Sion 27 avril 2017

Toux chronique – Nouveautés thérapeutiques

JD Aubert Service de Pneumologie CHUV

canton de vaud

UNIL | Université de Lausanne

CHUV

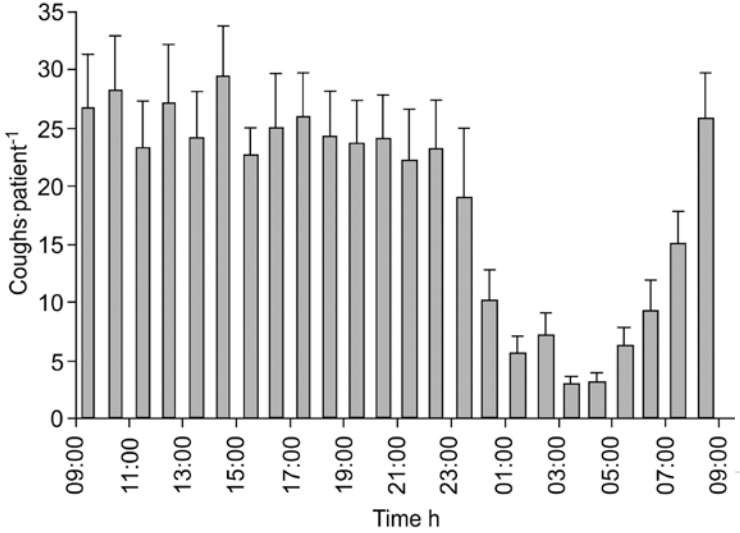
Agenda

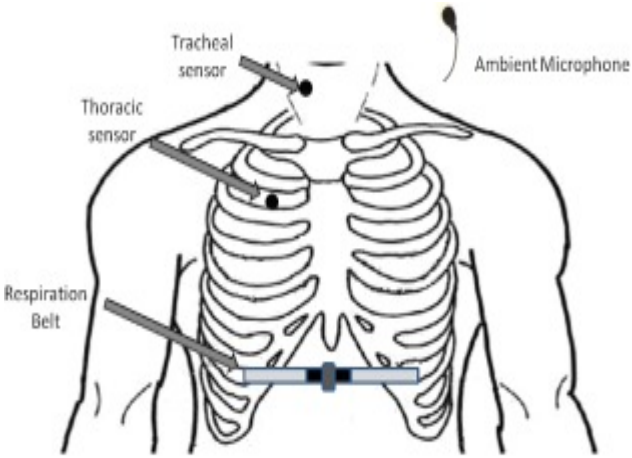
- Méthodes de mesure d’efficacité
- Essais cliniques avec des substances connues
- Essais cliniques avec de nouvelles substances
- Essais cliniques non pharmacologiques

Comment mesurer l’efficacité d’un anti-tussif ?

- Comptabiliser le nb de toux/heure (1h-24h)
- Scores subjectifs (nbx): Leicester cough questionnaire etc
- Test de sensibilité à la capsaïcine
- Visual analog score

Monitoring de la toux





Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ)

S S Birring, B Prudon, A J Carr, S J Singh, M D L Morgan, I D Pavord

This questionnaire is designed to assess the impact of cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1. In the last 2 weeks, have you had chest or stomach pains as a result of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

2. In the last 2 weeks, have you been bothered by sputum (phlegm) production when you cough?

1	2	3	4	5	6	7
Every time	Most times	Several times	Some times	Occasionally	Rarely	Never

3. In the last 2 weeks, have you been tired because of your cough?

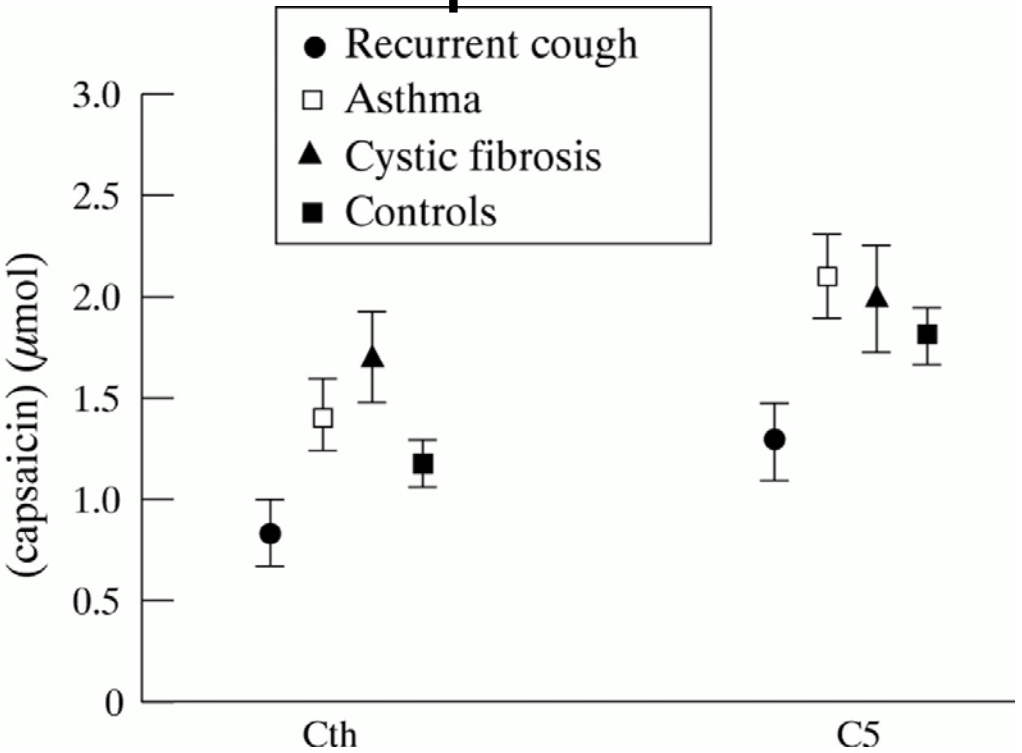
1	2	3	4	5	6	7
All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

4. In the last 2 weeks, have you felt in control of your cough?

1	2	3	4	5	6	7
None of the time	Hardly any of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time

