Biological E. Limited
Celebrating Life Every Day

NeoGyn
A Division of Biological E. Limited

In the management of Cough

Rx COSCOGEN®

Levocloperastine fendizoate 20mg/5ml Suspension

Restful night, playful days

Delicious Mango Flavour

DAILY DOSAGE
5ml TID



The Next-Generation *Cough Specialist*

SURVEY ARTICLE

Insights into Physician's Perceptions of Levocloperastine's Safety and Efficacy in Children: An Online Survey in Clinical Practice

KRISHNA DEEPAK SATHIRAJU

ABSTRACT

Cough is a common symptom in pediatric patients, often requiring effective and well-tolerated antitussive treatments. Although traditional agents like dextromethorphan and codeine are effective, they are associated with side effects like drowsiness, nausea, and dependency risks. Levocloperastine (LCP), a nonopioid antitussive, has emerged as a safer alternative with a dual mechanism of action targeting both central and peripheral pathways. This manuscript highlights the findings from an online survey that gathered insights from Indian physicians regarding their perceptions of LCP's safety and efficacy in children aged 2 to 15 years. The survey data came from 161 physicians through a structured electronic questionnaire. Results indicated high physician confidence in LCP's rapid onset of action, tolerability, and minimal side effects. Notably, 86.6% of participants prescribed LCP in their clinical practice to the children, with 69.6% finding it faster-acting than traditional agents. Additionally, 80.7% reported reduced night-time sleep disruptions, and 96.9% found it well-tolerated in pediatric patients. These findings align with existing literature and reinforce LCP's role as a preferred antitussive in pediatric cough management.

Keywords: Levocloperastine, pediatric cough, children, antitussive, physician perception, safety, efficacy, tolerability

Cough, although an essential innate defense mechanism of the respiratory tract to clear mucus, noxious substances, and infections from the larynx, trachea, and larger bronchi, can become bothersome to patients or signal underlying pathology when persistent[1]. Sensitization of cough receptors caused by elevated levels of inflammatory mediators (such as prostaglandins, bradykinin, histamine, and leukotrienes), chemical irritants (like aerosol sprays), pollutants, or bronchoconstriction can result in a dry cough[1]. When prolonged for more than 8 weeks, such a cough can interfere with normal breathing, disrupt sleep, and lead to absenteeism or general weakness[1]. Physicians frequently prescribe dextromethorphan and codeine to manage dry cough. However, their associated side effects, including drowsiness, nausea, vomiting, dizziness, and dry mouth, highlight the need for more effective and better-tolerated antitussive options[1]. Levocloperastine (LCP), the levorotatory isomer of DL-cloperastine, is a widely used nonopioid antitussive agent with a rapid onset of action[1]. It is known for its proven efficacy, safety, and tolerability in treating cough associated with various acute and chronic conditions[2].

Levocloperastine acts through a dual mechanism, targeting both the central bulbar cough center and peripheral receptors in the tracheobronchial tree, making it a promising medication in cough management[1]. LCP exerts its antitussive effect by peripherally inhibiting the release of inflammatory mediators and reducing bronchospasm[1]. This dual action not only suppresses the cough reflex but also addresses the underlying inflammatory and bronchial factors, which explains its high efficacy and excellent tolerability in managing cough across a wide range of acute and chronic respiratory conditions[1].

Safety and tolerability are critical factors in pediatric therapeutics, and LCP has consistently demonstrated a favorable profile. LCP does not exhibit central nervous system (CNS) adverse effects such as drowsiness or reduced attention levels, which are commonly associated with opioid-based antitussives like codeine[3].

Consultant Physician
Alkapur Township, Hyderabad, Telangana, India
Address for correspondence
Dr Krishna Deepak Sathiraju
Consultant Physician
Alkapur Township, Hyderabad, Telangana, India
E-mail: skrishnadeepak@gmail.com

Additionally, LCP does not cause dry mouth, nausea, dependence, or show significant drug-drug interactions[3]. Clinical trials have reported only mild and transient nausea as an adverse event and no significant changes in laboratory parameters with the use of LCP[3]. Furthermore, animal studies have shown no clinically relevant sedation effects with LCP, even at doses up to 450-fold higher than the therapeutic[3].

