Content available at: https://www.ipinnovative.com/open-access-journals

IP Indian Journal of Immunology and Respiratory Medicine

Journal homepage: https://www.ijirm.org/

Review Article

Levodropropizine: A promising peripherally acting antitussive agent

Amar Shirsat[1,*], Abhijit Trailokya[1], Shaijesh Wankhede[1]

[1] *Indoco Remedies Limited, Mumbai, Maharashtra, India*

ARTICLE INFO

Article history:
Received 30-04-2023
Accepted 05-07-2023
Available online 09-08-2023

Keywords:
Levodropropizine
Cough
Antitussive

ABSTRACT

Cough is one of the most frequent symptom for patients to seek medical attention. Cough can be associated with many disease processes and the ultimate treatment depends on determining the etiology and diagnosis. Antitussive agents with different mechanisms of action have been developed in the past, but there are still very few medications that seem to be effective without any side effects especially related to central nervous system (CNS). Levodropropizine is an antitussive agent which acts peripherally and is a non-opioid cough medication that is in use since many years as a symptomatic therapy for cough. Levodropropizine has potent antitussive activity mainly due to peripheral effects by inhibiting the activation of vagal C-fibers. In fact, levodropropizine has been proven effective in controlling cough and is devoid of the central depressant effect. Levodropropizine oral suspension (30mg/5ml) is approved by drug approval body of India, Drug Controller General of India (DCGI) for the management non-productive cough in adults. Levodropropizine is approved in some of the European countries and in Asian countries. It is widely used in Republic of Korea for the symptomatic treatment of cough in both adults and children above 2 years of age. Levodropropizine has the utmost level of benefit in comparison with central antitussive agents namely codeine and dextromethorphan for the patients with cough due to acute and chronic bronchitis.

1. Cough: A Distressing Symptom

Cough helps to remove inhaled foreign particles and other endogenous secretions and thus is an important defense mechanism. The immunological, chemical or mechanical stimulation of the unmyelinated nerve fibres (C-fibers), and the slowly and rapidly adapting stretch receptors at various sites play main role in the initiation of the cough reflex.[1] The cough reflex thus initiated helps clear the foreign particles and the excessive secretions from the airways. Thus cough has a protective role. If the cough is non-productive, or excessive it can be troublesome to patients. Most of the Individuals seek attention of a medical professional for cough.[2] Cough results in significant health care costs due to more drug prescriptions and frequent outpatient visits.[3]

The upper respiratory infection (URI) is a common cause for acute cough (< 3 weeks). The pulmonary conditions like asthma, chronic obstructive pulmonary disease (COPD) and lung carcinoma, and the gastro-oesophageal reflux disease are responsible for chronic cough (> 8 weeks).[2]

Approximately 35% of preschool children are affected with acute cough at any given time as per the data from epidemiological studies. Cough is an important health related issue in childhood. It is a very important reason for the significant increase in morbidity in children.[4] The episodes of acute cough are short-lived and rare in adolescents and older children.[4] The attendance of a new patient in the OPD settings of the primary health care and the admission for acute cough is more than 50%, with a significant impact on the patient and his family and also on

* *Corresponding author*.
E-mail address: amar.shirsat@indoco.com (A. Shirsat).

https://doi.org/10.18231/j.ijirm.2023.013

the treating doctor. Acute cough also puts burden on the pharmacoeconomics.[5]

Chronic cough hampers the quality of life with a higher economic burden on an individual. The prevalence of chronic cough is more than 12% in the overall population.[2]

Cough is responsible for reduced sleep, difficulty in breathing, pain, incontinence, sometimes syncopal attacks and fracture of the ribs. It may also cause an impact over your social relationships.[1]

2. Management of Acute Cough

Antitussive agents are divided into central and peripheral agents depending on their mechanism and the site of action. The centrally acting antitussive agents have their action directly on the central reflex pathway of the cough, whereas the peripherally acting antitussive agents inhibit the sensory receptors of the vagal nerves.[4] Most of the antitussive agents that are available in the market have poor tolerability as they have an effect on the central nervous system which increases their adverse effects potential.[2]

