Chronic Obstructive Pulmonary Disease: Management of adults with Chronic Obstructive Pulmonary Disease in Primary and Secondary Care

Managing Stable COPD
Antitussive therapy
Index

Author	Publication Date	ID
Sergysels, R. & Art, G. 2001, "A double-masked, placebo-controlled polysomnographic study of the antitussive effects of helicidine", *Current Therapeutic Research, Clinical & Experimental*, vol. 62, no. 1, pp. 35-47.	2001	1238
Barnabe, R., Berni, F., Clini, V., Pirrelli, M., Pisani, C. A., Robusch, M., Rossi, M., Sestini, P., Tana, F., Vaghi, A., Vagliasindi, M., & Bianco, S. 1995, "The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough", *Monaldi Archives for Chest Disease*, vol. 50, no. 2, pp. 93-97.	1995	1232
Del Donno, M., Aversa, C., Corsico, R., Foresi, A., Grassi, V., Malerba, M., Mastropasqua, B., Scoditti, S., & Olivieri, D. 1994, "Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough", *Drug Investigation*, vol. 7, no. 2, pp. 93-100.	1994	1233
Aversa, C., Cazzola, M., Clini, V., Dal Negro, R., Maiorano, V., Tana, F., & Allegra, L. 1993, "Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases", *Drugs Under Experimental & Clinical Research*, vol. 19, no. 6, pp. 273-279.	1993	1231

Wojcicki, J., Szwed, G., & Drozdowska, K. D. 1976, "The antitussive and expectorant drug Duopect evaluated by the preferential test", *Archivum Immunologiae et Therapiae Experimentalis*, vol. 24, pp. 549-552.	1976	80

Excluded references on full paper review
N=3

Author	**Publication Date**	ID	Exclusion Rationale
Light, R. W., Stansbury, D. W., & Webster, J. S. 1996, "Effect of 30 mg of morphine alone or with promethazine or prochlorperazine on the exercise capacity of patients with COPD", *Chest*, vol. 109, no. 4, pp. 975-981.	1996	1234	Outcome variable exercise tolerance, not cough. N=7
Sasaki, T., Sugiyama, M., & Sasaki, H. 1985, "Effects of the antitussive fominoben (PB89) on hypoxia in chronic obstructive lung disease: Comparison with dextromethorphan using a double-blind method", *Journal of International Medical Research*, vol. 13, no. 2, pp. 96-101.	1985	1237	Outcome variable hypoxia, not cough. Japanese subjects
Matthys, H., Erhardt, J., & Ruhle, K. H. 1985, "Objectifying of effect of antitussive agents by tussometry in patients with chronic cough", *SCHWEIZ MED WOCHENSCHR*, vol. 115, pp. 307-311.	1985	1235	Main text in Germany (abstract only English language)

Author / Title / Reference / Yr	Sergysels, R. & Art, G. 2001, "A double-masked, placebo-controlled polysomnographic study of the antitussive effects of helicidine", *Current Therapeutic Research, Clinical & Experimental*, vol. 62, no. 1, pp. 35-47. Ref ID: 1238
N=	N=30 Duration=3 nights / sleep recording was performed for 8 hrs. Location=Belgium. Sites=One
Research Design	Double masked, randomised placebo controlled study
Aim	To compare the antitussive effect of helicidine 10% syrup with a placebo
Operational Definition	Cough was defined as >20 cough episodes per night or 3 per sleeping hour for 2 consecutive nights Severity of COPD not specified
Population	Stable COPD
Intervention	Helicidine 10% syrup two 15 ml doses for 3 nights tds
Comparison	Identical placebo syrup two 15 ml doses for 3 nights tds.
Outcomes	Primary efficacy end point: Frequency and relative duration of cough episodes during the sleeping period. Secondary efficacy end points: Number of micro awakenings per night / Modified Spiegel score (modification consisted of adding an item regarding nocturnal cough). Scores from patient and investigator Clinical Global Impression assessments regarding cough improvement Tertiary (exploratory only) efficacy end points: Sleep efficacy / Frequency and relative duration of cough during the falling asleep and awakening periods.
Characteristics	Mean age 55yr for placebo group and 49 yrs for Helicidine group. Gender 6 males and 9 females in the placebo group / 9 males and 6 females in the Helicidine group FEV1 not provided, hence severity of COPD unavailable. N=13 placebo and N=11 in Helicidine group had “concomitant chronic treatment as maintenance therapy.“
Results	Intention-to-treat analysis: The frequency and duration of cough during the sleeping and awakening period were significantly less ($p<0.05$) with the use of Helicidine compared to placebo (parametric and nonparametric statistical methods). Per protocol analysis: The frequency of cough during the sleeping and awakening period were significantly less ($p<0.05$) with the use of Helicidine compared to placebo using parametric statistical methods. Duration of cough was significant only when applying a nonparametric approach. There were no significant differences between the Helicidine and placebo group for the secondary outcomes, both the intention-to-treat and the per–protocol analyses, regardless of the statistical method used (parametric and nonparametric). Only two of the five tertiary outcomes were statistically significant ($p<0.05$) in favour of the Helicidine group. Cough frequency at awakening was statistcally significant (intention to treat and per protocol, parametric and nonparametric analysis). Relative cough duration during the awakening period was only significant in the per protocol analysis utilising a non-parametric approach.
SIGN Quality Rating	-
Hierarchy of Evidence	1b