Despite proven efficacy and safety, data on its use in Indian pediatric patients is sparse. This study aims to fill that gap by exploring the perceptions of Indian physicians regarding LCP's efficacy and safety in children aged 2 to 15 years.

AIM AND OBJECTIVE

This study aimed to gain insights into physicians' perceptions of the safety and efficacy of LCP in managing dry cough in pediatric patients (children aged 2-15 years). Additionally, the study explored the physicians' (including Pediatricians, General Practitioners, Family Physicians, and Consultant Physicians) preferences for prescribing this medication and factors influencing prescribing decisions.

METHOD

The study is a physician perception-based survey. The survey tool was developed for the study in the form of a structured questionnaire comprising multiple-choice questions and rating scales, which was pilot-tested amongst a representative sample of doctors. The survey was correctly interpreted and understood by the doctors. Survey participants included physicians who have prescribed LCP to children for cough. The survey was distributed to 250 doctors (including Pediatricians, General Practitioners, Family Physicians, and Consultant Physicians) who have used LCP in their clinical practice. Participants were assured about the survey's purpose and the maintenance of their anonymity.

Data was collected through an electronic case report form (eCRF) distributed via an online survey platform with a specified deadline to ensure efficiency, which was then subjected to descriptive statistical analyses, including counts and percentages for categorical variables, using SPSS® Version 23.0 software.

RESULTS

The survey was sent to 250 physicians (including Pediatricians, General Practitioners, Family Physicians, and Consultant Physicians) who incorporate LCP in their clinical practice, and a response was received from 161 doctors. The results highly favored LCP in various aspects.

Most of the respondents were pediatricians (88.2%), who mainly (82.0%) practiced in urban areas. A small percentage of responders practiced in the rural (11.8%) and suburban areas (6.2%).

Among the responders, most physicians (43.5%) reported encountering 10 to 20 consultations for cough per week, next 22.4% reported 21 to 40 consultations, 22.4% reported more than 40 consultations weekly, and only 11.8% reported fewer than 10 consultations.

Prescribing Pattern

When asked about prescribing LCP to children aged 2 to 15 years, most physicians (46.0%) reported prescribing it frequently, 40.4% reported prescribing occasionally, while only 13.7% of physicians said they do not prescribe it but are considering it (Fig. 1).

Efficacy Outcomes

When asked about their insights on efficacy, particularly the time it takes for patients to experience relief from coughing with LCP, 46.0% said relief was seen in less than 6 days, 46.6% noted it took 6 to 10 days, and 7.5% reported it took 11 to 15 days (Fig. 2). Furthermore, on comparing with other cough medications like dextromethorphan and codeine, most physicians (69.6%) found that LCP acted faster, 29.2% reported it had a similar onset of action, while only 1.2% found its action slower (Fig. 3).

Regarding symptom relief, a significant percentage of physicians (80.7%) believed that LCP reduces sleep disruption due to night-time coughing and irritability in children, while 19.3% did not agree with this. Furthermore, a great majority of the physicians (85.7%)

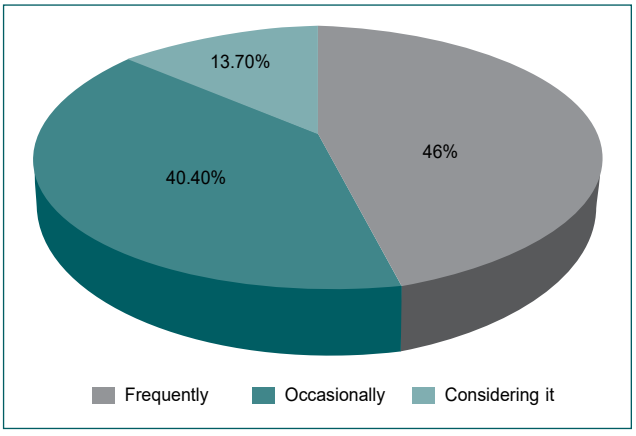


Figure 1. The prescribing pattern of LCP among physicians for children aged 2 to 15 years.

