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REVIEW ARTICLE

Chlorpheniramine, an Old Drug with New Potential Clinical Applications: A Comprehensive Review of the Literature

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Abstract: Chlorpheniramine Maleate (CPM), also known as chlorphenamine, is a potent alkylamine first-generation H1 antihistamine that has been used since the 1950s. CPM is a widely popular drug commonly used to treat allergic conditions, given its antihistamine properties. Although mainly used in over-the-counter treatment for cough and colds, various studies discuss a wide range of CPM's clinical uses, such as treating asthma, plasma cell gingivitis, chronic urticaria, and depression, among others. This antihistamine is usually taken orally; however, intravenous, intramuscular, and subcutaneous routes have been documented. Intranasal routes of this drug have recently been explored, especially due to its antiviral properties against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Accordingly, given CPM's extensive medical and safety profile, the present review explores this versatile drug's current and potential clinical applications. Although it is widely used mainly for treating common colds and aforementioned allergic conditions, CPM can be used for other clinical indications. The repurposing of CPM for other clinical indications, such as COVID-19, needs to be further explored through more extensive studies.

Keywords: Chlorpheniramine, allergy, rhinitis, urticarial, viral infections, intranasal route.

1. INTRODUCTION

Chlorpheniramine Maleate (Fig. **1**), also known as chlorphenamine, is a potent alkylamine first-generation antihistamine H1 blocker [1, 2]. This drug was patented in 1948 [1] and was introduced to clinical practice in the 1950s and has been a popular and widely available drug ever since [3]. However, CPM was approved by the US Food and Drug Administration (FDA) in 1981 [1]. With a potent antiallergic property, CPM helps in alleviating sneezing, nasal congestion, nasal discharge, itching, and rashes. Thereby, it is commonly prescribed for symptomatically treating allergic conditions mediated by histamine releases, such as allergic rhinitis, urticaria as well and common cold [1, 2, 4].

CPM is widely available as an over-the-counter medication for cough and cold in the pediatric age group [5, 6]. Also, according to The American College of Obstetricians and Gynecologists, CPM is the drug of choice for treating allergic conditions during pregnancy due to its safety and efficacy. Hence, this drug is categorized by the FDA as a category B drug [7]. However, CPM crosses the blood-brain barrier, causing sedative effects classically seen in using first-generation H1 blockers. Hence, it should be used cautiously amongst the elderly as the sedative and anticholinergic effects of CPM tend to be more pronounced in this age group [8].

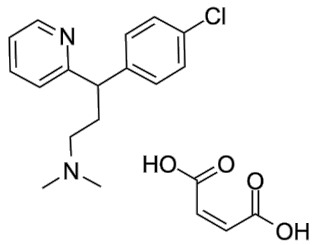

Fig. (1). Structure of the chlorpheniramine maleate.

CPM is mainly taken orally in the form of tablets [1], but other routes of administration include intravenous, intramuscular, and subcutaneous routes [1]. The benefits of administering CPM *via* nasal spray are currently under investigation for the indication of allergic rhinitis and, owing to its potent antiviral properties, against the SARS-CoV-2 virus [9, 10]. Amidst the COVID-19 pandemic, old and cost-effective drugs like CPM, which are readily available in the market, need to be further explored.

Thereby, in this article, we aim to discuss pharmacology, biological properties, clinical applications, and ongoing ac-

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tive clinical trials studying CPM to explore further and better understand the drug. Additionally, prospective clinically relevant applications of CPM are also discussed.

2. PHARMACOLOGY OVERVIEW

CPM is a tertiary amino acid compound that is substituted at the third position by a pyridin-2-yl group and a p-chlorophenyl group, of which the hydrogen ions are attached to the nitrogen, and replaced by methyl groups. It acts as an H1-receptor antagonist, a serotonin uptake inhibitor, an antidepressant, and an anti-allergic agent [11]. Following oral administration, CPM is absorbed by the small intestine with a bioavailability (F) of 25-50%, displaying a peak serum concentration between 1-6 hours [1] and a half-life ranging between 2–43 hours [1, 12, 13] due to its variable first-pass hepatic metabolism [12]. The half-life of CPM increases in the presence of renal dysfunction and tends to be shorter in children [1]. Interestingly, food delays the absorption of CPM but does not affect its function [1]. CPM is distributed mainly in the liver, lung, kidneys, and brain [1] and extensively metabolized by the cytochrome p450 enzyme in the liver [13]. The route of excretion of CPM, including its metabolites (Desmethylchlorpheniramine and Didesmethylchlorpheniramine), is mainly through the kidneys while acidic urine pH enhances urinary excretion of the main drug [13, 14]. Following intravenous administration, the bioavailability is 100%, while the drug follows a similar distribution and metabolism pattern to oral administration [1].

Alternatively, studies have shown that CPM could also be used intranasally [9, 10, 15, 16]. In addition, in a study by Van Toor, the systemic bioavailability of this drug at high doses (8 mg and higher) through intranasal administration was found to be comparable to that of the tablet [16]. Various studies utilized CPM in spray form [9] and intranasal gel form [17] and showed favorable outcomes as it was well-tolerated and exhibited safe clinical profiles. Table (**1**) lists the route of administration of CPM for various conditions.

3. PHARMACOLOGICAL PROPERTIES OF CHLORPHENIRAMINE

3.1. Anti-allergy/Antihistamine Effects

H1 Histamine receptors are expressed on mast cells, which play a central role in triggering an allergic response to an allergen in susceptible individuals. Degranulation of mast cells occurs in the early phase, causing the release of histamine, leading to numerous changes in the body. It mainly brings about dilation of blood vessels, causing increased levels of vascular permeability leading to tissue edema, smooth muscle contraction, and stimulation of nociceptive nerves. All of these histamine-dependent effects are seen in allergic diseases, such as asthma, allergic rhinitis,

Table 1. Routes of administration of CPM for various conditions.