Table 1: Antitussive agents' classification:[4]

Antitussive agents	Examples
Peripherally acting antitussive drugs	H1-receptor antagonists (Promethazine, Diphenhydramine, Clemastine, Chlorpheniramine)
	Local anesthetics (Lignocaine, lidocaine, and benzonatate)
	Mucolytics and Expectorants (Erdosteine, carbocisteine and N-acetylcysteine, Guaifenesin, ipecac, terpene hydrate, and ammonium chloride, Bromhexine and ambroxol)
	Dropropizine and Levodropropizine
	Menthol
	Honey
	Glycerol (Glycerine)
Centrally acting antitussive drugs	Opioids (Codeine)
	Non-opioids (Dextromethorphan, Caramiphen, Carbetapentane or pentoxyverine)

3. Limitations of the Current Antitussive Agents

The safety of cough medication, is a very important factor to be considered while using them in the management of cough. A lot number of evidences has shown that the current antitussive agents especially the centrally acting antitussives adversely affect the breathing.[2]

Opioid agents namely the codeine derivatives, are also used in patients with cough, but they impair the cognition and also alter the psychomotor function.[6]

Codeine is a centrally acting antitussive agent used in the management of acute cough, but the efficacy data does not supportive. In fact recent evidences demonstrate that codeine is not more effective than the placebo in the paediatric patients with acute cough.[7]

The cytochrome P450 2D6 (CYP2D6) enzyme is a major metabolizing enzyme with metabolizes the codeine in the liver. In the patients who are CYP2D6 "ultra-rapid metabolizers" the safety concerns are raised with codeine as it is converted to morphine more rapidly, causing an increase in the serum morphine levels. The increased morphine levels increase the risk of developing severe respiratory depression which could be life-threatening. In the post-marketing studies (PMS) including the paediatric population, codeine administration resulted in 41 serious cases and 9 fatal cases.[8]

Codeine use has been associated with depressed central response to hypercapnia. So the use is codeine is contraindicated in paediatric patients less than 12 years of age.[2]

As per the drug safety communication by the U.S. Food and Drug Administration (FDA), the usage of codeine or hydrocodone containing cough and cold medicines require the changes in their safety labels to utilize it in adults over 18 years and above, as their risk outweigh their benefits in children below 18 years of age. Also a boxed warning to be incorporated with regards to the risks of addiction, misuse, abuse, overdose, death and slowed or difficult breathing.[9]

4. Non-opioids (Dextromethorphan)

Dextromethorphan is a centrally acting cough suppressant. It received the regulatory approval in 1953.[2] Dextromethorphan administration in paediatric patients (n=327) did not show a significant effect in the reduction of the cough frequency, parent-recorded symptom scores, and child or parental sleep as demonstrated in four double-blind, placebo-controlled and randomized studies.[7]

As compared to placebo, dextromethorphan at standard doses was associated with dystonia, anaphylaxis. At higher doses dextromethorphan is associated with psychosis, ataxia, somnolence, hallucinations, peripheral neuropathy, cerebellar degeneration, and death.[7]

Cough and cold medications, containing the centrally acting antitussive agents which are available over the counter (OTC) are not recommended by Food and Drug

Administration (FDA) and Medicines and Healthcare Products Regulatory Agency (MHRA) in infants and young children.[10]

Dextromethorphan and codeine containing cough and cold preparation should not be used in the paediatric population as per the recommendations given by the American Academy of Paediatrics (AAP).[10]

5. Levodropropizine

Racemic dropropizine, or (±)-3-(4-phenyl-1-piperazinyl)-1,2-propanediol, was in use for long period as an antitussive drug. The levo (S) (-) and dextro (R) (+) isomers were separated in the late 1980s. The activity of the (S) (-) enantiomer was tested as against the racemate. The (S) (-) enantiomer (levodropropizine) was found to have similar antitussive activity as that of the racemate in different experimentally-induced cough animal models. Levodropropizine had a better safety and tolerability profile as compared to the racemate with less impact on the central nervous system.[11]