5. How often during the last 2 weeks have you felt embarrassed by your coughing?

Test de provocation à la capsaïcine



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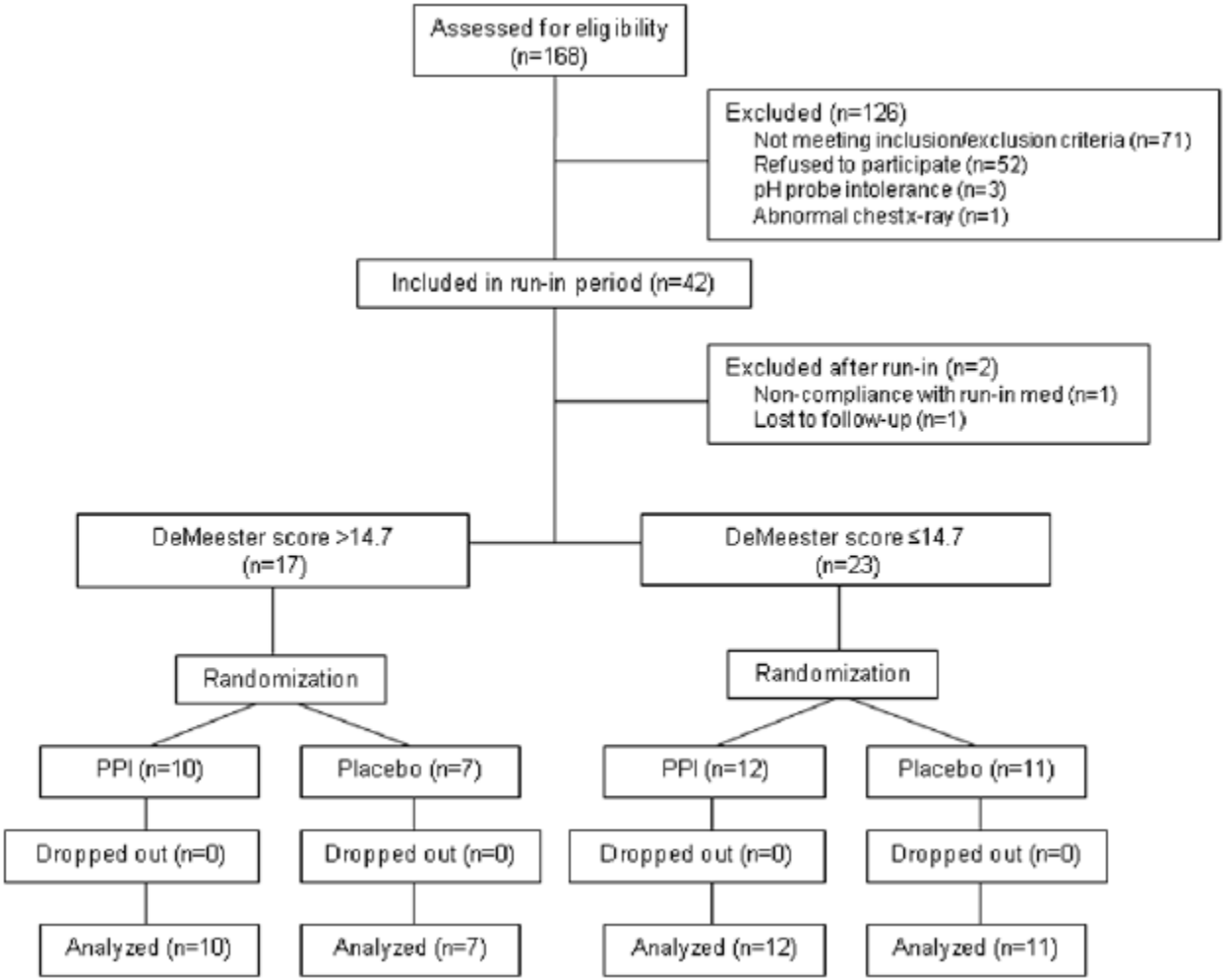
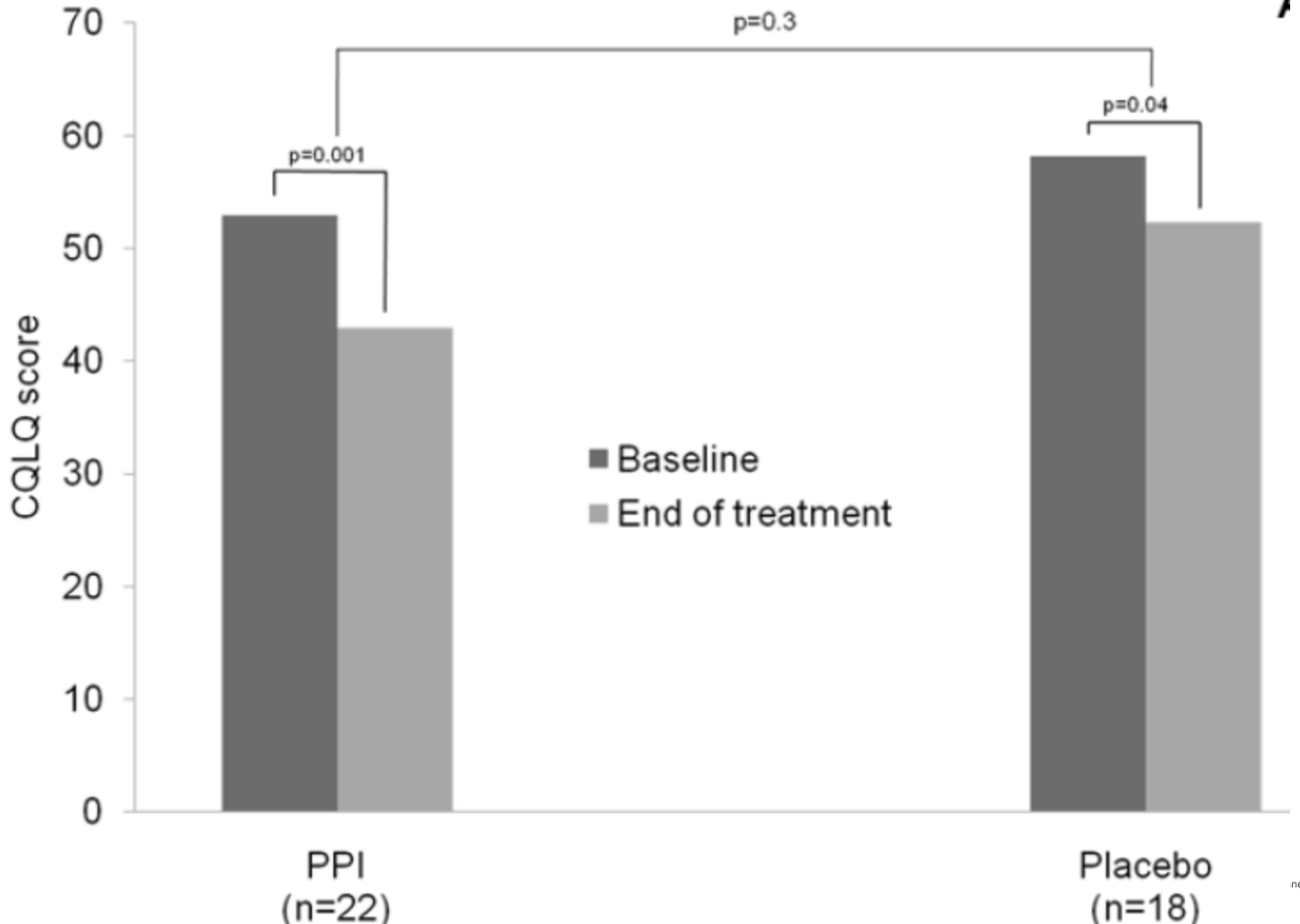
Les IPP

Aliment Pharmacol Ther. 2011 January ; 33(2): 225–234. doi:10.1111/j.1365-2036.2010.04511.x.

Clinical Trial: High-Dose Acid Suppression for Chronic Cough: A Randomized, Double-Blind, Placebo-Controlled Trial

Nicholas J. Shaheen, MD, MPH[1,2], Seth D. Crockett, MD, MPH[2], Stephanie D. Bright, BS[1,2], Ryan D. Madanick, MD[1,2], Robert Buckmire, MD[3], Marion Couch, MD, PhD[3], Evan S. Dellon, MD, MPH[1,2], Joseph A. Galanko, PhD[2], Ginny Sharpless[2], Douglas R. Morgan, MD, MPH[2], Melissa B. Spacek[1,2], Paris Heidt-Davis[1,2], and David Henke, MD, MPH[4]


Assessed for eligibility (n=168)
Excluded (n=126)
Not meeting inclusion/exclusion criteria (n=71)
Refused to participate (n=52)
pH probe intolerance (n=3)
Abnormal chest x-ray (n=1)
Included in run-in period (n=42)
Excluded after run-in (n=2)
Non-compliance with run-in med (n=1)
Lost to follow-up (n=1)
DeMeester score >14.7 (n=17)
DeMeester score ≤14.7 (n=23)
Randomization
Randomization
PPI (n=10)
Placebo (n=7)
PPI (n=12)
Placebo (n=11)
Dropped out (n=0)
Dropped out (n=0)
Dropped out (n=0)
Dropped out (n=0)
Analyzed (n=10)
Analyzed (n=7)
Analyzed (n=12)
Analyzed (n=11)


70
60
50
40
30
20
10
0
CQLQ score
p=0.3
p=0.001
p=0.04
Baseline
End of treatment
PPI
(n=22)
Placebo
(n=18)