Grading	
NCC CC ID	1238

Author / Title / Reference / Yr	Barnabe, R., Berni, F., Clini, V., Pirrelli, M., Pisani, C. A., Robusch, M., Rossi, M., Sestini, P., Tana, F., Vaghi, A., Vagliasindi, M., & Bianco, S. 1995, "The efficacy and safety of moguisteine in comparison with codeine phosphate in patients with chronic cough", *Monaldi Archives for Chest Disease*, vol. 50, no. 2, pp. 93-97. Ref ID: 1232
N=	N=119. Location=In patients and out patients. Geographic site=6 centres in Italy Duration=2 days
Research Design	Multicentre, double blind parallel group randomised phase 11 study.
Aim	To compare the clinical efficacy of moguisteine to the reference standard codeine.
Operational Definition	Degree of cough rated on arbitrary scale
Population	Dry or slightly productive cough due to respiratory disorders.
Intervention	N=41 Moguisteine 100mg tid
Comparison	N=39 Codeine 15mg tid N=39 Codeine 30 mg tid
Outcomes	Visual analogue scale (VAS) scores of cough frequency, cough intensity and sleep disturbance were recorded by the patient at baseline and on each of the two days of treatment. Tape recording monitored nocturnal cough
Characteristics	Mean age 54yrs. Age range 18 to75 yrs N=61 males / N=58 females Three treatment groups were homogeneous to demographic data and type, duration and severity of cough. Two thirds of the participants were receiving concomitant medication, homogeneous distribution between the groups. Smokers varied between groups, Moguisteine N=4 smokers, Codeine 15mg N=7 smokers, Codeine 30mg N=11 smokers. Disorders underlying the cough were similar between groups and included: COPD N=46 / Malignant neoplasm 34 / Pulmonary fibrosis N=12 / cough of unknown aetiology N=13 / Other N=8
Results	Number of morning coughs over 6 hrs after first dose compared to baseline - Non-significant. Number of nocturnal coughs/hr after last evening dose compared to baseline – Moguisteine 33%, codeine 15mg 46% and codeine 30mg 53%. No significance level is stated for this parameter. Authors go on to state, “At baseline, the number of coughs/hr during the night and in the morning were significantly correlated (Rho=0.51, $p<0.05$)”. Participants visual analogue scale scores of cough frequency, cough intensity and sleep disturbance, plus investigators ranking of cough severity demonstrated a similar improvement in cough symptoms in all treatment groups. There were no serious adverse events. N=19 adverse events were recorded, N=2 Moguisteine group, N=3 Codeine 15mg group and N=5 Codeine 30mg group. Discontinuation of treatment was required in N=2 participants in the Codeine 30mg group.

	Outcome data not stratified for severity of cough
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1232

Author / Title / Reference / Yr	Del Donno, M., Aversa, C., Corsico, R., Foresi, A., Grassi, V., Malerba, M., Mastropasqua, B., Scoditti, S., & Olivieri, D. 1994, "Efficacy and safety of moguisteine in comparison with dextromethorphan in patients with persistent cough", *Drug Investigation*, vol. 7, no. 2, pp. 93-100. Ref ID: 1233
N=	N=129 Location=Italy. Geographic site=7 centres. Duration=2 days
Research Design	Randomised, single blind short term treatment study
Aim	To evaluate the efficacy and safety of Moguisteine
Operational Definition	Subjective cough rating for severity at study inclusion
Population	N=124 patients with persistent cough associated with various respiratory disorders.
Intervention	N=61 Moguisteine 3 doses of 200mg over 2/7
Comparison	N=63 Dextromethorphan 3 doses of 30mg over 2/7
Outcomes	Primary efficacy variable: % Reduction in coughs during a 6hr period (tape recordings) Secondary efficacy variables: Pts subjective assessment VAS scores of cough frequency and cough troublesomeness at night and during the morning. Safety
Characteristics	50% of population obstructive chronic bronchitis Age 18 to 75 yrs. Mean age 47yrs Moguisteine / 59yrs Dextromethorphan. Gender male/female Moguisteine 17/32 Dextromethorphan 12/38 Subject scale for cough severity. Population included those with severity rated at 11 or higher (11 equates to frequent cough, but not limiting normal activities and / or sleep). Concomitant medication was allowed.
Results	N=99 analysed for efficacy % Reduction in coughs Per protocol analysis for 6 and 4 hour period the % reduction in coughs was approximately 30% in each group: 6 hours: Moguisteine 29% / Dextromethorphan 30% 4 hours: Moguisteine 33% / Dextromethorphan 29% Intention to treat analysis for 6 and 4-hour period % reduction in coughs similar post drug % to above. Secondary efficacy variables