6. Mechanism of Action

Levodropropizine is a peripherally acting antitussive agent. Levodropropizine inhibit the cough reflex by acting on the peripheral receptors and their afferent conductors.[12] Animal studies suggest that levodropropizine inhibit the C-fibers of the vagus nerves, and modulate the sensory neuropeptides production in the respiratory tract, involved in the cough reflex. Levodropropizine has a dose-dependent and short-term local anaesthetic activity. It also has a mild analgesic and a antihistaminic action.[12]

6.1. Indications:[13]

Levodropropizine is indicated for the symptomatic treatment of non-productive cough.

6.2. Pharmacokinetic properties:[13]

Levodropropizine has an oral bioavailability which is higher than 75% and a negligible plasma protein binding (11-14%). It is rapidly absorbed and distributed with a half-life of 1-2 hours. Levodropropizine and its metabolites (conjugated Levodropropizine and free and conjugated p-hydroxy- Levodropropizine) are mainly excreted through urine (35%).

Table 2: Dosage and administration:[13]

Adults	10 ml of syrup up to three times daily with at intervals of at least 6 hours.
Children over 2 years	10-20 kg- 3 ml of syrup three times daily 20-30 kg- 5 ml of syrup three times daily
Children under 2 years	Not recommended

Levodropropizine should be given for a maximum of 7 days**.**

6.3. Contraindications:[13]

Levodropropizine is contraindicated in patients with hypersensitivity to levodropropizine or its excipients. It is not recommended in patients with bronchorrhea and in patients with reduced mucociliary function (Kartagener syndrome, ciliary dyskinesia). It is contraindicated in pregnant females and during lactation. It is not recommended in children below 2 years of age.

Table 3: Special warnings and precautions for use:[13]

Elderly population	No dosage or interval modification needed in elderly people
Paediatric population	Contraindicated in children below 2 years of age
Renal impairment	Use cautiously in patients with severe renal failure (creatinine clearance < 35ml/min).
Driving/vehicle operating	Use cautiously in patients who intend to drive or operate vehicles mechanical devices

6.4. Undesirable effects:[13]

The undesirable effects occur very rarely with Levodropropizine as evaluated from the data from over 30 countries. The reactions are not severe and symptoms resolved after therapy discontinuation.

The adverse reactions which are very rare (< 1/10,000) include urticaria, erythema, exanthema, itching, angioedema, skin reactions.

