diphenhydramine for Insomnia: Efficacy, Safety, Convenience, and Cost," experts evaluated the following statements:

- For question 1, "Diphenhydramine is an effective medication for the management of acute insomnia," the panel of experts unanimously agreed, giving a rating of 5/5 with an interquartile range of 0 (100% agreement). This indicates complete agreement and consensus on the premise. This unanimous consensus highlights a shared confidence in diphenhydramine's efficacy in managing acute insomnia.

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- For question 2, "Diphenhydramine is a safe medication for the management of short-term insomnia," 80% of the experts agreed, demonstrating strong agreement with this premise. The interquartile range was 0.5, reflecting consensus. Frequency analysis revealed that 1 out of 5 experts was neutral, 4 out of 6 partially agreed, and 1 out of 6 fully agreed. These findings suggest a consensus regarding the safety of diphenhydramine for short-term use, although the neutral stance of one expert and partial agreements indicate a need for further exploration of specific safety concerns.

- For question 3, "If diphenhydramine were available in the Colombian market, do you consider this medication could be an accessible option for managing short-term insomnia?" The panel showed full agreement (100%) on this statement, with a median value of 5 and an interquartile range of 0. These results indicate unanimous consensus among the experts, affirming that diphenhydramine is perceived as an accessible option for managing short-term insomnia if made available in the Colombian market. This agreement reflects the experts' confidence in its potential affordability and practicality for patients.

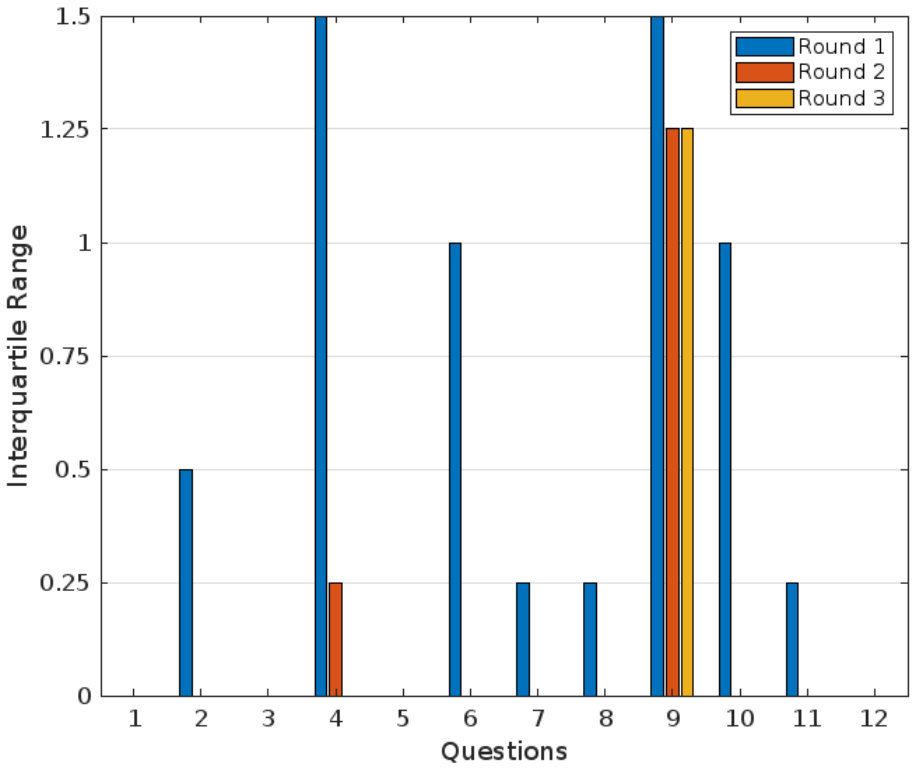

Figure 1. Interquartile range across rounds from expert's panel.

Grouped bars display the interquartile range across three rounds of questions. Questions 1, 3, 5, and 12 have an interquartile range of 0, indicating strong consensus with no variability among expert responses. Questions 2, 6, 7, 8, 9, and 11 show consensus with slight variability. In contrast, questions 4 and 9 did not reach consensus in the first round due to high variability in responses. Question 4 exhibited a decrease in the interquartile range, achieving consensus by round 2. However, question 9 did not reach consensus across all three rounds.