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

Chronic cough and esomeprazole: A double-blind placebo-controlled parallel study

SHOAIB FARUQI, IAN D. MOLYNEUX, HOSNIEH FATHI, CAROLINE WRIGHT, RACHAEL THOMPSON AND ALYN H. MORICE

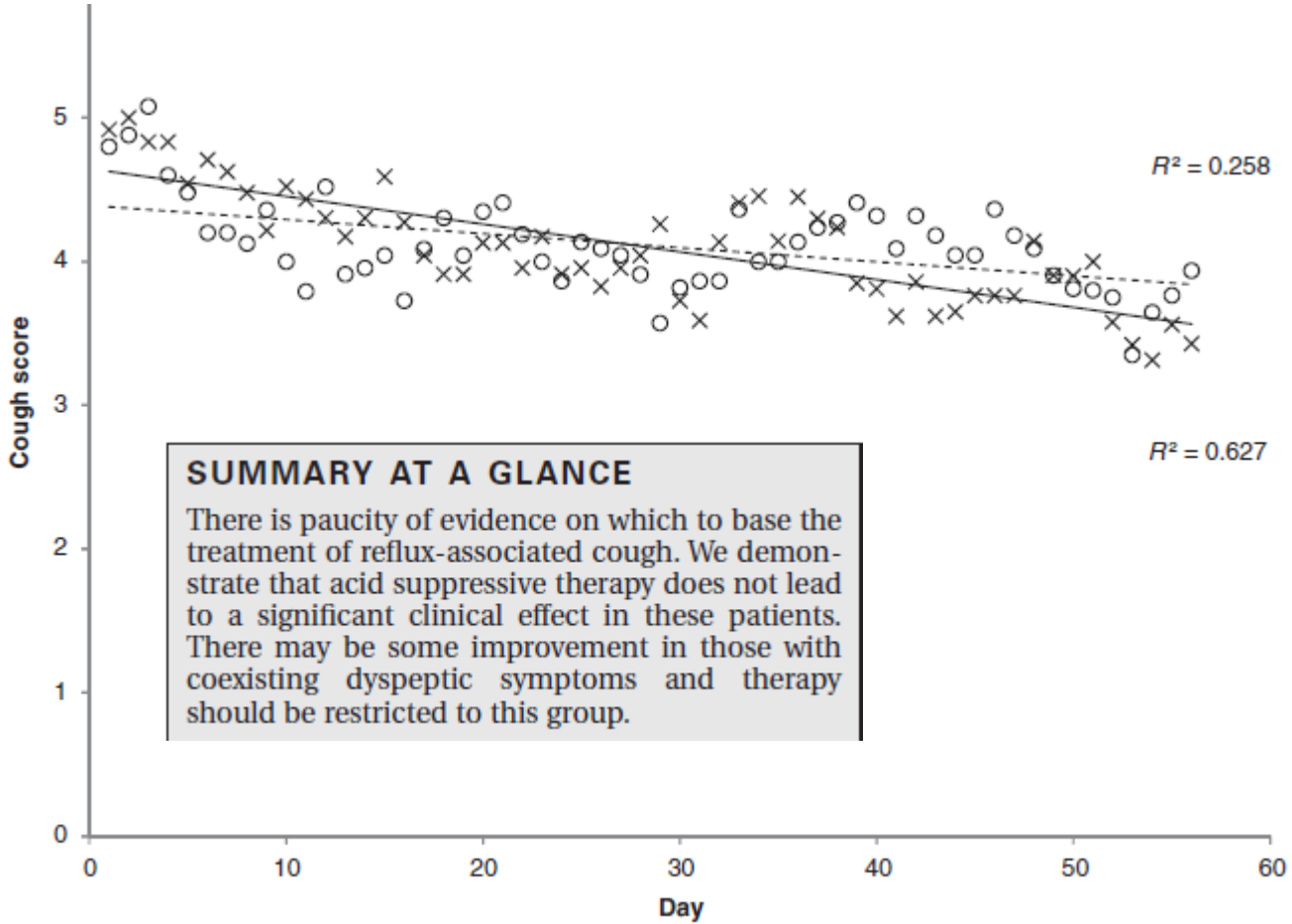


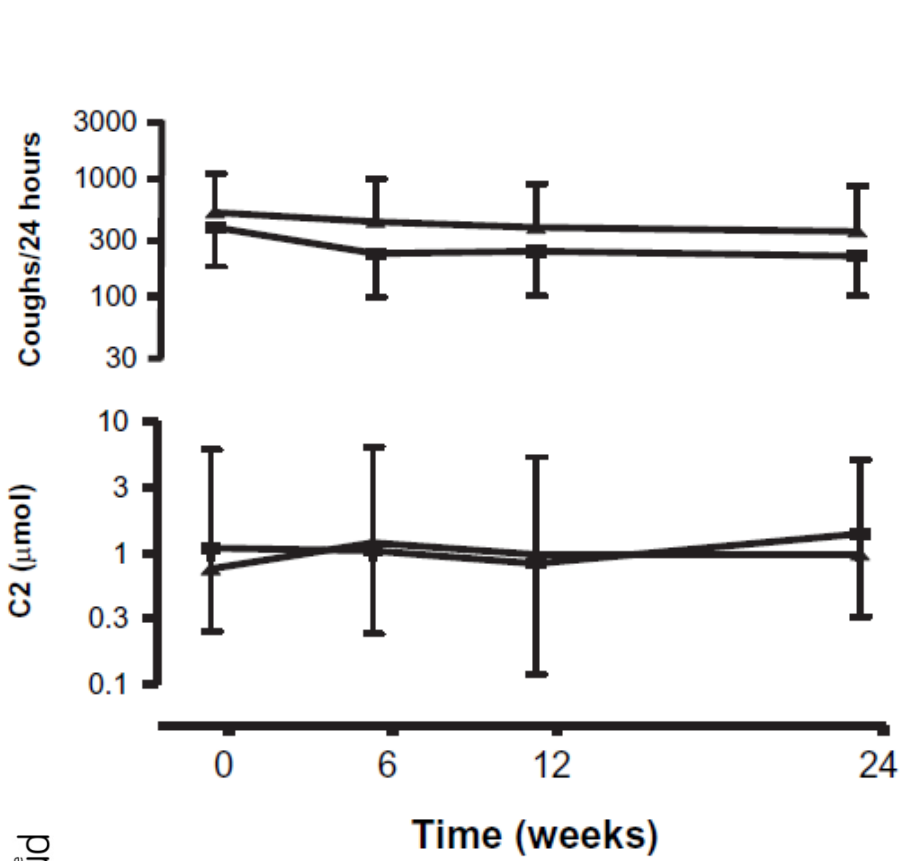
Figure 2 Mean diary cough scores during treatment period. (×) Treatment, (○) placebo, (——) linear (treatment), (- - -) linear (placebo).

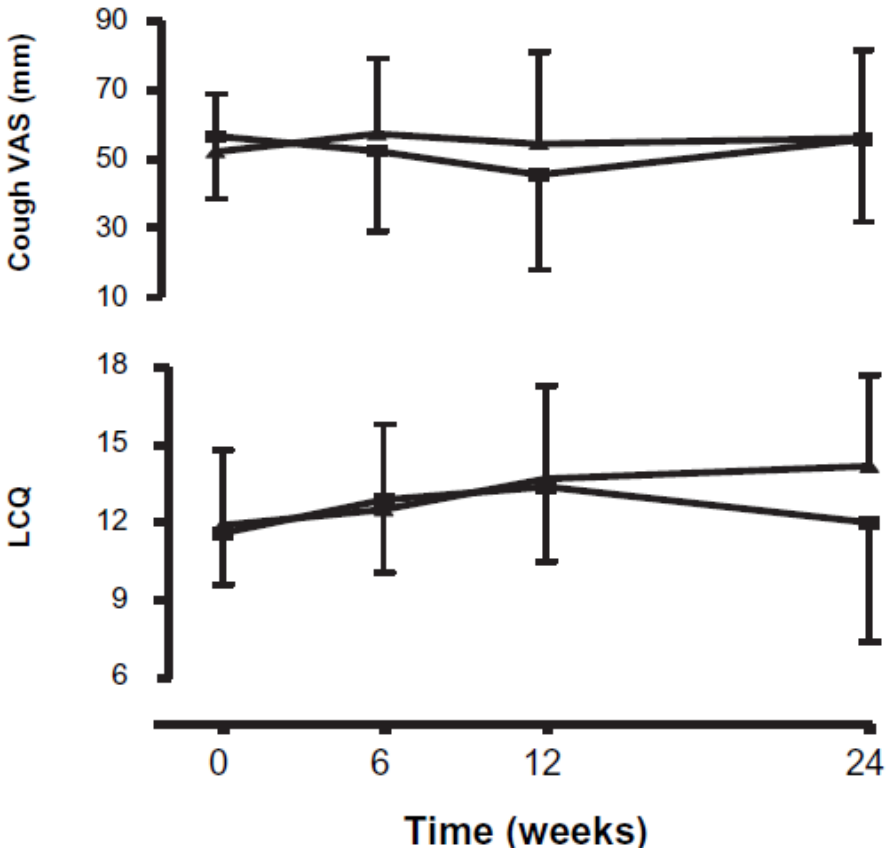
Macrolides

Long-term low-dose erythromycin in patients with unexplained chronic cough: a double-blind placebo controlled trial

Nadia Yousaf,[1] William Monteiro,[1] Debbie Parker,[1] Sergio Matos,[2] Surinder Birring,[3] Ian D Pavord[1]

Thorax 2010;**65**:1107–1110. doi:10.1136/thx.2010.142711


Coughs/24 hours
3000
1000
300
100
30
C2 (µmol)
10
3
1
0.3
0.1
0
6
12
24
Time (weeks)


Cough VAS (mm)
90
70
50
30
10
LCQ
18
15
12
9
6
0
6
12
24
Time (weeks)

Conclusions Treatment with low-dose erythromycin for 12 weeks reduces the induced sputum neutrophil count but not cough frequency or severity in patients with unexplained chronic cough.