Condition	Potential Routes of Administration
Asthma	Intranasal spray
Seasonal allergic rhinitis/ Hay fever	P.O., Intranasal spray
Chronic idiopathic urticaria	P.O.
Motion sickness	P.O.
Depression, panic disorder	P.O.
Plasma cell gingivitis	Topical
Malaria	P.O.
Influenza A and B	Not enough studies to determine the potential route of administration
Common Cold	Intranasal spray
COVID-19	Intranasal spray
Postoperative Emergence Agitation	I.V.

Abbreviations: P.O., Per os; I.V., Intravenous.

urticaria, allergic conjunctivitis, and atopic dermatitis [18-20].

CPM belongs to the first generation of H1 antihistamines, primarily used for the symptomatic treatment of allergy-mediated diseases. Competitive binding of H1 receptor antagonists to the target receptors inhibits mast cell degranulation, thereby blocking the histamine release [21, 22]. Moreover, allergic diseases are also commonly associated with excess eosinophils. Degranulation of eosinophils causes the release of various inflammatory mediators, such as cytokines and granular proteins. According to a study, CPM stimulated c-Jun N-terminal kinase (JNK), resulting in the upregulation of eosinophilic apoptosis. Stimulation of JNK also countered the effect of IL-5, resulting in a reduced life span of eosinophils [23]. Based on the studies mentioned earlier, CPM demonstrates both direct and indirect anti-allergy properties by blocking histamine as well as modulating the cells that participate in the allergic response, respectively.

3.2. Anti-Inflammatory/Decongestant Effects

AQP5, a type of aquaporin, is primarily present in the submucosal acinar cells and the columnar cells of the apical membrane of the nasal epithelium. It plays a significant role in regulating fluid transport and glandular secretion, which, along with the ciliary function, forms the first line of defense against the pathogens across the airway. Prior studies have established that histamine interferes with the functioning of AQP5 by instigating the nuclear factor -κB (NF-κB) pathway and stimulating the cyclic adenosine monophosphate-responsive element-binding protein (p-CREB) [24]. Downregulation of this aquaporin has been previously linked to the excessive and thick production of mucus and disruption of the nasal epithelium's ciliary function, causing decreased bacterial clearance, which is usually succeeded by an infection that triggers the inflammatory response [24]. Moreover, NF-κB is known to play a central role in triggering the cascade of inflammatory reactions by bringing about upregulation of the proinflammatory genes, activation of cytokines chemokines, adhesion molecules, activation of dendritic cells, macrophages, and T cells, induction of apoptotic pathways, and regulation of cell proliferation [25] A recent study demonstrated the anti-inflammatory effect of CPM by demonstrating its inhibitory effect on the NF-κB pathway. In addition, the H1 antagonistic effect of CPM significantly enhanced the activity of p-CREB. Both these factors, in turn, attenuate the downregulation of AQP5 expression, thereby suppressing hypersecretion of mucus and avoiding the flare of the inflammatory reactions [24].

3.3. Analgesic Effect

CPM has demonstrated a potential role in regulating the pathway responsible for the manifestation of symptoms of migraine. One of the preclinical studies has shown a positive correlation between CPM use and reduction in increased sensitivity to the pain afflicted due to the inflammation of the trigeminovascular pathway due to histamine's activation. However, CPM was not effective in subsiding the pain associated with migraines [26]. Another preclinical report was conducted to examine the effect of CPM combined with other pain medications generally used to treat headaches, such as acetylsalicylic acid (ASA), acetaminophen (paracetamol, PAR), and caffeine (CAF). This study demonstrated that adding CPM synergistically increased the analgesic effects of other pain medications [27].

Consequently, as an extension to the previous trial [27], a randomized controlled trial was conducted in Romania to evaluate the advantages of adding CPM to study ASA, PAR, and CAF. It was documented that the combination of medications and CPM was much more efficient in reducing migraine-associated pain than the control group, who received a combination without CPM. In addition, it also helped in minimizing the side effects of other pain medications, which are normally associated with their use [28].

3.4. Anticholinergic Effects

Prior *in-vitro* studies demonstrated the anticholinergic effects of CPM and brompheniramine on the nasal mucosa by blocking the overactive cholinergic parasympathetic reflexes, contributing to glandular hypersecretion associated with allergic rhinitis [29]. Also, according to a meta-analysis, CPM and other H1 antagonists are superior to placebo in blocking common cold symptoms, such as sneezing and rhinorrhea [30]. An investigation was carried out to study the efficacy of this drug in preventing bladder discomfort, followed by post-surgical insertion of the urinary catheter, which arose due to stimulation of muscarinic receptors in the bladder. CPM infusion was used after administering general anesthesia in patients who underwent surgery for the resection of bladder tumors. Huh *et al.* (2021) found lower occurrences of bladder discomfort in patients treated with CPM [31]. A prospective cohort study investigated the association of chronic use of anticholinergics with an increased risk of developing dementia in the elderly. Incidentally, CPM was listed among the most commonly used drugs that inadvertently exert anticholinergic effects [32]. However, CPM demonstrated a weaker anticholinergic response compared to other antihistamines as reported in a functional bioassay, and hence has a low probability of inducing such side effects [33].

3.5. Mucoregulatory and Antitussive Effects

Back in the 1980s, a randomized, double-blind trial demonstrated substantial mucociliary clearance and lower weight of nasal mucus secretions in the group of patients treated with CPM [34]. Anti-inflammatory effects exerted by CPM attenuated down-regulation of AQ5 expression in the nasal mucosa, which, in turn, facilitated improved mucociliary clearance [24, 29] as the anticholinergic effect might be responsible for the reduction in the mucus secretion [24, 29]. Moreover, some scientists believe that CPM might possess an antitussive property to some extent. This hypothesis is based on a study that demonstrates brompheniramine's antitussive properties, closely associated with CPM, but the anticholinergic effects are implicated [35].

