Evidence for Self-Medication
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Deciphering the daily disruption of cough: the role of ambroxol in patient recovery and quality of life

Heidemarie Graeter, Lara Jagwanth and Anne-Laure Tardy

Ambroxol is a mucoactive agent which has been widely used to treat acute and chronic respiratory diseases associated with a disturbance of mucus formation and transport. More recent data demonstrated that acute and chronic cough have also significant negative impact on the daily lives of adults and children. This article evaluates the impact of ambroxol on cough recovery speed and quality of life, aligning endpoints with patients' expectations for self-care cough remedies.

Real-world data to evaluate the burden of cough on patients' quality of life

In a prospective cross-sectional study, 101 English patients with a mean age of 54.9 ± 15.2 years and chronic cough were enrolled [1]. The primary objective was to assess the impact of chronic cough on patient-reported outcomes using four validated methods. The EuroQoL 5 dimension, 5 level (EQ-5D-5L) evaluated patient perspective on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D-VAS (Visual Analogue Scale) is a 0—100 scale where patients are asked to indicate their overall health. The Leicester Cough Questionnaire (LCQ) assessed the impact of cough on quality of life, and the Work Productivity and Activity Impairment Scale (WPAI) addressed outcomes related to patient productivity and activity. In the studied population, overall EQ-5D score and mean EQ-5D VAS score were 0.7 and 68.3 compared to a score of 0.8 and 81.7 in the general UK population aged 55–64 years consistent with the average age in this study. Notably, individual LCQ items with the highest reported burden included psychological factors (embarrassment; frustration; feeling fed-up; concerns about what other people think) and social factors (annoying to partner, family, and friends; interrupted conversations; interferes with overall enjoyment of life). Regarding the physical domain, frequent coughing bouts, disturbed sleep, and sputum production were reported as being disruptive at least some of the time by most respondents. WPAI revealed that the percentage of work time missed because of the participants' chronic cough (absenteeism) was 4.5% (±14.5), and the percentage of impairment while working (presenteeism) experienced because of participants' chronic cough was 27.6% (±23.6). Total work productivity loss due to chronic cough was 30.3% (±24.5). Patients are expecting cough treatment to prevent the worsening of their cough (51%), to improve their sleep quality (49%) and to improve their cough symptoms more quickly (49%).

Ambroxol shortens cough duration, improves cough severity and promotes patients' quality of life

Ambroxol is recommended in the German Society for Pneumology and Respiratory Medicine's guideline for the diagnosis and treatment of adult patients with cough to shorten the duration of acute and subacute cough and reduce its intensity [2].

A post-hoc analysis of unpublished data was performed to evaluate the time to recover from chronic cough [3]. Primary objective of the unpublished study was to assess if increasing ambroxol to 120 mg/day would improve uninfected chronic obstructive bronchitis. Patients were randomly treated with either 60 mg/day of ambroxol (N=14), 120 mg/day of ambroxol (N=13) or placebo (N=14). Ambroxol up to 120 mg/day is recommended for adults and children over 12 years old for the therapy of acute respiratory tract disorders and for the initial treatment of chronic conditions up to 14 days. Treatment lasted from 7 to 22 days (average: 11.6 days). The time of recovery was defined as the first time when an absence of cough occurs and remains until the end of study. Regarding cough "during the daytime", 21% and 42% of the patients treated with ambroxol 60 mg and 120 mg respectively had a cough that lasted for less than 12 days whereas none of the patients recovered before 12 days in the

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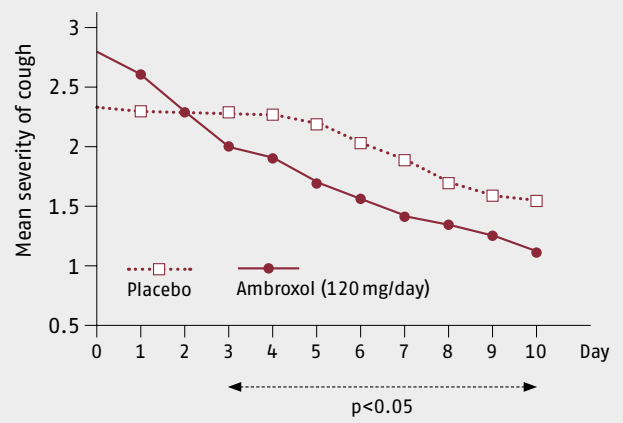