[Original Research **Signs and Symptoms of Chest Diseases**]

CHEST

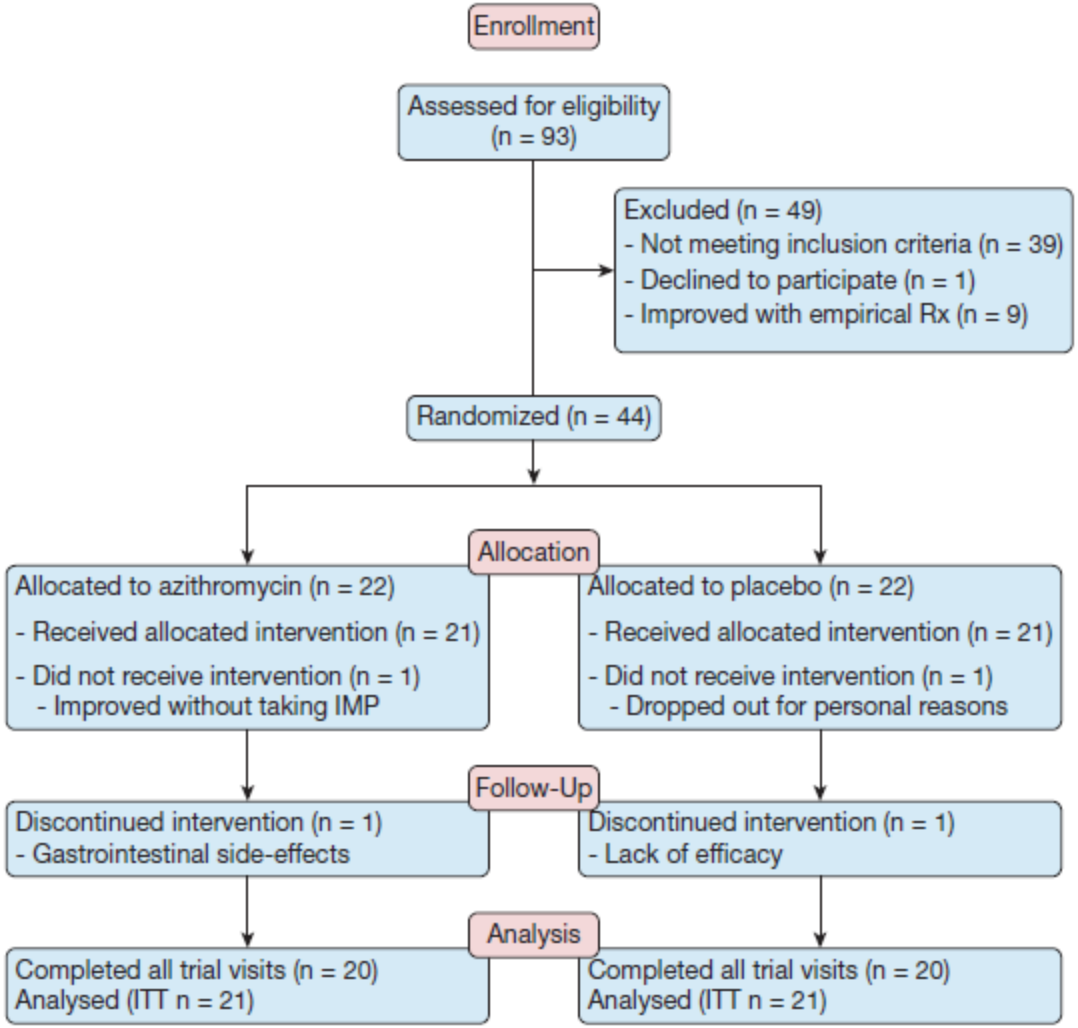
The Effects of Azithromycin in Treatment-Resistant Cough

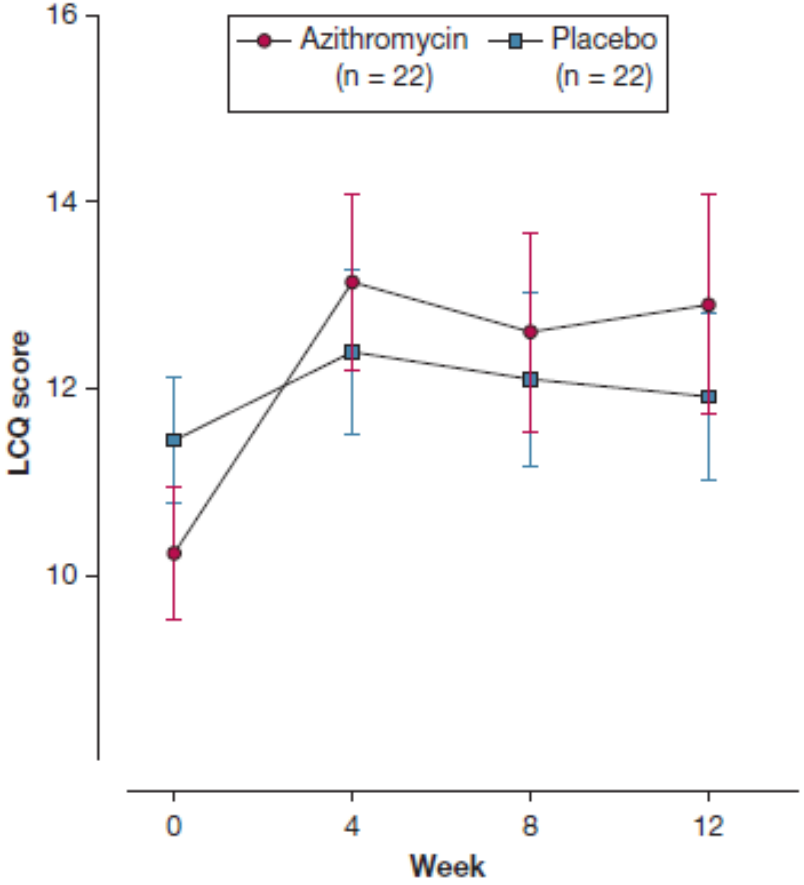
A Randomized, Double-Blind, Placebo-Controlled Trial

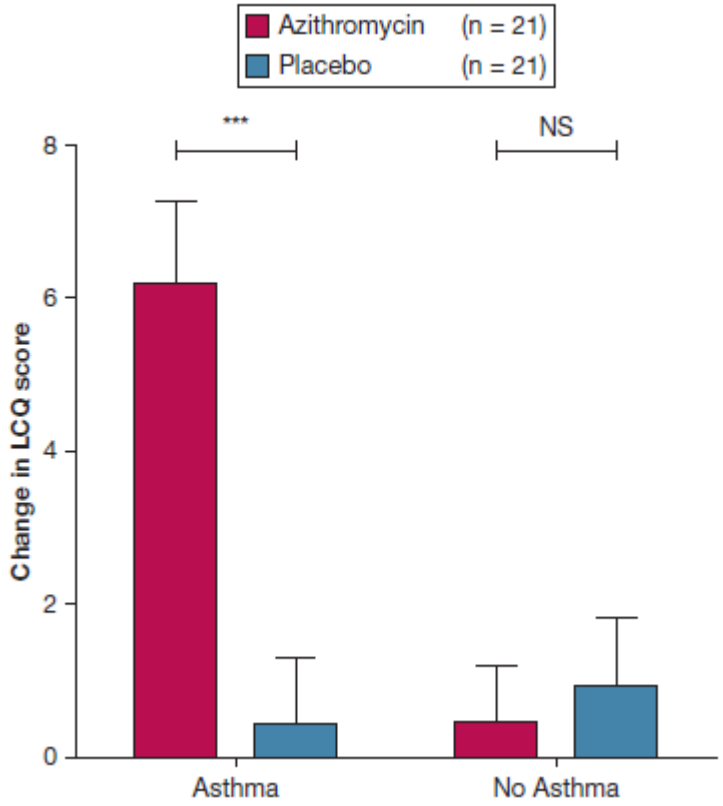
David Hodgson, PhD; John Anderson, PhD; Catherine Reynolds, BSc; Janet Oborne, BSc; Garry Meakin, BSc; Helen Bailey, MSc; Dominick Shaw, MD; Kevin Mortimer, PhD; and Tim Harrison, MD

TRIAL REGISTRY: WHO International Clinical Trials Registry; No.: ISRCTN75749391. URL: http://apps.who.int

CHEST 2016; 149(4):1052-1060


Enrollment
Assessed for eligibility (n = 93)
Excluded (n = 49)
- Not meeting inclusion criteria (n = 39)
- Declined to participate (n = 1)
- Improved with empirical Rx (n = 9)
Randomized (n = 44)
Allocation
Allocated to azithromycin (n = 22)
- Received allocated intervention (n = 21)
- Did not receive intervention (n = 1)
- Improved without taking IMP
Allocated to placebo (n = 22)
- Received allocated intervention (n = 21)
- Did not receive intervention (n = 1)
- Dropped out for personal reasons
Follow-Up
Discontinued intervention (n = 1)
- Gastrointestinal side-effects
Discontinued intervention (n = 1)
- Lack of efficacy
Analysis
Completed all trial visits (n = 20)
Analysed (ITT n = 21)
Completed all trial visits (n = 20)
Analysed (ITT n = 21)


Azithromycin (n = 22)
Placebo (n = 22)
LCQ score
16
14
12
10
0
4
8
12
Week


Azithromycin (n = 21)
Placebo (n = 21)
***
NS
Change in LCQ score
8
6
4
2
0
Asthma
No Asthma

CONCLUSIONS: Treatment with low-dose azithromycin for 8 weeks did not significantly improve LCQ score compared with placebo. The use of macrolides for treatment-resistant cough cannot be recommended from this study, but they may have a place in the treatment of chronic cough associated with asthma; this is worthy of further investigation.