3.6. Antiviral Effects

Interestingly, the SARS-CoV-2 virus triggers the degranulation of mast cells, causing the release of hista-

mine, actively contributing to the inflammatory response of the lungs [36]. Additionally, under the influence of histamine, stimulation of the Nf-κB mediated inflammatory pathway led to enhanced replication and multiplication of the SARS-CoV-2 in the epithelial cells of the lungs [36]. Prior studies have demonstrated the efficacy of H1 antagonists in inhibiting viral activity by suppressing the Nf-κB-mediated inflammation [37]. Based on these principles, preclinical studies were carried out that successfully demonstrated CPM's virucidal properties against the SARS-CoV-2 virus [38]. CPM has displayed strong antiviral activity against SARS-COV-2 in two independent studies [38, 39]. It inhibits SARS-COV-2 by blocking viral adsorption (the viral entry into the host cells) [40, 41] and also exerts antiviral activity by interfering with SARS-CoV-2 spike protein interactions *via* angiotensin-converting enzyme 2 (ACE2) receptor and sigma-1 receptor binding blockade [42].

Likewise, CPM has shown antiviral activity against several Influenza virus strains, including the avian influenza virus H7N9, influenza A, and influenza B virus. CPM also helps in reducing the viral load by inhibiting the viral entry into the host cell. However, the exact mechanism remains obscure and warrants further research [40]. These studies demonstrated the potential of CPM in diminishing the viral load, which would be highly beneficial in reducing the disease severity and duration of the course of the disease. This might help in reducing the morbidity and mortality associated with SARS-CoV-2 and influenza.

A randomized controlled, double-masked clinical trial for experimental rhinovirus colds was conducted using a combination antiviral-antimediator treatment with intranasal interferon (IFN)-alpha 2b plus oral CPM (12 mg extended-release) and ibuprofen (400 mg) given every 12 h for 4.5 days to 150 health adults. They found that the mean total symptom score was reduced by 33%-73% during the treatment period compared to placebo. Gwaltney *et al.* concluded that the combination of antiviral properties of IFN-alpha 2b with CPM and ibuprofen could be an effective symptom relief treatment for common colds [43].

3.7. Antiplasmodial Effects

Researchers studied CPM's effect when used concurrently with antimalarial drugs, such as chloroquine, mefloquine, quinine, or pyronaridine, on multidrug-resistant strains of Plasmodium *in vitro*. CPM rendered an additive effect to the antiplasmodial activity of all the tested drugs except artesunate [44]. Similarly, the combined effect of CPM and a combination of azithromycin and chloroquine were found to be highly effective against chloroquine-resistant strains of Plasmodium (PfCRT mutant strains), according to a preclinical study [45]. Back then, the mechanism of the synergistic effect was unknown, but recent investigations have established that the PfCRT gene is a chloroquine-resistant transporter protein found predominantly in the digestive vacuole of the Plasmodium. Upregulation of PfCRT causes Plasmodium to develop resistance toward chloroquine. It was found that CPM, to some extent, enabled re-sensitization of the chloroquine-resistant Plasmodium to chloroquine by suppressing the PfCRT gene. Moreover, CPM has been speculated to exert a mild inherent antiplasmodial effect [46].

3.8. Serotonergic Effects

The deficiency of neurotransmitters serotonin and norepinephrine plays a significant role in the pathophysiology of several mental health disorders, such as anxiety, panic attack, and major depressive disorder [47]. CPM is structurally similar to selective serotonin reuptake inhibitors (SSRI), which are widely used in the clinical setting to treat previously mentioned mental health disorders [48]. Presumably, the mechanism by which CPM alters the serotonergic pathway is the same as SSRIs by blocking the serotonin reuptake and inhibiting the serotonin transporter protein, thus promoting serotonergic activity [47, 48]. However, a larger clinical trial needs to be conducted to assess whether CPM can be utilized as an SSRI or adjunct to an SSRI to treat mental disorders.

3.9. Sedative Effects

First-generation H1 antihistamines are highly lipophilic, which facilitate the easy crossing of the blood-brain barrier, thereby leading to daytime drowsiness, a diminished span of attention, and sedation as H1 receptors play a significant role in the regulation of the circadian rhythm [49, 50]. CPM is less sedative than diphenhydramine [51]. However, it is more effective in inducing sedation than the other antihistamines (fexofenadine, epinastine, ebastine, loratadine, terfenadine, cetirizine, olopatadine, bepotastine, azelastine, mequitazine, cetirizine, astemizole, oxatomide, diphenhydramine, hydroxyzine, ketotifen) [50].

4. THERAPEUTIC APPLICATIONS OF CHLORPHENIRAMINE (CURRENT AND POTENTIAL)

CPM was approved by the FDA in 1981 with an indication for hay fever, rhinitis, urticaria, and asthma [40]. There are, however, other emerging indications that warrant further exploration. In this section, we discuss various FDA-approved clinical applications of CPM and other potential applications currently being studied.

4.1. Asthma

A well-noted clinical application of CPM is in the treatment of asthma. This drug induces bronchodilation of the alveolus, particularly during the resting period, by acting against the circulating histamine in asthmatic patients, contributing to the increased resting bronchomotor tone and its anticholinergic properties. In addition, giving the drug *via* aerosol route causes fewer side effects and faster onset of action [22], albeit used for exercise-induced asthma. Steroid-dependent patients can tolerate CPM without experiencing life-threatening side effects [52].