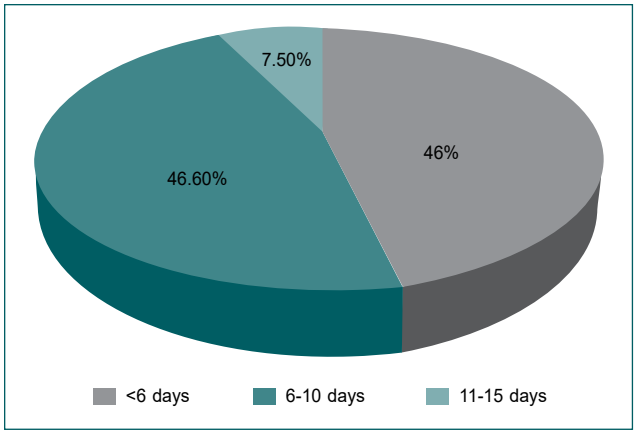


Figure 2. Time taken by patients to experience relief from coughing with LCP.

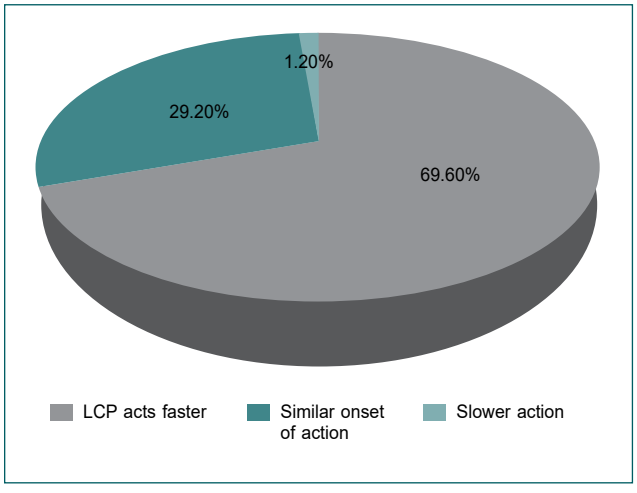


Figure 3. Action of LCP in comparison with dextromethorphan and codeine.

found LCP suitable for treating cough caused by respiratory tract infections, allergic rhinitis, chronic sinusitis, or other conditions causing cough in children aged 2 to 15 years.

Safety Outcomes

Various questions were asked to assess the safety profile of LCP. Regarding encountering central adverse events such as sedation, addiction, dependency, or interference with cardiovascular and gastrointestinal functions with LCP, 17.4% reported never encountering such events, 26.1% and 29.8% reported rare and occasional occurrences, respectively, while 26.7% said these events occurred very often. On comparing the safety profile of LCP to dextromethorphan and codeine, most physicians (67.1%) perceived that LCP has a markedly better safety profile, 28.0% considered LCP had a slightly better safety profile, and 5.0% believed it had side effects on par with dextromethorphan and codeine (Fig. 4).

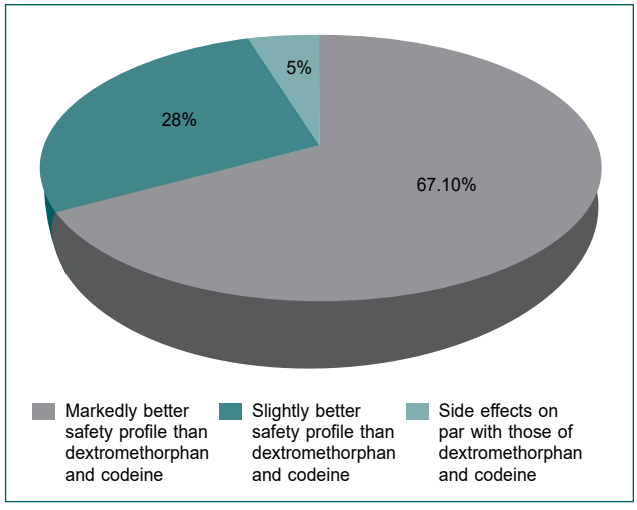


Figure 4. Safety profile of LCP in comparison to dextromethorphan and codeine.