Table 4: Levodropropizine clinical trials

Study design/No. of pts/ Age group/ Diagnosis/Treatment received	Outcome measures	Efficacy/ Safety	Conclusion
Prospective, parallel-group, randomized double blind trial[14] 258 patients 2-14 years Levodropropizine [2 mg per kg three times daily orally for 3 days] (n=132); Dropropizine [1 mg per kg three times daily orally for 3 days] (n=126)	Number of coughing spells Number of cough related nocturnal awakening (Recorded at baseline, first day and last day of treatment) Adverse event Somnolence present or absent	Statistically significant decrease was seen in the frequency of cough spells and nocturnal awakenings in both treatment group ($P < 0.001$). The patients (%) with cough related nocturnal awakenings decreased in both treatment group Levodropropizine group (Baseline [39%], day 1 [26%] and day 3 [14%]) Dropropizine group (Baseline [38%], day 1 [26%] and day 3 [18%]) **Safety** Somnolence was less frequent in levodropropizine group (5.3%) vs dropropizine group (10.3%)	Levodropropizine is as effective as an antitussive as dropropizine, but appears to carry a lower risk of day time somnolence.
Double-blind, randomized clinical trial[15] 209 adult patients [18 and 82 years (Mean age was 54.6 years)] moderate non-productive cough Levodropropizine syrup (60 mg three times daily for 5 days)(n=110) Dextromethorphan syrup (15 mg three times daily for 5 days) (n=99)	**Efficacy assessment** • Number of cough spells in a 6 h period, • Cough frequency • Cough intensity • Night awakenings related to cough. **Adverse event** Presence/Absence of somnolence	Levodropropizine and dextromethorphan both significantly reduced number of cough spells ($P < 0.05$). Significantly decreased cough intensity ($P < 0.01$) in both treatment group throughout the treatment, but early with levodropropizine. The number of night awakenings decreased significantly ($P < 0.05$), with levodropropizine Levodropropizine had a significantly ($P < 0.05$) higher improvement than dextromethorphan **Safety** Number of patients with adverse events was significantly higher ($P < 0.05$) in the dextromethorphan (12.1%) than in the levodropropizine (3.6%) group. Percentage of patients experiencing somnolence were 4.6% with levodropropizine as compared to 10.4% with dextromethorphan	Levodropropizine is an effective antitussive and has a favourable benefit/risk profile compared to dextromethorphan.
Multicentre, parallel group, double blind Study[16] 140 adults Levodropropizine (n=69) and dihydrocodeine (n=71) More than 18 yrs, Nonproductive cough with primary lung carcinoma or metastatic lung carcinoma. Levodropropizine drops (75 mg thrice daily for 7 days) was compared with dihydrocodeine drops (10 mg thrice daily for 7 days).	**Efficacy assessment** • Cough severity • Cough induced night awakenings • Overall antitussive efficacy. **Tolerability assessment** • somnolence Present/Absent	Levodropropizine and dihydrocodeine both significantly ($p < 0.05$) reduced the cough severity, and number of night awakenings **Safety** Both Levodropropizine (n=6) and dihydrocodeine (n=4) group had similar adverse event rate. Somnolence was significantly higher in dihydrocodeine group (15/69; 22%) as against Levodropropizine (5/66; 8%; $p < 0.05$)	Levodropropizine is an effective antitussive and has a favourable benefit/risk profile compared to dihydrocodeine

Continued on next page

Table 4 continued

Double blind randomized Study[17] n=77 age 2-3 years Bronchitis Randomized to Levodropropizine and Dextromethorphan	Cough Severity, frequency, efficacy score	Significant reduction in cough severity with levodropropizine than dextromethorphan group (P = 0.003) after 2-3 days of administration. Significant decrease in the cough frequency after 2 days (P = 0.009) and 3 days (P = 0.003) with levodropropizine. Levodropropizine group (3.2 ± 0.9) had a higher final efficacy score than dextromethorphan group (2.6 ± 1.0) (P = 0.003).	Levodropropizine is effective and has a favourable benefit profile as compared to dextromethorphan.
Observational study[18] n=433 children were enrolled (Outcome assessed in 241 children) 1month-14 years (mean age of 6.1 years) Acute cough with URI Levodropropizine (n = 101), Central antitussives (n = 60)[Cloperastine (n=51), codeine (n=9)]; No treatment (n = 80)	Efficacy assessment after 6 days • Cough resolution • Improvement, no change, or worsening of cough.	Both levodropropizine and central antitussives (cloperastine and codeine) reduced cough intensity and frequency. **Resolution of cough** Levodropropizine versus central antitussives (47% vs. 28%, p = 0.0012). **No change/worsening of cough** Levodropropizine (3%) versus central antitussives (18%) **No treatment group** Resolution of cough seen in 20% and improvement of cough seen in 55%.	Levodropropizine showed a better and higher resolution of cough than the central antitussives
A meta-analysis of four clinical studies[19] n=780 patients Levodropropizine vs. control	Efficacy assessment • Cough frequency • Cough severity • Night awakenings • Overall efficacy	A highly statistically significant difference in the overall antitussive efficacy in favor of levodropropizine vs. control treatments (p=0.0044) was seen in all the efficacy parameters (cough frequency, severity, and night awakenings)	Levodropropizine has a statistically significant and better overall efficacy outcomes vs. central antitussives (codeine, cloperastine, dextromethorphan). Levodropropizine is an efficient antitussive agent in the paediatric patients.