Fig. 1. Variation of mean severity of cough evaluated in a daily basis with a treatment with ambroxol (120 mg/day) or a placebo [adapted from 4].
0: no cough; 3: very severe cough, day and night

placebo group. Patients treated with ambroxol 60 mg and 120 mg are 8 (confidence interval 1.28–50.04) and 22 (3.08–157.34) times more likely to have a recovery of their cough "during the daytime" compared to placebo ($p = 0.0262$ and 0.0021). The median time to recovery was significantly shorter in the higher dose ambroxol group during the day ($p = 0.0014$ vs placebo). The effect is more pronounced for cough at night, where 54% and 58% of patients treated with ambroxol 60 mg and 120 mg respectively recovered from cough before 12 days, compared to 9% for the placebo group. Patients treated with ambroxol 60 mg and 120 mg are 12 (1.58–91.08) and 13 (1.80–101.12) times more likely to have a recovery of cough "during the night" compared to the placebo group ($p = 0.0163$ and 0.0113). The results demonstrated a significant reduction in the median time of cough at night recovery by four days for ambroxol 60 mg and 120 mg compared to placebo ($p = 0.0303$, 0.0215). No significant differences were found between ambroxol 60 mg and 120 mg. Ambroxol is known to be active at both doses and a major difference in time recovery was not expected since the study was not designed to primarily assess this endpoint but the overall improvement of symptoms.

In a double-blind, parallel-group study 60 patients with acute or obstructive airway disease were treated with ambroxol (120 mg/day, N=30) or a placebo (N=30) for 10 days. Mean patient self-reported severity of cough was significantly reduced after three days of treatment with ambroxol compared to placebo ($p < 0.05$). A cough severity graded at 2 (moderate, persistent at day and undisturbed at night) was reached after three days of treatment with ambroxol and more than six days in the placebo group (**Fig. 1**) [4].

Six hundred and seventy six patients with acute bronchitis were enrolled in a multicentre, randomised, double-blind, placebo-controlled, parallel-group study [5] and treated with ambroxol (N=163), an antibiotic (N=171), a phytopharmaceutical (N=170) or placebo (N=172) for two weeks. Particularly, patients received 90 mg/day of ambroxol for the first three days and 60 mg for the next eleven days. Treatment response rate evaluated by the physicians was significantly higher in the ambroxol (89.6%; 95% CI 83.8–93.8) compared to the placebo group (77.3%; 95% CI 70.3–83.4; $p < 0.05$) after 7±2 days. 50% of the patients experienced the absence of cough during the day after 14 days of treatment with ambroxol. This level of recovery of cough was never achieved in the placebo group. 40 % of the patients experienced the absence of cough at night after five days of treatment with ambroxol and after almost seven days of treatment with placebo. 50% of the patient experienced the absence of cough at night after seven days of treatment with ambroxol and after twelve days of treatment with placebo (**Fig. 2A**). Any improvement in night-time coughing is consistent with an improved sleep quality. The study also showed an improvement in disease-related quality of life. 40% of patients experienced good or very good well-being

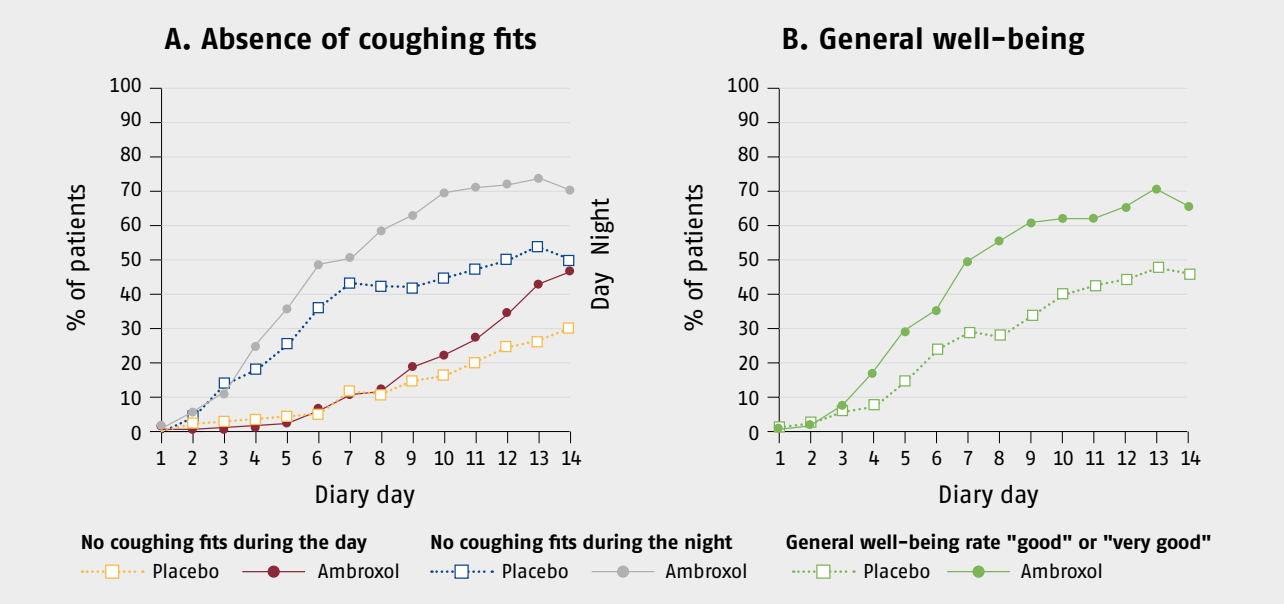

Fig. 2. (A) Percentage of patients with no coughing fits during the night and during the day, (B) Percentage of patients scoring a general well-being of at least as "good" during the treatment [adapted from 5].