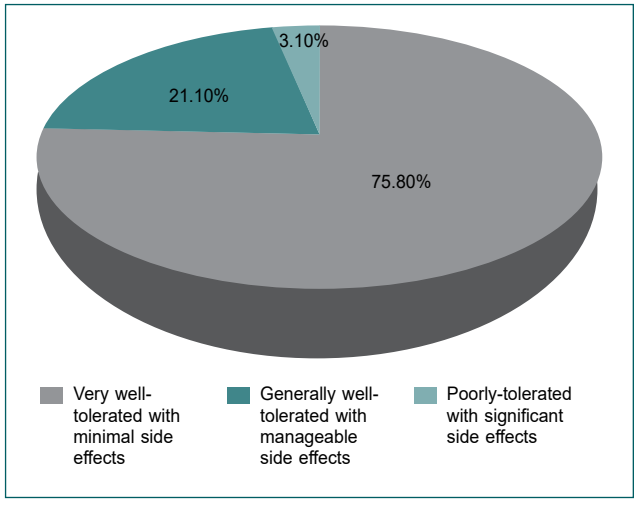


Figure 5. Tolerability of LCP.

Regarding the tolerability of LCP in children aged 2 to 15 years, a majority of physicians (75.8%) reported it was very well-tolerated with minimal side effects, 21.1% found it generally well-tolerated with manageable side effects, and only 3.1% reported it was poorly-tolerated with significant side effects (Fig. 5).

For assessing the optimum dose of LCP in children aged 2 to 15 years, various options were provided, among which the maximum responders (49.1%) recommended the dose of 1 mg/kg BD for 2 to 12 years and up to 60 mg BD for 12 to 15 years, for not more than 7 days. The next (36.0% of physicians) recommended dose was 2 mL (or 8 mg) BD for 2 to 4 years, 3 mL (or 12 mg) BD for 4 to 7 years, 4 mL (or 16 mg) BD for 7 to 12 years, and 5 mL (or 20 mg) BD for 12 to 15 years for not more than 7 days (each 5 mL suspension contains Levocloperastine fendizoate 35.4 mg equivalent to Levocloperastine

hydrochloride 20 mg); followed by (7.5% of physicians) 0.5 mg/kg BD for 2 to 12 years and 1 mg/kg for 12 to 15 years, both for up to 7 days. The remaining 7.4% of the physicians suggested other doses.

Considering no theoretical LD50 for LCP and no chances of death in doses as high as 2,000 mg/kg, 52.2% of the physicians felt very comfortable, 28.6% felt comfortable, and 19.3% felt considerate for prescribing LCP, as they previously were unaware of this (Fig. 6).

Finally, when asked to rate the effectiveness of LCP in reducing cough severity and frequency in children aged 2 to 15 years on a scale of 1 to 5, where 1 was minimum and 5 was maximum, the majority (54.0%) rated 5.00 followed by 28.6% as 4.00, underscoring the high preference for LCP particularly among the physicians (Fig. 7).

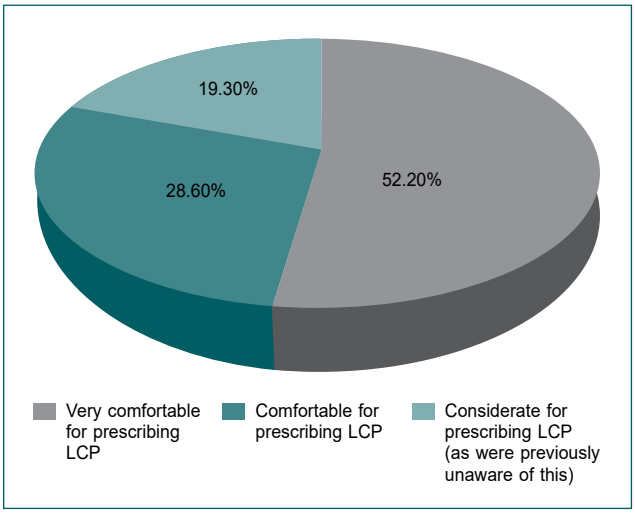


Figure 6. Prescribing comfort among physicians considering no theoretical LD50 for LCP and no chances of death in doses up to 2,000 mg/kg.