4.2. Seasonal Allergic Rhinitis/Hay Fever

In patients with seasonal allergic rhinitis, common complaints include nasal congestion, sneezing, clear rhinorrhea, nasal pruritus, headaches, and facial pain [53, 54]. Standard over-the-counter therapy involves antihistamines, like CPM and nasal decongestants, which often do not completely relieve these symptoms [54]. In a multicenter, randomized, double-blind, 30-day pilot study, it was concluded that the intranasal use of CPM effectively improved symptoms of

allergic rhinitis with minimal side effects. A major difference between the visual analog scale (VAS) and rhinitis daily symptoms score was noted in participants given CPM compared to placebo after five days of use [9]. Based on the recommendations by the American Academy of Family Physicians, aside from allergen avoidance and patient education, intranasal corticosteroid remains to be the initial treatment for allergic rhinitis with symptoms affecting the quality of life. In patients with mild intermittent symptoms, second-generation are preferred over first-generation antihistamines due to their less sedating effect and better adverse effect profile. However, first- and second-generation antihistamines have been known to be efficacious in relieving the histamine-mediated symptoms associated with allergic rhinitis [55]. In a study by Sur, DK (2010), it was suggested that CPM can still be considered to treat allergic rhinitis despite the preference for second-generation antihistamines [56].

4.3. Chronic Idiopathic Urticaria

Chronic idiopathic urticaria, also known as chronic spontaneous urticaria, is mainly identified with the development of multiple red, itchy, raised wheals or hives. In a multicenter randomized, double-blind study, CPM combined with cimetidine, an H2 antagonist, showed beneficial effects when used for chronic idiopathic urticaria with no identifiable external cause. The appearance of new wheals and severity of itching showed marked improvement without any significant side effects in individuals treated with the CPM/cimetidine combination [57].

4.4. Motion Sickness

Given that most treatments for motion sickness have sedative effects, CPM was also studied as a possible treatment for motion sickness. In a placebo-controlled, double-blind, dose-ranging trial, researchers concluded that a significant sedative effect was found in patients given high doses of CPM. They also concluded that CPM did not affect cognitive testing performance and thus recommended CPM as a potential candidate for relieving motion sickness symptoms [58].

4.5. Depression, Panic Disorder

As early as 1969, first-generation antihistamines were noted to have SSRI properties, which were discovered by Nobel Laureate Professor Arvid Carlsson. CPM was one of the drugs with the property to block 5-HT. However, it was also found to have an effect on the noradrenaline neurons. Given these properties, Hellbom suggested that CPM might be one of the first, well-tolerated, non-cardio-toxic antidepressants [3].

4.6. Plasma Cell Gingivitis

Plasma cell gingivitis is a rare condition characterized by disseminated infiltration of plasma cells into the subepithelial connective tissue. In practice, it is typically seen as diffuse erythema and edematous swelling of the gingiva with a sharp demarcation along the mucogingival border [59]. The typical course of treatment usually involves the removal of the offending agent. In a case study, it was hypothesized that as an H1 blocker, CPM would be able to antagonize the H1 receptors expressed by gingival fibroblasts. The subject was instructed to use topical CPM 25 mg/day for 10 days and was noted to have no recurrence even after ten months. The researchers concluded that the topical application of CPM could be a potential treatment option for plasma cell gingivitis [60].

4.7. Malaria

A study was conducted to assess the outcome in patients with uncomplicated malaria, by treating one group of patients with amodiaquine alone and the other with a combination of amodiaquine and CPM. A total of 103 children were included in the study. The group treated with combination therapy demonstrated better results as compared to the one treated with amodiaquine alone. CPM resulted in the enhanced antimalarial effect of amodiaquine by prolonging the lifespan of amodiaquine, an effect that can be employed in clinical practice for better outcomes [61].

4.8. Influenza A and B

Researchers conducted a study to identify chemical compounds with broad antiviral activity against divergent influenza viruses. It was found that two antihistamines, carbinoxamine maleate, and CPM maleate, exhibited potent inhibitory activity against various strains of influenza A and one strain of influenza B virus. These antihistamines worked by inhibiting the influenza virus by targeting the early stage of the virus life cycle and its entry into the host cell. The results of this study suggested that both of these drugs could be potentially included in the treatment and prophylaxis of influenza [40].

4.9. Common Cold

The anti-histamines CPM and diphenhydramine hydrochloride are widely used for the symptomatic treatment of seasonal allergic rhinitis. Although the exact role of histamine in the pathogenesis of infectious rhinitis is not clear, it seems to play a role in the pathogenesis of nasal symptomatology in rhinovirus colds [62]. Accordingly, CPM 0.5 mg was found to significantly inhibit histamine-induced tickling ($p < 0.01$), sneezing ($p = 0.01$), and discharge ($p < 0.01$) when used as a topical intranasal spray [15]. However, antihistamine-analgesic-decongestant combinations have some general benefits in adults and older children, but there is no evidence of effectiveness in young children [63].

4.10. COVID-19

Recently, antihistamines, including CPM, have been proposed as one of the drugs for the treatment of COVID-19 [36]. It has been studied that in patients who have minimal to moderate morbidity and mortality risk from COVID-19, the use of CPM nasal spray is associated with significant improvement in symptoms and a 50% reduction in the clinical course of the disease [10]. Moreover, in a retrospective study, treating COVID-19 patients with CPM and azithromycin during the early course of the disease generated positive clinical outcomes [64].

Fig. (2). Current and potential clinical applications of CPM. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. Ongoing active clinical trials studying the use of CPM.

NCT	Intervention/Treatment	Condition	Phase	Status	Location
NCT04688736	Drug: Placebo Drug: CPM	Allergic Transfusion Reaction	Phase 2	Not yet recruiting	Tianjin, China
NCT04790487	Drug: CPM Drug: Placebo	Allergic Rhinitis Nasal Congestion	Phase 2 Phase 3	Active, not recruiting	South Miami, Florida, United States,
NCT04937101	Drug: CPM-Codeine	Inflammatory Skin Disease	Not Applicable	Recruiting	Zhejiang, China
NCT03940391	Drug: CPM and midazolam Drug: Midazolam	Endoscopy	Not Applicable	Enrolling by invitation	Seoul, Republic of Korea

4.11. Postoperative Emergence Agitation

Emergent agitation after general anesthesia is a common complication in adult nasal surgery, with an incidence of 22.2% - 55.4% [65, 66]. A prospective comparative double-blind study was done by Abdelrahman *et al.*, which studied the effect of preemptive administration of CPM IV 30 minutes prior to induction of anesthesia. The study included 90 adult patients undergoing functional endoscopic sinus surgery procedures for chronic sinusitis with bilateral postoperative nasal packing. They concluded that patients given the test dose were noted to have reduced incidence and severity of postoperative agitation as measured by their Richmond Agitation and Sedation Scale scores at 0, 5, 10, 15, and 20 min postoperatively.