	Improvements were seen in both groups for symptoms, there were no differences between the treatments. Mean values of VAS scores for cough frequency were similar in both groups: Night time: Baseline 43% Moguisteine and 40% Dextromethorphan. Treatment was associated with a score reduction both on Moguisteine 30% and Dextromethorphan 26%. Morning: Baseline 48% Moguisteine and 45% Dextromethorphan. Treatment was associated with a score reduction both on Moguisteine 26% and Dextromethorphan 30% Safety No serious adverse events. Drug related adverse events were reported in 3/61 Moguisteine pts and 4/63 Dextromethorphan patients. Treatment was discontinued in 1 pt on Dextromethorphan. Compliance - 122/124 pts
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1233

Author / Title / Reference / Yr	Aversa, C., Cazzola, M., Clini, V., Dal Negro, R., Maiorano, V., Tana, F., & Allegra, L. 1993, "Clinical trial of the efficacy and safety of moguisteine in patients with cough associated with chronic respiratory diseases", *Drugs Under Experimental & Clinical Research*, vol. 19, no. 6, pp. 273-279. Ref ID: 1231
N=	N=87 Duration=4/7 Location=Italy Sites=5 centres / in and out patients
Research Design	Randomised, double-blind, placebo-controlled, multicentre trial
Aim	To evaluate the antitussive activity and safety of Moguisteine.
Operational Definition	Cough severity had to be equal to or higher than 11 (frequent cough not limiting normal activities and or sleep)
Population	Persistent dry or slightly productive coughs associated with chronic respiratory disorders (asthma and exacerbations excluded).
Intervention	N=42 Moguisteine 200 mg tid
Comparison	N=45 Placebo
Outcomes	N=73 per protocol efficacy analyses / N=83 ITT efficacy analysis / N=87 Safety analysis % Reduction of the total number of coughs during a 2 hour tape-recorded period (post drug treatment). Post drug % reduction of cough frequency score for day and nighttime. Safety.
Characteristics	Age range not given (inclusion criteria state 18 to 75yrs). Mean age 58yrs Gender male/female Moguisteine group 22/14, placebo 22/15

	Underlying disease disorders per Moguisteine / placebo groups: COPD 25/19=N44, unknown aetiology 5/8=N13, malignant neoplasm 3/4=N7, pulmonary fibrosis 2/4=N6, other resp conditions 1/2=N3. Concomitant medication permitted providing it was not new medication (>7 days), homogenous distribution for both groups.
Results	Mean number of coughs for 2 hour interval at baseline and after the last dose of drug overall: Moguisteine reduction from 121 to 64 coughs / Placebo reduction from 108 to 87 on placebo The mean % change of the number of coughs after treatment was 42 for Moguisteine and 14 for placebo. A significant difference was found in favour of Moguisteine ($p=0.028$) – per protocol analysis and ($p=0.012$) ITT analysis. Moguisteine did not show variation either by diagnosis or type of cough (dry / slight / productive). Analysis of diary cough scores during the day showed no significant differences between treatments. Nocturnal cough frequency score demonstrated mean % reductions significant for the Moguisteine group compared to the placebo group ($p<0.01$) (pre protocol analysis with similar result with the ITT analysis). Safety: No serious adverse events. 1 participant in the Moguisteine group complained of vomiting and 1 hypertensive participant in the placebo group experienced further increases in BP.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	1b
NCC CC ID	1231

Author / Title / Reference / Yr	Jerzy Wojcicky, Grazyna Szwed and Danuta Drozdowske-Ksiazek. The antitussive and expectorant drug Duopect evaluated by the preferential test. Archivum Immunologiae et therapiae experimentalis 1976 Vol24 p549-553.
N=	N=62 Duration=14 days Location=Poland Sites=Not stated
Research Design	Double blind preferential test (free choice).
Aim	To evaluate the effect of Duopect compared to Narcotine and Placebo on intensity and frequency of cough and expectoration in patients with chronic bronchitis.
Operational Definition	Nil stated
Population	N=62 heterogeneous disease population, see characteristics.
Intervention	Duopect, containing 0.017g narcotine hydrochloride and 0.12 glycerol guiacolate, one capsule qds Pts divided into groups A & B. Group A received Duopect & Narctoine N=31, Group B received Duopect and Placebo N=31. “The pts were given the drugs on the basis of personal preference”.
Comparison	Narcotine – 0.017g per capsule, one capsule qds. Placebo

Outcomes	Intensity and frequency of cough and expectoration. Evaluated on a preferential basis.
Characteristics	Age range disproportionate between groups - Group A 23-70 / Group B 37-72. However, mean 58yrs. Duration of illness varied from 1 to 28 yrs overall. Heterogeneous disease population: Chronic bronchitis N=45 / Asthmatic bronchitis N=10 / TB N=7
Results	Results not reviewed in light of large number of methodological weaknesses. Authors not contacted for clarification due to time limitation of project.
SIGN Quality Rating	-
Hierarchy of Evidence Grading	111
NCC CC ID	80