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A Novel Combination of Levodropropizine and Low-Dose Chlorpheniramine Maleate for the Management of Refractory Chronic Cough with Upper Airway Cough Syndrome (UACS) Components

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ABSTRACT
Chronic refractory cough (CRC) represents a significant clinical challenge, often persisting despite treatment of known etiologies like asthma or GERD. Upper Airway Cough Syndrome (UACS), frequently linked to post-nasal drip, is a common contributor. This paper proposes a novel therapeutic strategy: the combination of Levodropropizine, a well-established non-opioid antitussive with peripheral action, and a sub-sedating dose of Chlorpheniramine Maleate, a first-generation antihistamine. We hypothesize that this combination will provide a synergistic effect—Levodropropizine directly dampening the cough reflex at the peripheral level and Chlorpheniramine managing the underlying UACS pathology by reducing histamine-mediated mucus secretion and nasal congestion—thereby offering a superior efficacy and safety profile compared to existing treatments, particularly opioid-based antitussives.

I. INTRODUCTION

Chronic cough, defined as a cough lasting more than eight weeks, affects a substantial portion of the global population and severely impairs quality of life [1]. A significant subset of patients is diagnosed with Refractory Chronic Cough (RCC) or UACS, where the cough persists despite guideline-based treatment [2]. Current central antitussives, such as codeine or dextromethorphan, often provide inadequate relief and carry risks of sedation, dependence, and gastrointestinal side effects [3].

Levodropropizine is an effective, well-tolerated antitussive agent. Its mechanism of action is primarily peripheral, modulating sensory neuropeptide release (like Substance P) from C-fibers in the airwaysandacting on sensory nerves to reduce afferent signals to the cough center [4, 5]. Its key advantage is a notably low incidence of drowsiness compared to central agents.Chlorpheniramine Maleate is a first-generation alkylamine antihistamine. While its use has declined due to sedative properties at standard doses, it possesses potent anticholinergic and anti-inflammatory properties that are highly effective in managing UACS symptoms, such as rhinorrhea and post-nasal drip [6]. Its effectiveness in cough associated with the common cold is well-documented [7].

Rationale for New Use: The novel use proposed here is the combination of these two drugs for RCC with UACS features. The rationale is multi-modal targeting:

1. Levodropropizine addresses the hyperactive cough reflex itself.
2. Low-Dose Chlorpheniramine addresses the underlying inflammatory and secretory triggers of UACS, but at a dose (e.g., 2mg BID) low enough to minimize sedation while maintaining efficacy on nasal and sinus secretions.

This approach moves beyond monotherapy to a targeted, pathophysiologically-sound combination, potentially filling a significant gap in the management of this debilitating condition.

II. PROPOSED METHODOLOGY FOR CLINICAL VALIDATION

A. Study Design: A randomized, double-blind, active-controlled, parallel-group phase III clinical trial.

B. Participants:

· Inclusion Criteria: Adults (18-75 years) with chronic cough (>8 weeks) diagnosed as refractory or with dominant UACS features, who have failed standard first-line therapies. Confirmed by Cough Visual Analog Scale (VAS) > 60mm and Leicester Cough Questionnaire (LCQ) score < 12.

· Exclusion Criteria: Asthma, active GERD, renal/hepatic impairment, pregnancy, known hypersensitivity to study drugs, and use of other sedatives or antitussives.

C. Intervention Groups (N=120 each group):

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1. Combination Group: Levodropropizine (60 mg) + Chlorpheniramine Maleate (2 mg) oral suspension, thrice daily.
2. Levodropropizine Monotherapy Group: Levodropropizine (60 mg) + Placebo, thrice daily.
3. Standard Care Group: Guaifenesin (for expectation) + as-needed Dextromethorphan (as a central antitussive control).

D. Primary Endpoint: Change from baseline in 24-hour cough frequency (objective measure using a validated cough monitor) at Week 4.

E. Secondary Endpoints:
· Change in Leicester Cough Questionnaire (LCQ) score.
· Change in Cough Severity VAS.
· Subjective assessment of post-nasal drip and throat clearing.
· Incidence of treatment-emergent adverse events, particularly sedation (using the Stanford Sleepiness Scale).

III. ANTICIPATED RESULTS AND DISCUSSION

We anticipate that the Combination Group will demonstrate a statistically significant and clinically meaningful greater reduction in 24-hour cough frequency compared to both the Levodropropizine Monotherapy and Standard Care groups. Furthermore, we expect a significant improvement in LCQ scores and VAS related to post-nasal drip.

Discussion Points:

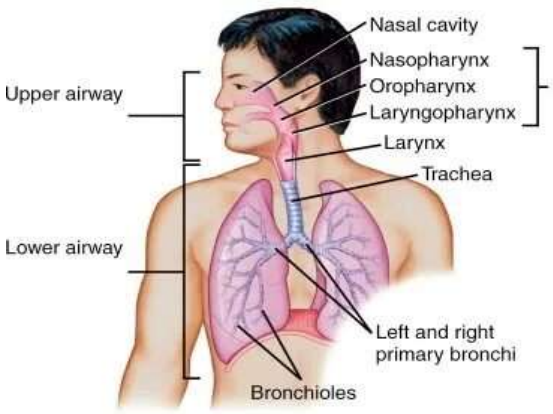
The superior efficacy would support the hypothesis of a synergistic mechanism.Levodropropizine's peripheral antitussive action would be complemented by Chlorpheniramine's ability to reduce the afferent trigger(post-nasal drip) originating in the upper airway. This "dual-blockade" approach could effectively break the cycle of cough hypersensitivity.

A critical discussion point will be the safety profile. By employing a low dose of Chlorpheniramine, we anticipate the sedative side effect—the primary drawback of first-generation antihistamines—will be markedly reduced, making the combination tolerable for daytime use. This positions the combination favorably against codeine, which causes significant drowsiness and constipation [3, 8].

This research could redefine a segment of the RCC/UACS treatment paradigm, offering a non-narcotic, multi-targeted therapeutic option that is both effective and has a low potential for abuse or significant central nervous system depression.

IV. CONCLUSION

The proposed combination of Levodropropizine and low-dose Chlorpheniramine Maleate represents a novel, rational, and promising approach to managing Refractory Chronic Cough with UACS components. By simultaneously targeting the peripheral cough reflex and the underlying rhinopathic triggers, this strategy has the potential to achieve superior symptom control with an improved safety and tolerability profile. Clinical validation through the proposed trial is strongly warranted.



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