The findings of this study lead to a hypothesis that CPM reduces postoperative agitation and nasal congestion causing the obstruction, owing to its histamine blocking and sedative effects, respectively. They further concluded that a single dose of CPM preoperatively is an effective medication that may prevent or reduce the severity of emergence agitation with minimal cardio-respiratory depression [66]. The uses of CPM have been summarized in Fig. (**2**).

4.12. Premedication for Anticancer Drugs

In order to prevent possible infusion reactions associated with administering anticancer drugs, often patients are premedicated with glucocorticosteroids and antihistamines [67, 68]. It has been shown that IV chlorpheniramine maleate in combination with dexamethasone is sufficient in the prevention of allergic and hypersensitivity reactions without the use of diphenhydramine (commonly employed) [69]. Given the fact that diphenhydramine could act as a weak anticholinergic agent with the possibility of inducing mydriasis and glaucoma episodes, cancer patients with closed-angle glaucoma can be given chlorpheniramine maleate as a safe alternative [70].

5. ACTIVE CLINICAL TRIALS

Various clinical trials are being conducted across the globe to evaluate the use of CPM in a broader range of clinically relevant conditions. A non-comprehensive list of the active trials has been summarized in (Table **2**) [71-74].

CONCLUSION

CPM is one of the oldest first-generation H1 antihistamines. Given its extensive clinical profile, it has been found to have a wide array of medicinal properties and can be used for various indications. Although it is widely used mainly for treating common colds and aforementioned allergic conditions, CPM can be used for other clinical indications. The repurposing of CPM for other clinical indications, such as COVID-19, needs to be further explored through more extensive studies.

LIST OF ABBREVIATIONS

CPM	=	Chlorpheniramine Maleate
FDA	=	US Food and Drug Administration
NF-κB	=	Nuclear factor -κB
PfCRT mutant strains	=	Chloroquine-resistant Strains of Plasmodium
SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2
SSRI	=	Selective Serotonin Reuptake Inhibitors
VAS	=	Visual Analog Scale

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Rumore MM. Clinical pharmacokinetics of chlorpheniramine. Drug Intell Clin Pharm 1984; 18(9): 701-7. http://dx.doi.org/10.1177/106002808401800905 PMID: 6383755

[2] Hall EJ, Hall GJ. Chlorpheniramine. Encyclopedia of Toxicology. Elsevier 2014; pp. 923-4. http://dx.doi.org/10.1016/B978-0-12-386454-3.00711-9

[3] Hellbom E. Chlorpheniramine, Selective Serotonin-Reuptake Inhibitors (SSRIs) and Over-The-Counter (OTC) treatment. Med Hypotheses 2006; 66(4): 689-90. http://dx.doi.org/10.1016/j.mehy.2005.12.006 PMID: 16413139

[4] Xu W, Xia S, Pu J, *et al.* The antihistamine drugs carbinoxamine maleate and chlorpheniramine maleate exhibit potent antiviral activity against a broad spectrum of influenza viruses. Front Microbiol 2018; 9(NOV): 2643. http://dx.doi.org/10.3389/fmicb.2018.02643 PMID: 30459739

[5] Woo T. Pharmacology of cough and cold medicines. J Pediatr Health Care 2008; 22(2): 73-9. http://dx.doi.org/10.1016/j.pedhc.2007.12.007

[6] Isbister GK, Prior F, Kilham HA. Restricting cough and cold medicines in children. J Paediatr Child Health 2012; 48(2): 91-8. http://dx.doi.org/10.1111/j.1440-1754.2010.01780.x PMID: 20598066

[7] Kar S, Krishnan A, Preetha K, Mohankar A. A review of antihistamines used during pregnancy. J Pharmacol Pharmacother 2012; 3(2): 105-8. http://dx.doi.org/10.4103/0976-500X.95503 PMID: 22629082

[8] Slavin RG. Treating rhinitis in the older population: Special considerations. Allergy Asthma Clin Immunol 2009; 5(1): 9. http://dx.doi.org/10.1186/1710-1492-5-9 PMID: 20016692

[9] Sanchez-Gonzalez M, Rizvi SA, Torres J, Ferrer G. A Randomized controlled pilot trial to test the efficacy of intranasal chlorpheniramine maleate with xylitol for the treatment of allergic rhinitis. Cureus 2021; 13(3): e14206. http://dx.doi.org/10.7759/cureus.14206 PMID: 33816038

[10] Torres J, Go CC, Chohan F, Camacho L G, Sanchez-Gonzalez MA, Ferrer G. Chlorpheniramine maleate nasal spray in COVID-19 patients: Case series. J Clin Exp Pharmacol 11(1): 275-6.

[11] Serotonin | C10H12N2O Available from: https://pubchem.ncbi.nlm.nih.gov/compound/serotonin (Accessed on May 20, 2022).