Berkhof *et al. Respiratory Research* 2013, **14**:125
http://respiratory-research.com/content/14/1/125

RESPIRATORY RESEARCH

RESEARCH Open Access

Azithromycin and cough-specific health status in patients with chronic obstructive pulmonary disease and chronic cough: a randomised controlled trial

Farida F Berkhof[1*], Nynke E Doornewaard-ten Hertog[1], Steven M Uil[1], Huib AM Kerstjens[2] and Jan WK van den Berg[1]

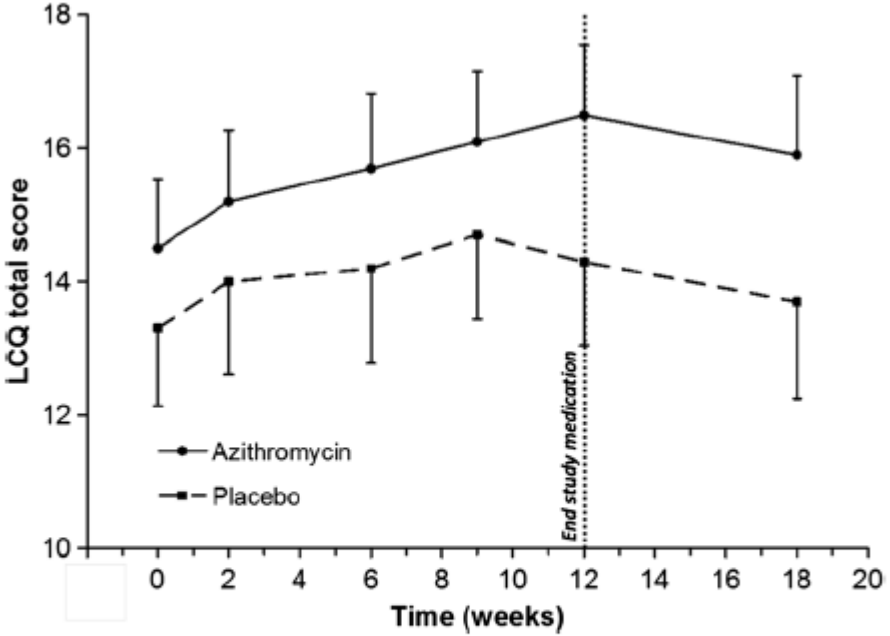


Figure 2 Change over time in LCQ total score. Repeated measures of the Leicester Cough Questionnaire (LCQ) total scores at 0, 2, 6, 9, 12 and 18 weeks between the azithromycin (n = 38) and placebo (n = 39) group. Error bars indicate 95% confidence intervals.

Gabapentine (Neurontin et générique)

Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

Nicole M Ryan, Surinder S Birring, Peter G Gibson

Lancet 2012; 380: 1583–89

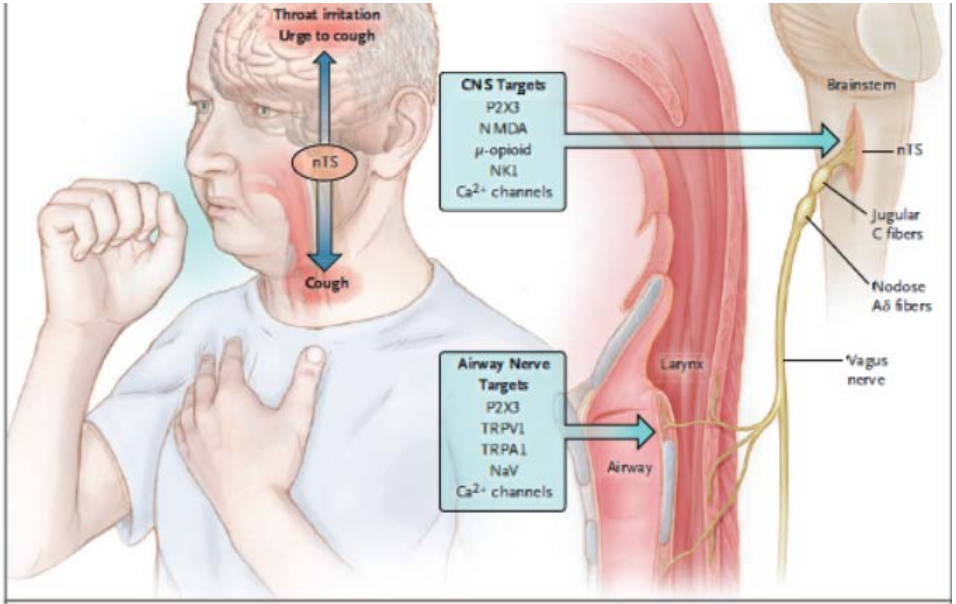
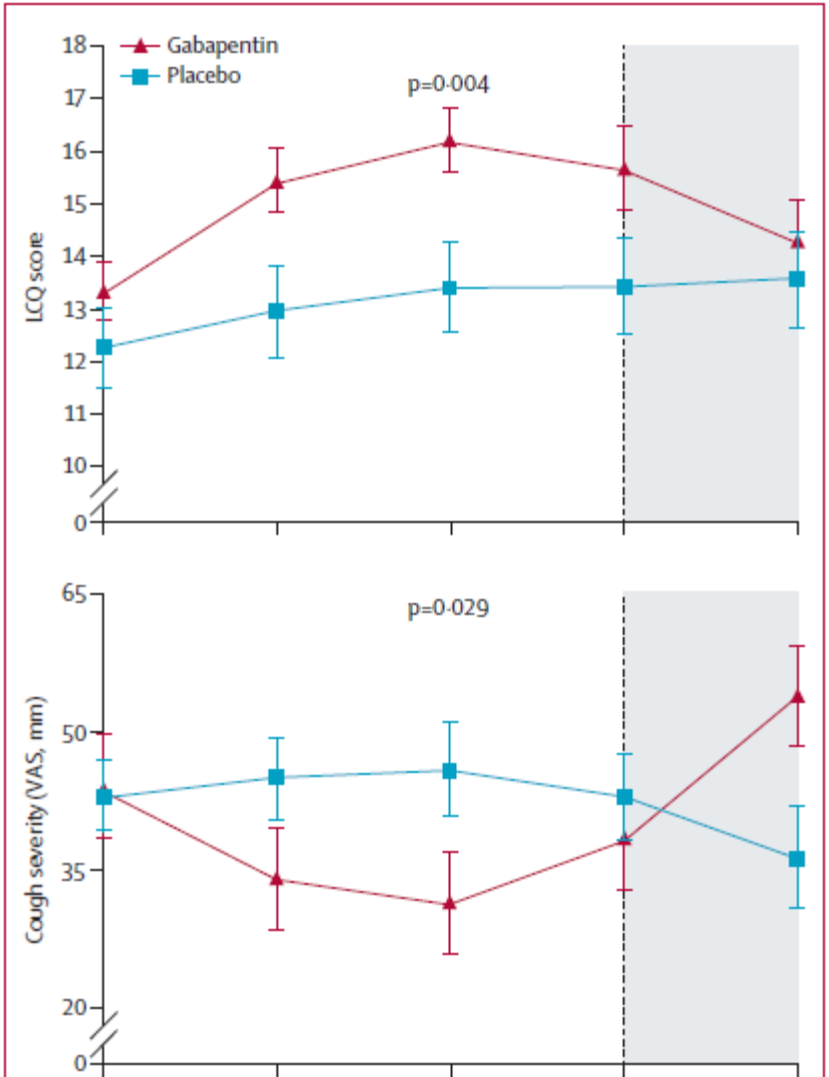