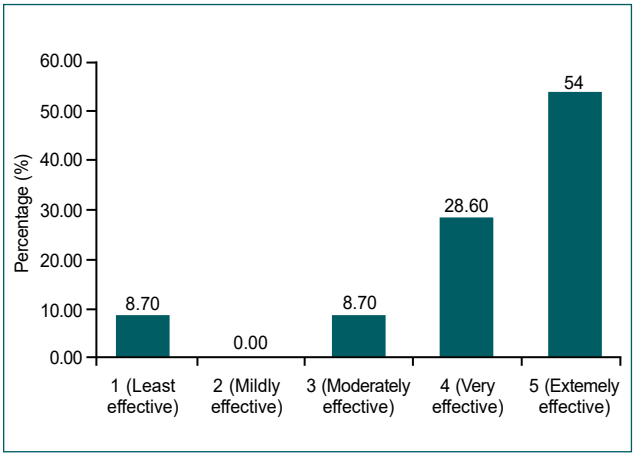


Figure 7. Physicians' rated effectiveness of LCP in reducing cough severity and frequency in children aged 2 to 15 years.

DISCUSSION

Levocloperastine's efficacy and tolerability, as observed in this study, align with previous research.

It was noted that 86.6% of the physicians prescribed LCP either frequently or occasionally. An expert survey by Vogelberg et al (2023) also proved the preference for antitussives among experts for reducing cough frequency and cough-related sleep disruptions[4].

A substantial 46.0% of the physicians said that they saw relief in coughing in less than 6 days, which aligns with the findings of Satish et al (2018), who reported minimal important difference in 5.3 days, reflecting the high antitussive effect of LCP in Indian patients[1].

Most physicians (69.6%) perceived LCP as faster-acting than traditional antitussives like dextromethorphan and codeine. It is in accordance with the randomized comparative trials carried out by Belloni and Gelsomini in 160 children, who found that LCP caused more rapid improvements in clinical symptoms than their comparators[5-7].

A significant percentage of physicians (80.7%) believed that LCP reduces sleep disruption due to night-time coughing and irritability in children. Belloni and Gelsomini, also in their studies, found that LCP reduced the intensity of cough and night-time awakenings, and improved sleep patterns, with a subsequent reduction in irritability[5-7].

In our study, 85.7% of physicians considered LCP suitable for treating respiratory tract infections, allergic rhinitis, chronic sinusitis, or other conditions causing cough in children aged 2 to 15 years. Satish et al (2018) also found LCP to provide a similar improvement in respiratory symptoms across cases of acute, subacute, and chronic dry cough, thus proving its efficacy irrespective of cough duration[1].

The safety and tolerability findings in our study were notably favorable. Among physicians surveyed, 17.4% reported that central adverse events such as sedation, addiction, dependency, or interference with cardiovascular and gastrointestinal functions never occurred with LCP, while 26.1% reported them as rare. Aliprandi et al (2002) have also described LCP as devoid of central antinociceptive activities, addiction, or dependence phenomena, and also does not interfere with cardiovascular or gastrointestinal functions[7]. Additionally, they found its efficacy comparable to codeine and superior to dextromethorphan[7]. Similarly, Satish et al (2018) confirmed these findings, reinforcing the drug's favorable safety and tolerability profile, likely

attributable to its dual mechanism of action and distinct stereoisomeric configuration (levoisomer)[1].

In our study, a higher percentage of physicians (96.9%) considered LCP to have a good tolerability profile with minimal and manageable side effects, and 95.1% of physicians considered the safety profile of LCP better than dextromethorphan and codeine, which is in accordance with a study by Ghosh et al (2019), who found the occurrence of adverse events only in the dextromethorphan group and not in the LCP group[8].

Maximum physicians (49.1%) recommended 1 mg/kg BD dose of LCP for 2 to 12 years and up to 60 mg BD dose for 12 to 15 years, for not more than 7 days. The next commonly recommended dose (36.0%) was 2 mL BD for 2 to 4 years, 3 mL BD for 4 to 7 years, 4 mL BD for 7 to 12 years, and 5 mL BD for 12 to 15 years for not more than 7 days. Belloni (1992), in children aged 2 to 11 years and Gelsomini (1992), in children aged 2 to 13 years, utilized the dose of 8 mg bid for less than 4 years, 12 mg BD for 4 to 7 years, and 20 mg BD for more than 7 years for 8 to 10 and 6 to 8 days, respectively, for the treatment of pediatric cough[5-7].