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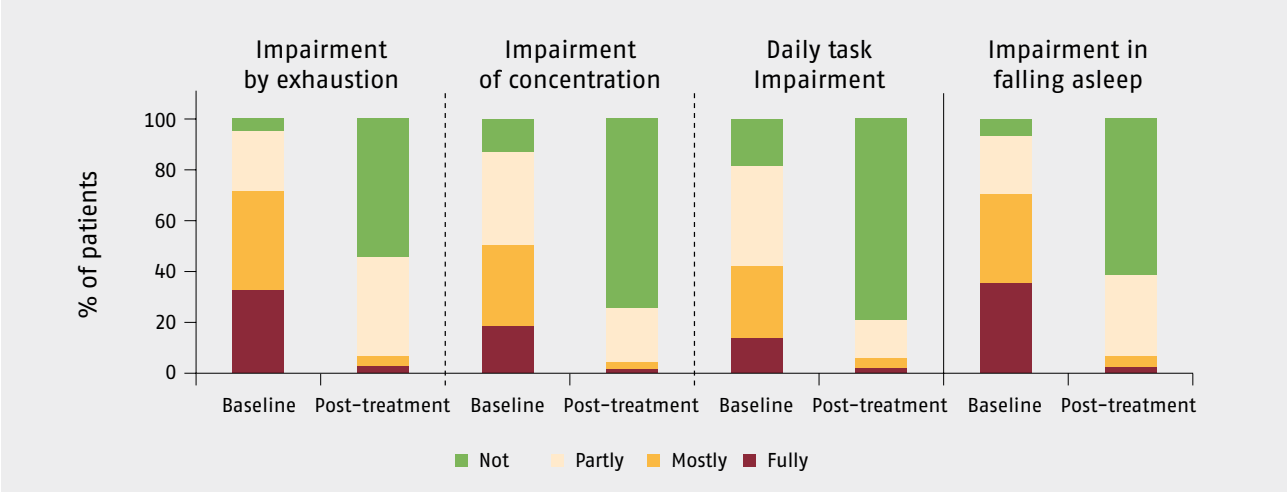

Fig. 3. Impairment in falling asleep and in ability to execute daily tasks before and after treatment with ambroxol (all preparations). Data are % of participants within a category [adapted from 6].

after six to seven days of treatment with ambroxol, while the placebo group did not achieve a comparable result before ten days of treatment (**Fig. 2B**).

Nine hundred and sixty five subjects with acute respiratory tract infections treated with ambroxol (extended-release capsules, adult syrup, paediatric syrup, or soft pastilles) were enrolled in a pharmacy-based survey [6]. 60.2% patients started treatment within the first two days of their cough and mean duration of treatment was 4.3 days (±0.9 days). Treating with any of the four formulations improved not only the symptom of cough but also the overall impact on quality of life. The percentage of patients experiencing full and most impairment in falling asleep decreased from 70% at baseline to less than 20% after treatment. The percentage of patients experiencing no exhaustion, no impairment of concentration and no impairment in performing daily task increased from around 3%, 15% and 20% respectively at baseline to 55%, 75% and 80 % after treatment with ambroxol (**Fig. 3**).

Patients with chronic bronchitis were enrolled in a double-blind placebo controlled multicentre trial and were treated with ambroxol (75 mg/day, N=86) or placebo (N=87) for 24 months [7]. The personal and economic importance of the treatment was reflected in a 32% reduction in the total number of days of incapacity to work due to chronic bronchitis compared to placebo (placebo: 1789 days, verum 1216 days; $p < 0.01$). Related to one month, this meant an average of 74.5 lost working days in the 87 patients of the placebo group compared with 50.6 days for the 86 patients treated with ambroxol ($p < 0.01$).

Conclusion

Recent data highlights the burden of cough on patient quality of life and illustrates current patients' expectation regarding treatment benefits. Considering these needs, the existing data on the well-known mucoactive agent ambroxol has been reviewed. Overall, studies demonstrated that ambroxol shortens cough duration by several days compared to placebo, decreases cough severity, and improves quality of life especially related to better quality of sleep resulting in better ability to perform daily tasks the following day. It's important to note that while existing data provides valuable insights, further robust studies are needed to fully explore ambroxol's potential benefits.

Summary

Patient-reported outcomes and insights demonstrated the burden of cough on their daily life and the importance of finding effective treatments. Ambroxol, well known in self-medication for acute and subacute cough, addresses patients' needs by shortening cough duration, reducing cough severity, lessening mucus production, improving quality of sleep and restoring the ability to work and to perform daily tasks.

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