[12] Walsh GM. Antihistamines (H1 receptor antagonists). Side Effects of Drugs Annual 2012; 34: 271-6. http://dx.doi.org/10.1016/B978-0-444-59499-0.00015-5

[13] Swanson-Biearman B. Chlorpheniramine. Encyclopedia of Toxicology. Elsevier 2005; pp. 577-8. http://dx.doi.org/10.1016/B0-12-369400-0/00226-X

[14] Aronson JK. Chloroquine and hydroxychloroquine. Meyler's Side Effects of Drugs, 16th ed; Elsevier 2006; pp. 722-30. http://dx.doi.org/10.1016/B0-44-451005-2/00710-5

[15] Kirkegaard J, Secher C, Borum P, Mygind N. Inhibition of histamine-induced nasal symptoms by the H1 antihistamine chlorpheniramine maleate: Demonstration of topical effect. Br J Dis Chest 1983; 77(2): 113-22. http://dx.doi.org/10.1016/0007-0971(83)90017-7 PMID: 6347231

[16] Van Toor BS, Buchwald A, Stengele E, Trenk D, Gercek C, de Mey CM. Systemic bioavailability of nasally applied chlorphenamine maleate (0.4% nasal spray) relative to tablets administered perorally. Int J Clin Pharmacol Ther 2001; 39(4): 173-8. http://dx.doi.org/10.5414/CPP39173 PMID: 11332874

[17] Kumar M, Upadhayay P, Shankar R, Joshi M, Bhatt S, Malik A. Chlorpheniramine maleate containing chitosan-based nanoparticle-loaded thermosensitive *in situ* gel for management in allergic rhinitis. Drug Deliv Transl Res 2019; 9(6): 1017-26. http://dx.doi.org/10.1007/s13346-019-00639-w PMID: 31049842

[18] Mandola A, Nozawa A, Eiwegger T. Histamine, histamine receptors, and anti-histamines in the context of allergic responses. LymphoSign Journal 2019; 6(2): 35-51. http://dx.doi.org/10.14785/lymphosign-2018-0016

[19] Thangam EB, Jemima EA, Singh H, *et al.* The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. Front Immunol 2018; 9(8): 1873. http://dx.doi.org/10.3389/fimmu.2018.01873 PMID: 30150993

[20] Patel RH, Mohiuddin SS. Biochemistry, Histamine. StatPearls Publishing 2021.

[21] Baroody FM, Naclerio RM. Antiallergic effects of H1-receptor antagonists. Allergy 2000; 55 Suppl 6(64): 17-27. http://dx.doi.org/10.1034/j.1398-9995.2000.00803.x

[22] Chugh J, Yadav YR, Kulkarni HS, Maheshwari S. The effect of aerosolized chlorpheniramine maleate on exercise induced bronchospasm and gas exchange in asthmatics. J Assoc Physicians India 2020; 68(4): 21-5. PMID: 32610841

[23] Hasala H, Moilanen E, Janka-Junttila M, Giembycz MA, Kankaanranta H. First-generation antihistamines diphenhydramine and chlorpheniramine reverse cytokine-afforded eosinophil survival by enhancing apoptosis. Allergy Asthma Proc 2007; 28(1): 79-86. http://dx.doi.org/10.2500/aap.2007.28.2961 PMID: 17390763

[24] Chang YL, Lin CS, Wang HW, Jian KR, Liu SC. Chlorpheniramine attenuates histamine-mediated aquaporin 5 downregulation in human nasal epithelial cells *via* suppression of NF-κB activation. Int J Med Sci 2017; 14(12): 1268-75. http://dx.doi.org/10.7150/ijms.21573 PMID: 29104484

[25] Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther 2017; 2: 17023. http://dx.doi.org/10.1038/sigtrans.2017.23 PMID: 29158945

[26] Yuan H, Silberstein SD. Histamine and migraine. Headache 2018; 58(1): 184-93. http://dx.doi.org/10.1111/head.13164 PMID: 28862769

[27] Blendea D, Mircioiu I, Sandulovici R, *et al.* Non-inferiority study concerning a new analgesic formulation *versus* an acetylsalicylic acid, acetaminophen and caffeine fixed combination in patients with headache. Ther Pharmacol Clin Toxicol 2011; 15(3): 190-6.

[28] Voicu VA, Mircioiu I, Sandulovici R, *et al.* Chlorpheniramine potentiates the analgesic effect in migraine of usual caffeine, acetaminophen, and acetylsalicylic acid combination. Front Pharmacol 2017; 8(OCT): 758. http://dx.doi.org/10.3389/fphar.2017.00758 PMID: 29114224

[29] Fang SY, Druce HM, Baraniuk JN. Anticholinergic properties of brompheniramine, chlorpheniramine, and atropine in human nasal mucosa *in vitro*. Am J Rhinol 1998; 12(2): 131-3. http://dx.doi.org/10.2500/105065898781390271 PMID: 9578932

[30] D'Agostino RB Sr, Weintraub M, Russell HK, *et al.* The effectiveness of antihistamines in reducing the severity of runny nose and sneezing: A meta-analysis. Clin Pharmacol Ther 1998; 64(6): 579-96. http://dx.doi.org/10.1016/S0009-9236(98)90049-2 PMID: 9871423

[31] Huh H, Lee SW, Cho JE, Kim HC. Effect of chlorpheniramine administration on postoperative catheter-related bladder discomfort in patients undergoing transurethral excision of bladder tumor: A prospective randomized study. J Anesth 2021; 35(5): 646-53. http://dx.doi.org/10.1007/s00540-021-02970-4 PMID: 34245368

[32] Gray SL, Anderson ML, Dublin S, *et al.* Cumulative use of strong anticholinergics and incident dementia: A prospective cohort study. JAMA Intern Med 2015; 175(3): 401-7. http://dx.doi.org/10.1001/jamainternmed.2014.7663 PMID: 25621434

[33] Orzechowski RF, Currie DS, Valancius CA. Comparative anticholinergic activities of 10 histamine H1 receptor antagonists in two functional models. Eur J Pharmacol 2005; 506(3): 257-64. http://dx.doi.org/10.1016/j.ejphar.2004.11.006 PMID: 15627436

[34] Doyle WJ, McBride TP, Skoner DP, Maddern BR, Gwaltney JM Jr, Uhrin M. A double-blind, placebo-controlled clinical trial of the effect of chlorpheniramine on the response of the nasal airway, middle ear and eustachian tube to provocative rhinovirus challenge. Pediatr Infect Dis J 1988; 7(3): 229-38. http://dx.doi.org/10.1097/00006454-198803000-00033 PMID: 3282216