- For question 4, "Diphenhydramine is a convenient medication for most patients with short-term insomnia, regardless of their comorbidities or clinical situations, and therefore has the potential to be marketed as an over-the-counter (OTC) medication for managing short-term insomnia." For this statement, 80% of experts agreed, showing strong agreement but not unanimous consensus. The median value was 4, with an interquartile range of 1.5, indicating slight variability in

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responses. Frequency analysis revealed that: 1 out of 6 experts partially disagreed, 2 out of 6 partially agreed, and 2 out of 6 fully agreed. This variability suggests differing perspectives on the convenience of diphenhydramine, particularly regarding its suitability for patients with comorbidities or diverse clinical situations. The partial disagreement and variability highlight that while there is general agreement, additional research or clarification may be necessary to address specific concerns.

In the second round, consensus was achieved with an interquartile range of 0.25. Frequency analysis revealed that 1 of 5 experts remained neutral, 4 out 5 strongly agreed with the statement. The median value was 3.8, indicating that after the first round and subsequent revisions, experts agreed that diphenhydramine is a convenient medication for most patients with short-term insomnia and has the potential to be marketed as an OTC medication.

In Section 2, "Type(s) of insomnia where diphenhydramine could be used," the results were the following:

- For question 5, "Diphenhydramine is a useful medication for short-term insomnia (less than 3 months in duration)." The median value was 5, and the interquartile range was 0, reflecting unanimous agreement and consensus (100% agreement). Frequency analysis revealed that all 5/5 experts rated this statement with a 5, further affirming the unanimity of the consensus.

- For question 6, "Diphenhydramine is a useful medication for chronic insomnia (more than 3 months in duration)." The median value was 1.6, and the interquartile range was 1, reflecting total disagreement and consensus (0% agreement) within the panel. Frequency analysis showed that 2 out of 5 experts rated it as 1, and 3 out of 5 rated it as 2. This result indicates the panel does not recommend diphenhydramine for chronic insomnia.

In Section 3, "Use of diphenhydramine as a hypnotic-sedative by age group," the results were the following:

- For question 7, "Diphenhydramine is an effective and safe medication for children aged 7 and older." The panel showed a median value of 4.2 and an interquartile range of 0.25, reflecting unanimous agreement and consensus (100% agreement). Frequency analysis revealed that 4 out 5 experts rated it as 4, and 1 out of 5 rated it as 5. This indicates a consistent and strong level of agreement with the statement.

- For question 8, "Diphenhydramine is an effective and safe medication for young adults (18 to 65 years) for managing short-term insomnia." The median value was 4.8, and the interquartile range was 0.25, reflecting unanimous agreement and consensus (100% agreement). Frequency analysis showed that 1 out of 5 experts rated it as 4, while 4 out of 5 rated it as 5, demonstrating a high level of agreement with slight variability.

- For question 9, "Diphenhydramine is an effective and safe medication for elderly individuals (65 years and older) for managing short-term insomnia." The median value was 3, and the interquartile range was 1.5, reflecting no agreement and no consensus (20% agreement). Frequency analysis indicated that 2 out of 5 experts rated it as 2, 2 out of 5 as 3, and 1 out of 5 as 5. This wide distribution of ratings underscores the lack of consensus and varying perspectives on this statement in the first round.

Since consensus was not achieved in the first round, a debrief was conducted on the use of diphenhydramine for elderly individuals. However, rounds two and three showed an interquartile range of 1.25, indicating significant variability in responses, and thus, no consensus was reached. In round two, frequency analysis revealed that 1out of 5 experts partially disagreed, 1 out of 5 remained neutral, and 3 out of 5 partially agreed, with a median value of 3.4. In round three, 1 out of 5 experts partially disagreed, 1 out of 5 experts remained neutral, 2 out of 5 partially agreed, and 1 out of 5

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fully agreed, with a median value of 4.2. Although there was a slight shift toward agreement, consensus was still not achieved.

In Section 4, "Duration of diphenhydramine treatment for managing insomnia," the results were the following:

- For question 10, "The maximum recommended duration for using diphenhydramine as a hypnotic/sedative for short-term insomnia should be around four weeks." The median value was 4.6, and the interquartile range was 1, showing strong agreement and tight consensus (100% agreement). Frequency analysis revealed that 2 out 5 experts rated it as 4, while 3 out of 5 rated it as 5. This indicates a shared belief in limiting the duration of diphenhydramine use, with a small degree of variability.

In Section 5, "Evidence and levels of evidence on the use of diphenhydramine for managing short-term insomnia," the results were the following:

- For question 11, "There is a sufficient body of clinical evidence to recommend the use of diphenhydramine in patients with short-term insomnia." The panel's answers showed a median value of 4.8 and an interquartile range of 0.25, reflecting strong agreement and consensus (100% agreement). Frequency analysis showed that 1 out of 5 experts partially agreed and 4 out of 5 strongly agreed with the statement.