Continued on next page

Table 4 continued

Meta-analysis of seven clinical studies[20] N=1,178 patients Paediatric and adults Levodropropizine vs. control	**Efficacy parameters** Frequency of cough Severity of cough Number of night awakenings	The efficacy of levodropropizine was statistically significant as compared to control group (including the centrally acting cough suppressants), with p = 0.0015 In the seven clinical studies Levodropropizine was found to be better than or equivalent to the control group. In four clinical studies the efficacy outcomes were statistically significant (p < 0.05) in favor of levodropropizine.	Levodropropizine is an efficient and a better antitussive agents, and Levodropropizine is better than central antitussive drugs (codeine, cloperastine, dextromethorphan) in term of reduction of cough intensity, cough frequency, and nocturnal awakenings.
Prospective observational study[21] 330 children URTI with acute cough. 4 months to 14 years Antibiotic (n = 89) Antitussives (n = 123) [central antitussives (codeine or cloperastine) (n=44;13%) and peripheral antitussives (levodropropizine) (n=79; 24%), without antibiotics] Combination (n = 38) [central agents (codeine or cloperastine) (n=16; 5%, and peripheral agents (levodropropizine) (n=22; 7%)] No Treatment (n=80)	Standardized Pediatric Cough Questionnaire (PCQ) was prepared to assess the study outcomes Severity, frequency and type of cough were assessed at baseline and after 6 days of treatment resolution (disappearance of cough), improvement (fewer spells of sporadic cough), no change in cough or cough worsening (increased frequency and severity of cough).	**Overall antitussive agents** Cough improvement (51%) Cough resolution (41%) No change in cough (7%). **Levodropropizine group** Cough improvement (49%) Cough resolution (47%) No change in cough (4%). **Central antitussives group** Cough improvement (54.5%) Cough resolution (29.5%) No change in cough (14%). Worsening of cough (6%). **Antibiotics plus antitussives combination group** Cough improvement (53%) Cough resolution (37%) No change in cough (8%). Worsening of cough (3%). **Antibiotics plus levodropropizine combination group** Cough improvement (54.5%) Cough resolution (45%) **Antibiotics plus central antitussives combination group** Cough improvement (50%) Cough resolution (25%) No change in cough (19%). Worsening of cough (6%). **Antibiotics only group** Cough improvement (63%) Cough resolution (24%) No change in cough (13.5%). **Levodropropizine vs antibiotics only group** The resolution of cough between children treated with levodropropizine or antibiotics only was statistically significant (p < 0.01) in favor of levodropropizine. **Central antitussive vs antibiotic only group** The resolution of cough was not statistically different between children treated with central antitussives or antibiotics (p=NS).	Levodropropizine, is effective for acute cough associated by URTIs in pediatric patients.

6.5. Tolerability profile of levodropropizine

The peripheral activity of levodropropizine and the absence of the effect on the central nervous system (CNS) is responsible for the better tolerability of levodropropizine.[2]

In a randomized, double-blind, cross-over trial, levodropropizine or placebo were administered orally thrice daily in 12 healthy human volunteers and 12 chronic obstructive pulmonary disease (COPD patients with chronic respiratory impairment. The mouth occlusion pressure (P0.1), minute ventilation (Ve) and end-tidal CO2 (EtCO2) were not modified by levodropropizine. This study confirmed the lack of interference with breathing with levodropropizine.[22]

Author Mannini et al., assessed the impact and effect of levodropropizine (60 mg) versus dihydrocodeine (15 mg) or placebo in twenty four patients with chronic cough. The respiratory response was evaluated in standard CO2 re-breathing testing. The hyperventilatory response to hypercapnia was not affected by either levodropropizine or placebo unlike dihydrocodeine, confirming the peripheral action of levodropropizine.[23]

6.6. Guideline recommendations

As per the Diagnosis and the management of adult cough: An Indian Environmental Medical Association (EMA)[24] position paper, the recommendation for levodropropizine are (Table 5):