[35] Gwaltney JM Jr, Druce HM. Efficacy of brompheniramine maleate for the treatment of rhinovirus colds. Clin Infect Dis 1997; 25(5): 1188-94. http://dx.doi.org/10.1086/516105 PMID: 9402380

[36] Qu C, Fuhler GM, Pan Y. Could histamine H1 receptor antagonists be used for treating COVID-19? Int J Mol Sci 2021; 22(11): 5672. http://dx.doi.org/10.3390/ijms22115672 PMID: 34073529

[37] Roumestan C, Henriquet C, Gougat C, *et al.* Histamine H1-receptor antagonists inhibit nuclear factor-kappaB and activator protein-1 activities *via* H1-receptor-dependent and -independent mechanisms. Clin Exp Allergy 2008; 38(6): 947-56. http://dx.doi.org/10.1111/j.1365-2222.2008.02990.x PMID: 18498541

[38] Westover JB, Ferrer G, Vazquez H, Bethencourt-Mirabal A, Go CC. *In vitro* virucidal effect of intranasally delivered chlorpheniramine maleate compound against severe acute respiratory syndrome coronavirus 2. Cureus 2020; 12(9): e10501. http://dx.doi.org/10.7759/cureus.10501 PMID: 32963923

[39] Mostafa A, Kandeil A, A M M Elshaier Y, *et al.* FDA-approved drugs with potent *in vitro* antiviral activity against severe acute respiratory syndrome coronavirus 2. Pharmaceuticals (Basel) 2020; 13(12): 1-24. http://dx.doi.org/10.3390/ph13120443 PMID: 33291642

[40] Black SD. Molecular modeling and preliminary clinical data suggesting antiviral activity for chlorpheniramine (chlorphenamine) against COVID-19. Cureus 2022; 14(1): e20980. http://dx.doi.org/10.7759/cureus.20980

[41] Yang L, Pei RJ, Li H, *et al.* Identification of SARS-CoV-2 entry inhibitors among already approved drugs. Acta Pharmacol Sin 2021; 42(8): 1347-53. http://dx.doi.org/10.1038/s41401-020-00556-6 PMID: 33116249

[42] Reznikov LR, Norris MH, Vashisht R, *et al.* Identification of antiviral antihistamines for COVID-19 repurposing. Biochem Biophys Res Commun 2021; 538: 173-9. http://dx.doi.org/10.1016/j.bbrc.2020.11.095 PMID: 33309272

[43] Gwaltney JM Jr, Winther B, Patrie JT, Hendley JO. Combined antiviral-antimediator treatment for the common cold. J Infect Dis 2002; 186(2): 147-54. http://dx.doi.org/10.1086/341455 PMID: 12134249

[44] Nakornchai S, Konthiang P. Potentiation of antimalarial drug action by chlorpheniramine against multidrug-resistant Plasmodium falciparum *in vitro*. Parasitol Int 2006; 55(3): 195-9. http://dx.doi.org/10.1016/j.parint.2005.11.058 PMID: 16750932

[45] Pereira MR, Henrich PP, Sidhu ABS, *et al. In vivo* and *in vitro* antimalarial properties of azithromycin-chloroquine combinations that include the resistance reversal agent amlodipine. Antimicrob Agents Chemother 2011; 55(7): 3115-24. http://dx.doi.org/10.1128/AAC.01566-10 PMID: 21464242

[46] Deane KJ, Summers RL, Lehane AM, Martin RE, Barrow RA. Chlorpheniramine analogues reverse chloroquine resistance in plasmodium falciparum by inhibiting PfCRT. ACS Med Chem Lett 2014; 5(5): 576-81. http://dx.doi.org/10.1021/ml5000228 PMID: 24900883

[47] Chu A, Wadhwa R. Selective Serotonin Reuptake Inhibitors. StatPearls Publishing 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554406/

[48] Gammoh O, Mayyas F, Darwish Elhajji F. Chlorpheniramine and escitalopram: Similar antidepressant and nitric oxide lowering roles in a mouse model of anxiety. Biomed Rep 2017; 6(6): 675-80. http://dx.doi.org/10.3892/br.2017.901 PMID: 28584640

[49] Parisi GF, Leonardi S, Ciprandi G, *et al.* Antihistamines in children and adolescents: A practical update. Allergol Immunopathol 2020; 48(6): 753-62. http://dx.doi.org/10.1016/j.aller.2020.02.005 PMID: 32448753

[50] Yanai K, Zhang D, Tashiro M, *et al.* Positron emission tomography evaluation of sedative properties of antihistamines. Expert Opin Drug Saf 2011; 10(4): 613-22. http://dx.doi.org/10.1517/14740338.2011.562889 PMID: 21521134

[51] Malamed SF, Orr DL. Preparation. In: Medical Emergencies in the Dental Office. Elsevier 2015; 62: 112. http://dx.doi.org/10.1016/B978-0-323-17122-9.00003-2

[52] Ricci AR, Settipane RJ, Goldstein BM, Kalliel JN, Settipane GA. The effect of chlorpheniramine on asthma. Allergy proceedings: The official journal of regional and state allergy societies 1990; 11(5): 229-33. http://dx.doi.org/10.2500/108854190778879873

[53] Akhouri S, House SA. Allergic Rhinitis (Nursing). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022.