- For question 12, "There is a sufficient level of clinical evidence to recommend the use of diphenhydramine in patients with short-term insomnia." The median value was 4, and the interquartile range was 0, reflecting partial agreement and strong consensus (100% agreement). Frequency analysis revealed that all experts rated this statement as a 4, emphasizing a unified agreement.

4. Discussion

As shown above, several studies have consistently demonstrated that diphenhydramine is effective for the treatment of short-term insomnia (27,29,33,38,41,42). Therefore, it is important to compare its efficacy with that of other medications currently used for insomnia.

One such study, conducted by Stewart in 1987, evaluated the efficacy of diphenhydramine in comparison with temazepam. In the study, diphenhydramine was administered at a dose of 50 milligrams for five consecutive nights, with two nights of placebo between each five-day treatment period. Sleep-related metrics, including sleep quality, sleep onset latency, number of awakenings, and total sleep duration, were assessed to determine the effects of both treatments. The results indicated that diphenhydramine was as effective as temazepam as a hypnotic agent in older adults. Moreover, diphenhydramine significantly improved self-perceived sleep latency, and by the fifth night of treatment, self-reported sleep duration was significantly longer with diphenhydramine than with temazepam. Regarding neurological adverse effects, neither diphenhydramine nor temazepam produced significant impairments (35).

In a similar study, Glass et al. compared the efficacy of temazepam and diphenhydramine, this trial was conducted over a 14-night treatment period. Both medications demonstrated hypnotic efficacy, temazepam was more effective than diphenhydramine when compared with placebo at the doses tested. The authors noted that this difference was offset by the increased risk of falls associated with temazepam use.

When comparing diphenhydramine with a non-benzodiazepine hypnotic, Katayose et al. evaluated the effects of diphenhydramine (50 milligrams), ketotifen (1 milligram), and the Z-drug zolpidem (10 milligrams). This study was a randomized, double-blind, placebo-controlled trial in which overall sleep quality, daytime sleepiness, and psychomotor performance were assessed. Among the most significant findings, diphenhydramine and zolpidem produced comparable effects on overall sleep quality. However, diphenhydramine significantly prolonged rapid eye movement (REM) sleep latency and reduced the percentage of REM sleep. Regarding daytime effects, diphenhydramine showed a tendency to increase next-day sedation and led to a significant reduction

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in psychomotor performance. The authors concluded that both diphenhydramine and ketotifen significantly increased subjective and objective sleepiness while significantly impairing next-day psychomotor performance, resulting in clinically relevant sedative–hypnotic carryover effects (43). Some other studies have shown that diphenhydramine can impact next day post administration performance (44)

Regarding safety, Erb and Bschor conducted a systematic review of the literature from 1972 to 2012 and reported a clinical case providing evidence of the addictive potential of diphenhydramine. Their findings highlight the need for caution, particularly in patients with a history of substance use disorders (45). Other studies have also emphasized the importance of careful use of diphenhydramine (46). There is similar preoccupant scenario as there is substantial evidence demonstrating the addictive potential of benzodiazepines and Z-drugs (47,48). Overall, the long-term use of hypnotic agents carries a significant risk of dependence. While benzodiazepines and Z-drugs have been extensively studied in this regard, fewer studies have addressed the potential for diphenhydramine dependence.

The expert consensus highlighted several points in favor of diphenhydramine. There was strong agreement regarding its efficacy, safety, and short duration of action, supporting its use exclusively for short-term insomnia. However, there was substantial disagreement regarding its use in chronic insomnia and in elderly. These concerns align with available evidence, as the effectiveness of diphenhydramine has only been demonstrated for short-term-insomnia. Furthermore, in older adults, all medications, including diphenhydramine, should be prescribed with caution due to potential risks. Regarding its availability as an over-the-counter medication, its recent approval by the Food and Drug Administration represents a significant milestone (49). Diphenhydramine is widely accessible and affordable, making it a practical option for many individuals.

5. Conclusions

Diphenhydramine in dose of 50 mg before sleep has been shown to be effective for short-term insomnia and can be used safely in most individuals, though caution is advised in older adults. When compared to other medications, diphenhydramine demonstrates a similar efficacy profile; however, next-day side effects, such as residual sedation and cognitive impairment, are frequently reported. The available evidence and expert consensus support its use as an OTC option for short-term insomnia. Nevertheless, patients should always be informed about its potential adverse effects, including next-day drowsiness and impaired psychomotor performance. Additionally, while the risk of dependence is lower than that of other hypnotics, its addictive potential should not be overlooked. Given these factors, diphenhydramine remains a viable short-term treatment, provided that its risks and benefits are carefully considered.

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