As per the standard treatment guidelines 2022 on the management-of-Cough-in-Office-Practice levodropropizine improved elimination of cough compared with antibiotics at day 6 of the viral illness. (SOR: C, cohort study).[25]

As per the management algorithm of the Italian Society of Pediatric Allergy and Immunology, Levodropropizine should be preferred in children for the symptomatic cough management because of its proven and beneficial efficacy and tolerability profile and the risk–benefit ratio.[4]

As per the CHEST Guideline and Expert Panel Report, a peripherally acting antitussive such as levodropropizine, moguisteine, levocloperastine or sodium cromoglycate is suggested in adult patients with carcinoma of the lung who develop opioid-resistant cough (Grade 2C).[26]

Levodropropizine the peripherally acting cough suppressants is recommended by the American College of Chest Physicians (ACCP) guidelines for short-term symptomatic relief in adult patients with cough due to acute or chronic bronchitis. Levodropropizine has the highest benefit as compared to central antitussive drugs (codeine and dextromethorphan) in cough due to acute or chronic bronchitis.[10]

6.7. Authorization

Levodropropizine oral suspension (30mg/5ml) is approved by drug approval body of India, Drug Controller General of India (DCGI) on 25^{th} February 2005 in the management of non-productive cough in adults.[27] Levodropropizine is approved in some of the European countries and in Asian countries. It is widely used in Republic of Korea for the symptomatic treatment of cough in both adults and children above 2 years of age.[28]

Table 5:

Recommendation	LOE*/Strength
Levodropropizine is effective in the management of upper respiratory infection (URI) associated dry cough	Level IIB, Strong
Levodropropizine, dextromethorphan, and levocloperastine have documented clinical effects on Dry cough in patients with acute bronchitis	Level IIB, Strong
Levodropropizine has a more favorable benefit/risk profile when compared to dextromethorphan in patients with chronic bronchitis with dry cough	Level IIB, Strong
Levodropropizine (60 mg thrice daily) and/or Levocloperastine (20 mg thrice daily) given for 7–20 days is found to be effective in cough variant Asthma (CVA)	Level IIIC, Weak
Levodropropizine 60 mg thrice daily is effective in dry cough due to pulmonary tuberculosis	Level IVB, Strong
Levodropropizine 60 mg thrice daily for 4 days is effective for symptomatic treatment of dry cough in patients with interstitial lung disease (ILD)	Level IVB, Strong
Levodropropizine is recommended for dry and non-productive cough in patients suffering from primary or metastatic lung carcinoma.	Level IIB; Strong

LOE: Level of evidence

7. Conclusion

Cough is one of the common symptom for which the patients seek medical attention. Cough impairs the quality of life and is detrimental to the well-being. Cough as a symptom could be very difficult to control. Thus there is a need for a tolerable and an effective antitussive which would be beneficial in all the individuals including children, and elderly and also patients with respiratory disorders. The current medications that are used in the management of cough have their own side effects especially the depressant effect on the central nervous system. This restricts their use as an antitussive agent.[2] The pharmacological management of acute cough in children is not recommended by the evidence-based guidelines and systematic reviews published earlier. A significant area of unmet need lies in for an availability of a safe and effective antitussive drug. Most of the cough suppressants cause excessive sedation (narcotics as codeine and hydrocodone) and they have an unacceptable risk–benefit profile when used in children.[4]

The non-pharmacological management and the supportive therapies in the form of honey, hot beverages, lozenges, and analgesics are most commonly used by many of the doctors. But most often these supportive care seems to be ineffective. Cough is a highly distressing symptom. Cough impact the sleep of both the children and their parents and also affect their daily activities.[4] Among the currently available therapies for the management of cough, the peripherally acting antitussive agents seem to be effective and better tolerated. Levodropropizine is a peripherally acting antitussive drug which block the sensory fibres of vagal nerves.[2]It is an important antitussive agent which is useful in the management of the different types and forms of cough in both pediatric and adult patients and also in the patients suffering from respiratory disorders. A number of evidences support the efficacy and tolerability of levodropropizine as an antitussive agent with the lack of central depressant activity.[2] Since the launch, more than 30 years ago, the antitussive activity of Levodropropizine has been extensively studied and the drug has been proven to be effective and safe.[29]

8. Conflicts of Interest

Dr. Amar B Shirsat, Dr. Shaijesh Wankhede & Dr. Abhijit Trailokya are associated with Indoco Remedies Limited Mumbai.