[54] Meltzer EO, Berman GD, Corren J, *et al.* Addition of ibuprofen to pseudoephedrine and chlorpheniramine in the treatment of seasonal allergic rhinitis. Ann Allergy Asthma Immunol 2004; 93(5): 452-9. http://dx.doi.org/10.1016/S1081-1206(10)61412-3

[55] Sur DKC, Plesa ML. Treatment of allergic rhinitis. Am Fam Physician 2015; 92(11): 985-92. http://dx.doi.org/10.5005/jp/books/12714_15 PMID: 26760413

[56] Sur DK, Scandale S. Treatment of allergic rhinitis. Am Fam Physician 2010; 81(12): 1440-6. PMID: 20540482

[57] Bleehen SS, Thomas SE, Greaves MW, *et al.* Cimetidine and chlorpheniramine in the treatment of chronic idiopathic urticaria: A multi-centre randomized double-blind study. Br J Dermatol 1987; 117(1): 81-8. http://dx.doi.org/10.1111/j.1365-2133.1987.tb04095.x PMID: 3307890

[58] Buckey JC, Alvarenga D, Cole B, Rigas JR. Chlorpheniramine for motion sickness. Journal of vestibular research: Equilibrium & orientation 2004; 14(1): 53-61.

[59] Janam P, Nayar BR, Mohan R, Suchitra A. Plasma cell gingivitis associated with cheilitis: A diagnostic dilemma! J Indian Soc Periodontol 2012; 16(1): 115-9. http://dx.doi.org/10.4103/0972-124X.94618 PMID: 22628976

[60] Ranganathan AT, Chandran CR, Prabhakar P, Lakshmiganthan M, Parthasaradhi T. Plasma cell gingivitis: Treatment with chlorpheniramine maleate. Int J Periodont Restor Dent 2015; 35(3): 411-3. http://dx.doi.org/10.11607/prd.2111 PMID: 25909529

[61] Falade CO, Michael SO, Oduola AMJ. Enhanced efficacy of amodiaquine and chlorpheniramine combination over amodiaquine alone in the treatment of acute uncomplicated Plasmodium falciparum malaria in children. Med Princ Pract 2008; 17(3): 197-201. http://dx.doi.org/10.1159/000117792 PMID: 18408387

[62] Gaffey MJ, Gwaltney JM Jr, Sastre A, Dressler WE, Sorrentino JV, Hayden FG. Intranasally and orally administered antihistamine treatment of experimental rhinovirus colds. Am Rev Respir Dis 1987; 136(3): 556-60. http://dx.doi.org/10.1164/ajrccm/136.3.556 PMID: 3307567

[63] De Sutter AIM, van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. Cochrane Database Syst Rev 2012; 86(2): CD004976. http://dx.doi.org/10.1002/14651858.CD004976.pub3 PMID: 22336807

[64] Morán Blanco JI, Alvarenga Bonilla JA, Homma S, Suzuki K, Fremont-Smith P, Villar Gómez de Las Heras K. Antihistamines and azithromycin as a treatment for COVID-19 on primary health care - A retrospective observational study in elderly patients. Pulm Pharmacol Ther 2021; 67: 101989. http://dx.doi.org/10.1016/j.pupt.2021.101989 PMID: 33465426

[65] Kim HJ, Kim DK, Kim HY, Kim JK, Choi SW. Risk factors of emergence agitation in adults undergoing general anesthesia for nasal surgery. Clin Exp Otorhinolaryngol 2015; 8(1): 46-51. http://dx.doi.org/10.3342/ceo.2015.8.1.46 PMID: 25729495

[66] Abdelrahman TN, Kasem AA. Role of preemptive chlorpheniramine maleate in reducing postoperative agitation after Functional Endoscopic Sinus Surgeries (FESS). Ain-Shams J Anesthesiol 2020; 12(1): 26. http://dx.doi.org/10.1186/s42077-020-00074-x

[67] Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: A systematic review. Met Based Drugs 2010; 2010. Article ID 207084. http://dx.doi.org/10.1155/2010/207084 PMID: 20886011

[68] Harada T, Doi M, Yamada Y, Akase T. Evaluation of short-time premedication with d-chlorpheniramine maleate injection for paclitaxel-induced hypersensitivity reaction. Gan to kagaku ryoho. Cancer Chemother 2008; 35(8): 1347-51. PMID: 18701846

[69] Ikegawa K, Suzuki S, Nomura H, *et al.* Retrospective analysis of premedication, glucocorticosteroids, and H_1-antihistamines for preventing infusion reactions associated with cetuximab treatment of patients with head and neck cancer. J Int Med Res 2017; 45(4): 1378-85. http://dx.doi.org/10.1177/0300060517713531 PMID: 28606015

[70] Komatsubara K, Miyoshi K, Kogure Y, Matsuhisa T, Eguchi H. Administration of premedication with fexofenadine for paclitaxel-induced hypersensitive reactions in breast cancer patients complicated with closed-angle glaucoma. Gan to kagaku ryoho. Cancer Chemother 2010; 37(1): 107-10. PMID: 20087041

[71] Effect of the antihistamine injection to prevent paradoxical reaction during sedative endoscopy. ClinicalTrialsgov Available from: https://clinicaltrials.gov/ct2/show/NCT03940391?term=chlorpheniramine&recrs=abdf&draw=2&rank=4 (Accessed on May 21, 2022).

[72] The Safety and Effectiveness of Local Injection of Antihistamines in Treatment of Inflammatory Skin Diseases. ClinicalTrialsgov Available from: https://clinicaltrials.gov/ct2/show/NCT04937101?term=chlorpheniramine&recrs=abdf&draw=2&rank=3 (Accessed on May 21, 2022).

[73] Chlorpheniramine maleate nasal spray for chronic rhinitis. ClinicalTrialsgov Available from: https://clinicaltrials.gov/ct2/show/NCT04790487?term=chlorpheniramine&recrs=abdf&draw=2&rank=2 (Accessed on May 21, 2022).

[74] Efficacy of placebo *versus* chlorpheniramine for the prevention of allergic transfusion reactions. ClinicalTrialsgov Available from: https://clinicaltrials.gov/ct2/show/NCT04688736?term=chlorpheniramine&recrs=abdf&draw=2&rank=1 (Accessed on May 21, 2022).