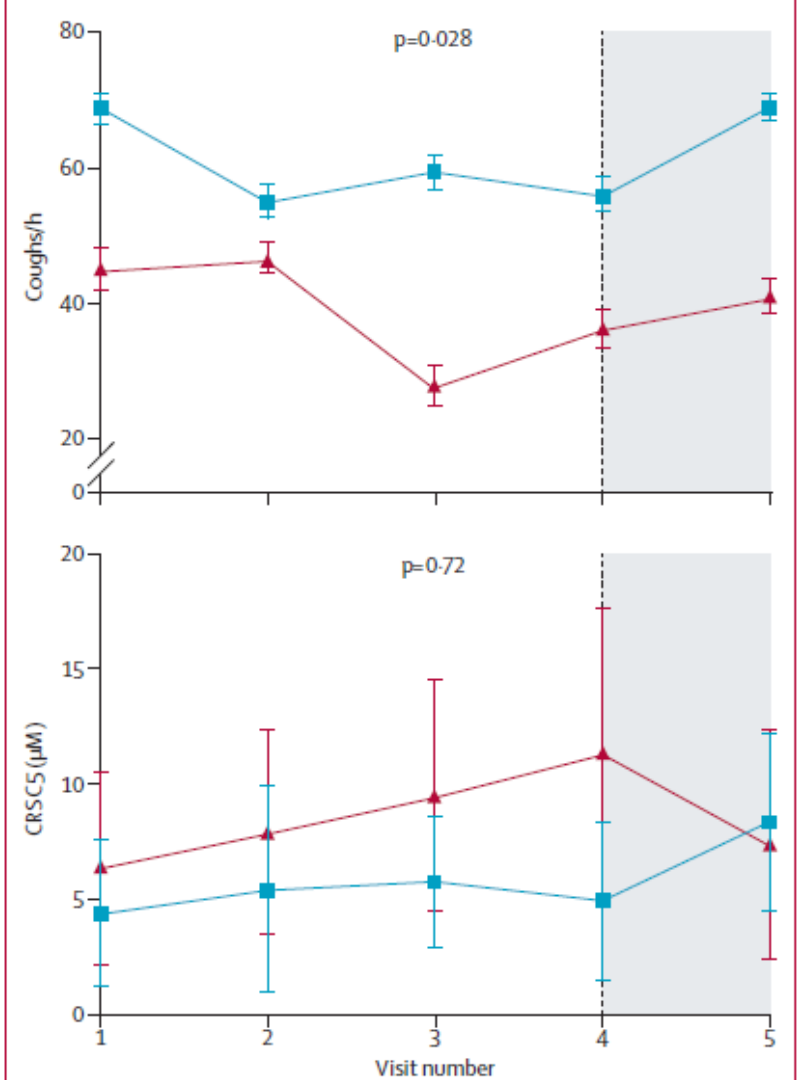
Figure 2. Neuronal Pathways Controlling Cough, and Targets of Available Antitussive Agents and of Those in Development.

C fibers, with bodies in the superior vagal (jugular) ganglion, and Aδ fibers, with cell bodies in the inferior vagal (nodose) ganglion, are the main vagal fibers mediating cough.[46] The key receptors and ion channels located on the terminals of airway sensory afferent vagal nerves that are capable of modulating cough are shown. P2X3 purinergic receptors are found mainly on peripheral sensory nerves, with some expression in the nucleus tractus solitarius (nTS) of the brainstem. Transient receptor potential ankyrin 1 (TRPA1) and transient receptor potential vanilloid 1 (TRPV1) are found on nerve terminals and are capable of initiating action potentials, and voltage-gated sodium channels (NaV) are responsible for action potential transmission. Antagonists for these targets are in development or early-phase clinical trials. In the central nervous system (CNS), the *N*-methyl-D-aspartate (NMDA) receptor is the main target for the over-the-counter therapy dextromethorphan. Morphine is thought to exert antitussive effects through the μ-opioid receptor, whereas gabapentin and pregabalin modulate calcium channels in central and peripheral pathways. The neurokinin-1 (NK1) receptor has been implicated in the sensitization of synapses in the nTS, and its antagonist (aprepitant) was recently found to reduce cough in patients with lung cancer.[47]

← Gabapentine

N Engl J Med 2016;375:1544-51.
DOI: 10.1056/NEJMcp1414215


Gabapentin
Placebo
p=0·004
LCQ score
18
17
16
15
14
13
12
11
10
0
p=0·029
Cough severity (VAS, mm)
65
50
35
20
0


p=0·028
Coughs/h
80
60
40
20
0
p=0·72
CRSCS (μM)
20
15
10
5
0
1
2
3
4
5
Visit number

Interpretation

This study is the first randomised placebo-controlled trial to investigate gabapentin for the treatment of refractory chronic cough. Gabapentin resulted in a significant improvement in cough-specific quality of life, cough severity, and cough frequency and was well tolerated; therefore, it could be considered a viable alternative to current chronic cough treatment, especially for refractory chronic cough. The addition of gabapentin to chronic cough standard practice guidelines should be considered, although replication studies are necessary before this happens.

Pregabaline (Lyrica ou générique)

[Original Research **Signs and Symptoms of Chest Diseases**]

CHEST

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

Anne E. Vertigan, PhD; Sarah L. Kapela, BSpPath; Nicole M. Ryan, PhD; Surinder S. Birring, MB, ChB (Hons), MD; Patrick McElduff, PhD; and Peter G. Gibson, MBBS (Hons)

CHEST 2016; 149(3):639-648

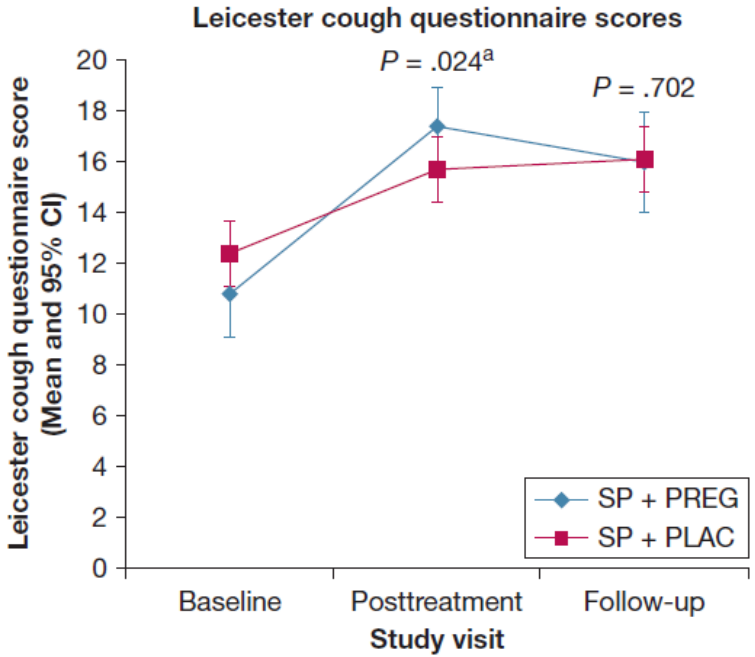


Figure 3 – *Mean (95% CI) Leicester Cough Questionnaire health-related quality of life by visit and treatment group. See Figure 1 and 2 legends for expansion of abbreviations.* $^{a}P < .05$.

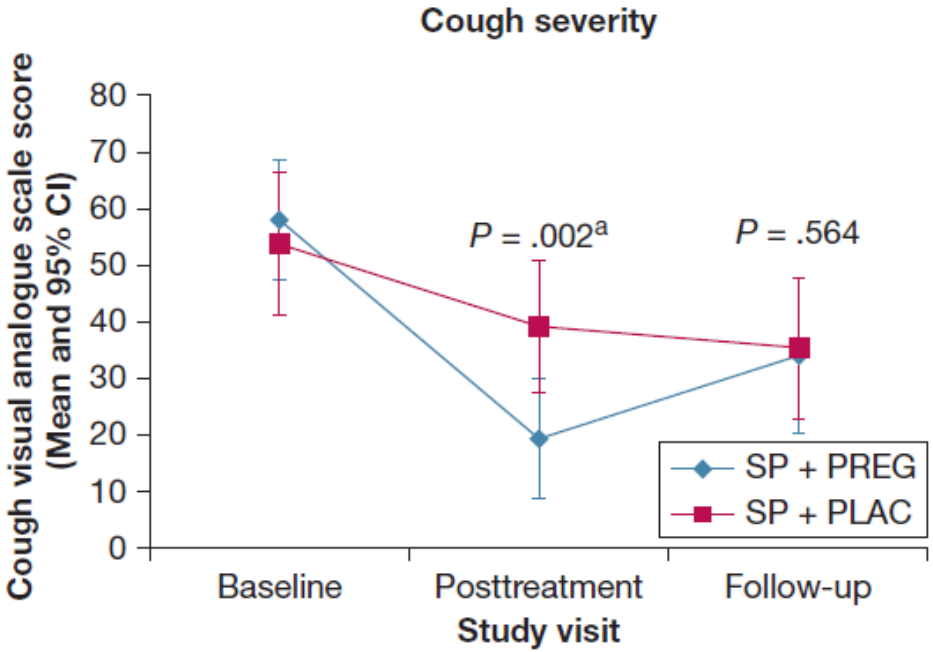


Figure 4 – *Mean (95% CI) cough severity visual analog scale by visit and treatment group. See Figure 1 and 2 legends for expansion of abbreviations.* $^{a}P < .05$.