9. Source of Funding

None.

Acknowledgements

None.

References

1. Schildmann EK, Rémi C, Bausewein C. Levodropropizine in the management of cough associated with cancer or nonmalignant chronic disease–a systematic review. *J Pain Palliat Care Pharmacother*. 2011;25(3):209–18.
2. Birring S, De Blasio F, Dicpinigaitis PV. Antitussive therapy: A role for levodropropizine. *Pulm Pharmacol Ther*. 2019;56:79–85. doi:10.1016/j.pupt.2019.03.003.
3. Sharma OP, Jindal SK. Diagnoses and management of adult cough: An Indian Environmental Medical Association (EMA) position paper. *Respir Med*. 2020;168:105949. doi:10.1016/j.rmed.2020.105949.
4. Marseglia GL, Manti S, Chiappini E. Acute cough in children and adolescents: A systematic review and a practical algorithm by the Italian Society of Pediatric Allergy and Immunology. *Allergol Immunopathol (Madr)*. 2021;49(2):155–69.
5. Morice A, Kardos P. Comprehensive evidence-based review on European antitussives. *BMJ Open Resp Res*. 2016;3:137. doi:10.1136/bmjresp-2016-000137.
6. Luporini G, Barni S, Marchi E, Daffonchio L. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. *Eur Respir J*. 1998;12(1):97–101.
7. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. *Cochrane Database Syst Rev*. 2014;(11):1831. doi:10.1002/14651858.CD001831.
8. Codeine containing medicinal products for the treat¬ment of cough and/or cold in pediatric patients. Article 31 of Directive 2001/83/EC resulting from pharmacovig¬ilance data. 12 March 2015EMA/235820/2015 . Available from: https://www.ema.europa.eu/en/documents/referral/codeine-article-31-referral-prac-assessment-report_en-0.pdf.
9. US Food and Drug Administration: FDA requires labeling changes for prescription opioid cough and cold medicines to limit their use to adults 18 years and older . [Accessed April 28, 2023]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-labeling-changesprescription-opioid-cough-and-cold.Accessed.
10. Zanasi A, Lanata L, Fontana G, Saibene F, Dicpinigaitis P, Blasio FD, et al. Levodropropizine for treating cough in adult and children: a meta-analysis of published studies. *Multidiscip Respir Med*. 2015;10(1):19. doi:10.1186/s40248-015-0014-3.
11. De Blasio F, Dicpinigaitis PV, Danieli GD, Lanata L, Zanasi A. Efficacy of levodropropizine in pediatric cough. *Pulm Pharmacol Ther*. 2012;25(5):337–42. doi:10.1016/j.pupt.2012.05.010.
12. Machado A, Nemitz MC, Todeschini V, Sangoi MDS. Characteristics, Properties and Analytical Methods for Determination of Dropropizine and Levodropropizine: A Review. *Crit Rev Anal Chem*. 2021;51(2):174–82.
13. Levodropropizine ELC 30 mg/5 ml syrup SMPC. [Last accessed on 15th May 2023]. Available from: https://file.wuxuwang.com/hma/MT_H_0294_001_FinalSPC.pdf.
14. Banderali G, Riva E, Fiocchi A, Cordaro CI, Giovannini M. Efficacy and tolerability of levodropropizine and dropropizine in children with non-productive cough. *J Int Med Res*. 1995;23(3):175–83.
15. Catena E, Daffonchio L. Efficacy and tolerability of levodropropizine in adult patients with non-productive cough. Comparison with dextromethorphan. *Pulm Pharmacol Ther*. 1997;10(2):89–96.
16. Luporini G, Barni S, Marchi E, Daffonchio L. Efficacy and safety of levodropropizine and dihydrocodeine on nonproductive cough in primary and metastatic lung cancer. *Eur Respir J*. 1998;12(1):97–101.
17. Kim DS, Sohn MH, Jang GC. Levodropropizine in children with bronchitis. *Diagn Treatment*. 2002;22(9):1029–34.
18. De Blasio F, Dicpinigaitis PV, Rubin BK, De Danieli, G, Lanata L, Zanasi A, et al. An observational study on cough in children: epidemiology, impact on quality of sleep and treatment outcome. *Cough*. 2012;8(1):1. doi:10.1186/1745-9974-8-1.
19. De Blasio F, Lanata L, Dicpingaitis PV, Federico S, Rossella B, Alessandro Z, et al. Efficacy of levodropropizine in the pediatric setting: A meta-analysis of published studies. *Trends Med* . 2013;13(1):9–14.
20. Zanasi A, Lanata L, Fontana G, Federico S, Peter D, De F, et al. Levodropropizine for treating cough in adult and children: a meta-analysis of published studies. *Multidiscip Respir Med*. 2015;10(1):19–19.
21. Zanasi A, Lanata L, Saibene F, Fontana G, Dicpinigaitis PV, Venier V, et al. Prospective study of the efficacy of antibiotics versus antitussive drugs for the management of URTI-related acute cough in children. *Multidiscip Respir Med*. 2016;13(11):29. doi:10.1186/s40248-016-0059-y.
22. Bruschi C, Crotti P, Dacosto E, Fanfulla F, Daffonchio L, Novellini R. Levodropropizine does not affect P0.1 and breathing pattern in healthy volunteers and patients with chronic respiratory impairment. *Pulm Pharmacol Ther*. 2003;16(4):231–6.
23. Mannini C, Lavorini F, Zanasi A, Federico S, Luigi L, Giovanni F, et al. A Randomized Clinical Trial Comparing the Effects of Antitussive Agents on Respiratory Center Output in Patients With Chronic Cough. *Chest*. 2017;151(6):1288–94.
24. Shankar PS, Korukonda K, Bendre S. Diagnoses and management of adult cough: An Indian Environmental Medical Association (EMA) position paper. *Respir Med*. 2020;168:105949–105949.
25. Amdekar Y, Chokhani R, Palaniraman R. Standard treatment guidelines. Available from: https://iapindia.org/pdf/Ch-150-Management-of-Cough-in-Office-Practice.pdf.