About 80.8% of physicians comfortably prescribed it as they knew that there is no theoretical LD50 for LCP; thus, there would be no death or major side effects at doses as high as 2,000 mg/kg, ensuring a high level of safety. Notably, the oral LD50 of codeine is 427 mg/kg^{-1} (rats)[9], and that of dextromethorphan is 116 mg/kg (rats)[10].

Finally, when asked to rate the effectiveness of LCP in reducing cough severity and frequency in children aged 2 to 15 years on a scale of 1 to 5, the majority (91.3%) rated it as good to excellent.

Comparatively, the survey's findings highlight a preference for LCP among physicians over codeine and dextromethorphan for pediatric patients.

CONCLUSION

The findings of this survey underscore LCP's favorable safety and efficacy profile in managing pediatric cough. Physicians reported significant improvements in cough frequency, severity, and associated symptoms such as night-time sleep disruptions and irritability. Compared to traditional antitussives, LCP demonstrated faster action, better tolerability, and a reduced risk of central adverse effects. The high level of physician comfort in prescribing LCP, even at higher therapeutic doses, further highlights its safety. These insights, combined with supporting evidence from clinical studies, reinforce LCP as a reliable and effective choice for pediatric cough management in Indian clinical practice. Further real-world studies are recommended to strengthen these findings and optimize treatment protocols for broader adoption.

Acknowledgments

The authors express their sincere gratitude to all the participating physicians for their valuable insights. They also thank Dr. Nikita Agrawal from the IJCP Group for her medical writing support.

Ethical Declaration

As this study is based on a survey, ethical approval was not required.

Data Availability

All relevant data supporting the findings of this study are included in this article.

Funding

This study was conducted by Biological E Ltd. under a medical grant.

REFERENCES

1. Satish K, Sholapuri D, Niranjane V, Garg S. Efficacy and safety of levocloperastine in the treatment of dry cough: a prospective observational study. J Assoc Physicians India. 2018;66(5):71-5.
2. Aliprandi P, Castelli C, Bernorio S, Dell'Abate E, Carrara M. Levocloperastine in the treatment of chronic nonproductive cough: comparative efficacy versus standard antitussive agents. Drugs Exp Clin Res. 2004;30(4):133-41.
3. Milani M. Levocloperastine: A review on pharmacodynamics, clinical efficacy, tolerability and safety in the treatment of chronic cough. Online J Med Med Sci Res. 2013;2(1):1-5.
4. Vogelberg C, Cuevas Schacht F, Watling CP, Upstone L, Seifert G. Therapeutic principles and unmet needs in the treatment of cough in paediatric patients: review and expert survey. BMC Paediatr. 2023;23(1):34.
5. Belloni C. Controlled evaluation of the efficacy and tolerability of LCPR/F in the treatment of cough in children. Clinical study of oral suspension of levocloperastine (Aesculapius) vs levodropropizine syrup. Data on file. Aesculapius Farmaceutici SpA, Magis Farmaceutici SpA, 1992.
6. Gelsomini S. Efficacy and tolerability of L-clofend in the treatment of paediatric cough: a controlled, randomised study of L-CP oral suspension vs levodropropizine syrup. Data on file. Aesculapius Farmaceutici SpA, Magis Farmaceutici SpA, 1992.

7. Aliprandi P, Cima L, Carrara M. Therapeutic use of levocloperastine as an antitussive agent. Clin Drug Invest. 2002;22(4).
8. Ghosh A. Comparison of safety and efficacy of dextromethorphan and levocloperastine in treatment of dry cough: a randomized open label phase IV clinical trial. Int J Basic Clin Pharmacol. 2019;8(10):2284-7.
9. Drugbank Online [Internet]. Codeine. Updated January 3, 2025. Available from: https://go.drugbank.com/drugs/DB00318. Accessed January 3, 2025.
10. Sigma-Aldrich [Internet]. Safety Data Sheet. Updated March 29, 2022. Available from: https://www.sigmaaldrich.com/IN/en/sds/SIGMA/D2531?userType=undefined. Accessed January 3, 2025.

■■■■