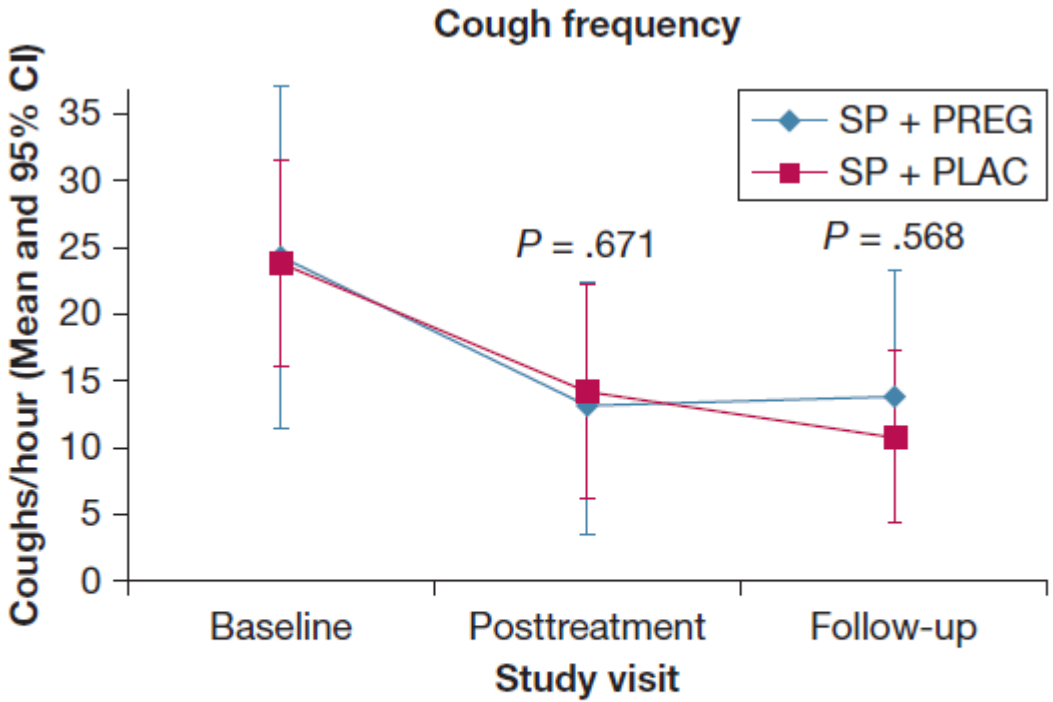
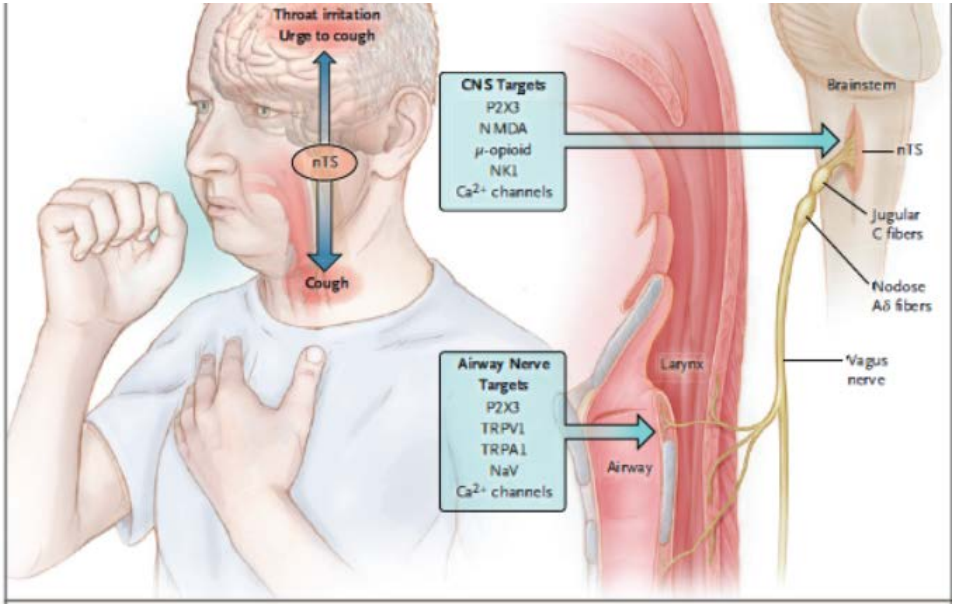


Figure 5 – *Mean (95% CI) objective cough frequency by visit and treatment group using the 24-hour ambulatory cough monitoring with the Leicester Cough Monitor. See Figure 1 and 2 legends for expansion of abbreviations.*



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← Gabapentine
Pregabaline

N Engl J Med 2016;375:1544-51.
DOI: 10.1056/NEJMcp1414215

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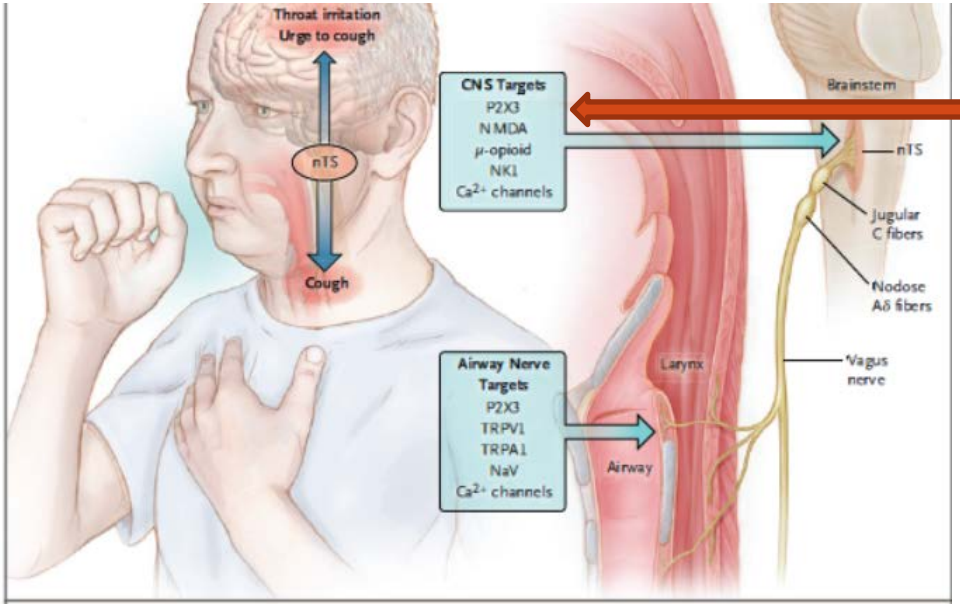
Speech therapy ?

Speech Pathology Treatment Speech pathology treatment was provided by two speech pathologists with previous experience treating chronic refractory cough. A standardized treatment program was used (1). The treatment program consisted of four components, education, reducing laryngeal irritation, cough control techniques and psychoeducational counselling. All participants received each of the four components of the treatment program. The education component consisted of information relating to the voluntary control of cough, the fact that cough is not always necessary and that coughing exacerbates further laryngeal irritation. Reducing laryngeal irritation was targeted through vocal hygiene training and reducing phonotraumatic vocal behaviours during speech and other vocal activities. Cough Control Techniques involve teaching the patient to identify the precipitating urge to cough and replacing it with an alternative response. These responses may include PVFM release breathing, Cough Control Breathing and the Cough Suppression Swallow. Psychoeducational counselling aims to increase the patient's motivation and adherence to the therapy program.