26. Molassiotis A, Smith JA, Mazzone P, Blackhall F, Irwin RS. CHEST Expert Cough Panel. Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report. *Chest*. 2017;151(4):861–74. doi:10.1016/j.chest.2016.12.028.
27. Levodropropizine Oral suspension DCGI approval . [Accessed on 29th May 2023]. Available from: https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=MzIxOQ==.Accessedon29th.
28. Lee S, Nam KY, Oh J, Lee S, Cho SM, Choi Y, et al. Evaluation of the effects of food on levodropropizine controlled-release tablet and its pharmacokinetic profile in comparison to that of immediate-release tablet. *Drug Des Devel Ther*. 2018;12:1413–20. doi:10.2147/DDDT.S146958.
29. Ciprandi G, Licari A, Tosca MA, Marseglia GL. Levodropropizine in children: over thirty years of clinical experience. *J Biol Regul Homeost Agents*. 2021;35(4). doi:10.23812/21-176-L.

Author biography

Amar Shirsat, Manager Medical Services

Abhijit Trailokya, Head Medical Services

Shaijesh Wankhede, Senior Manager Medical Services

Cite this article: Shirsat A, Trailokya A, Wankhede S. Levodropropizine: A promising peripherally acting antitussive agent. *IP Indian J Immunol Respir Med* 2023;8(2):53-61.