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P2X3 antagonist
=AF-219

N Engl J Med 2016;375:1544-51.
DOI: 10.1056/NEJMcp1414215

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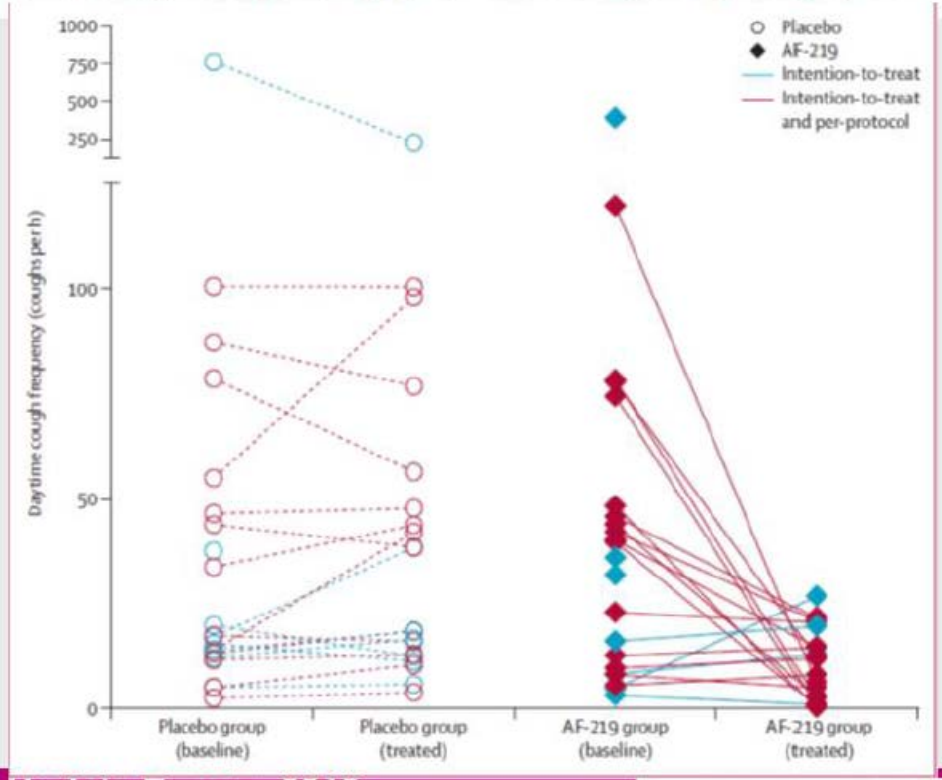
P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study

Rayid Abdulqawi, Rachel Dockry, Kimberley Holt, Gary Layton, Bruce G McCarthy, Anthony P Ford, Jaclyn A Smith



www.thelancet.com Published online November 25, 2014

	Percentage change in day cough rate	Percentage change in day VAS severity	Global rating of change in cough severity
17	−99%	−98%	Very great deal better
12	−98%	−98%	Very great deal better
06	−96%	−81%	Great deal better
19	−94%	−96%	Very great deal better
13	−93%	−84%	Good deal better
18	−83%	−89%	Very great deal better
08	−63%	−70%	Good deal better
20	−52%	−11%	Good deal worse
09	−50%	−92%	Very great deal better
05	−37%	13%	A little better
26	−11%	33%	Same
11	14%	87%	A little worse
01	22%	26%	Same
14	42%	205%	Very great deal worse

VAS=visual analogue scale.

***Table 3*: Outcome concordance in individual patients (by patient number) during AF-219 treatment in per-protocol dataset, ranked by percentage change in daytime cough frequency**

	Placebo (n=22)	AF-219 (n=24)
Dysgeusia	0	21 (88%)
Hypogeusia*	0	13 (54%)
Nausea	1 (5%)	9 (38%)
Oropharyngeal pain	1 (5%)	5 (21%)
Headache	1 (5%)	3 (13%)
Salivary hypersecretion	1 (5%)	3 (13%)
Cough	1 (5%)	3 (13%)
Anosmia	0	2 (8%)
Constipation	0	2 (8%)
Gastro-oesophageal reflux disease	0	2 (8%)
Glossodynia	0	2 (8%)
Depressed mood	0	2 (8%)
Vision blurred	0	2 (8%)

Adverse events were classified according to MedDRA Version 14.0 and displayed by preferred term.*Reports of hypogeusia or ageusia were categorised as hypogeusia. Every patient reported at least one type of taste adverse event during AF-219 treatment.

***Table 4*: Treatment-emergent adverse events reported by more than one AF-219-treated patient**

Prim Care Respir J 2013; 22(3): 325-330

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

RESEARCH PAPER

Honey plus coffee versus systemic steroid in the treatment of persistent post-infectious cough: a randomised controlled trial

Mohammad Ali Raeessi[1], Jafar Aslani[2], *Neda Raeessi[3], Homa Gharaie[4], Ali Akbar Karimi Zarchi[5], Fereshteh Raeessi[6]

[1] Department of Otolaryngology, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Department of Pulmonology, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3] Research Center of Tehran University of Medical Sciences, Tehran, Iran
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[5] Department of Epidemiology and Biostatics, Faculty of Health, Baqiyatallah University of Medical Sciences, Tehran, Iran
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Table 1. Characteristics of participants

Factors	HC group (n=29)	S group (n=30)	C group (n=26)
Age groups			
≤30	6 (21)	12 (40)	5 (19)
31-40	7 (24)	8 (27)	6 (23)
41-50	8 (28)	6 (20)	9 (31)
51-60	7 (24)	4 (13)	6 (23)
≥61	1 (3)	0 (0)	0 (0)
Sex			
Male	18 (62)	20 (67)	13 (50)
Female	11 (38)	10 (33)	13 (50)
Level of schooling			
Primary & Diploma	7 (24)	12 (40)	6 (23)
Technical & Higher education	19 (65)	13 (43)	20 (77)
Occupation			
Housewife	8 (28)	5 (17)	7 (27)
Student and employee	2 (41)	13 (43)	9 (31)
Physician	6 (21)	9 (30)	9 (31)

Data are presented as n (%) within each treatment group.
C=control, HC=honey plus coffee, S=steroid.

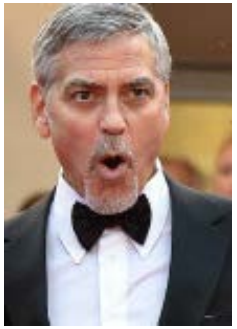
Table 2. Mean (SD) differences between treatments and some explanatory variables

Variables	HC group	S group	C group	p Value
Age (years):	42.3 (13.2)	36.1 (11.9)	42.0 (11.8)	0.103 (NS)
Weight (kg):	76.1 (12.9)	77.1 (8.8)	73.9 (9.9)	0.534 (NS)
Duration of illness (months):	3.0 (2.9)	2.9 (1.5)	2.9 (2.7)	0.973 (NS)
Frequency of cough (degree):				
Before treatment	2.9 (0.3)	3.0 (0.0)	2.8 (0.4)	0.082 (NS)
After treatment	0.2 (0.5)	2.4 (0.6)	2.7 (0.5)	<0.001 (S)

C=control, HC=honey plus coffee, S=steroid, (NS)=not significant, (S)=significant.

The included participants were randomly distributed into three groups. Three regimens of medical jam-like pastes were prepared, as follows:
(1) Each 600g of the first regimen consisted of **500g of honey and 70g of original instant coffee**, given to every member of the first group (honey plus coffee group, n=29)
(2) Each 600g of the second regimen consisted of 320mg prednisolone given to every member of the second group (steroid group, n=30).
(3) Each 600g of the third regimen consisted of only guaifenesin as a supportive treatment given to every member of the third group (control/placebo group, n=26).

1) HC group: **20.8g of honey** and **2.9g of coffee** three times daily
2) Steroid group: 13.3mg of prednisolone three times daily
3) Control group: 25g of guaifenesin three times daily



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Cough reduction using capsaicin

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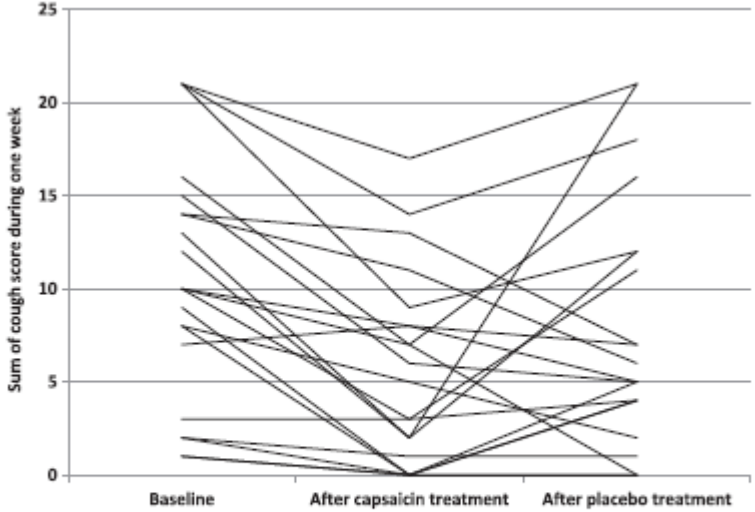

Figure 2 Sum of cough symptom scores (0–21) in 21 patients during the week prior to the start of the study and the last week of the capsaicin and placebo treatments, respectively.

After treatment with capsaicin, the thresholds for C2 were higher (improved) both in patients ($p < 0.020$) and in controls ($p < 0.0061$) compared to after the placebo period. Among patients, the concentration needed to reach C2 ($p < 0.0004$) and C5 ($p < 0.0009$) increased after the period with the active substance compared to cough thresholds at baseline. The cough symptom scores improved after 4 weeks of active treatment ($p < 0.0030$) compared to the baseline scores

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Improvement in health status following cough-suppression physiotherapy for patients with chronic cough

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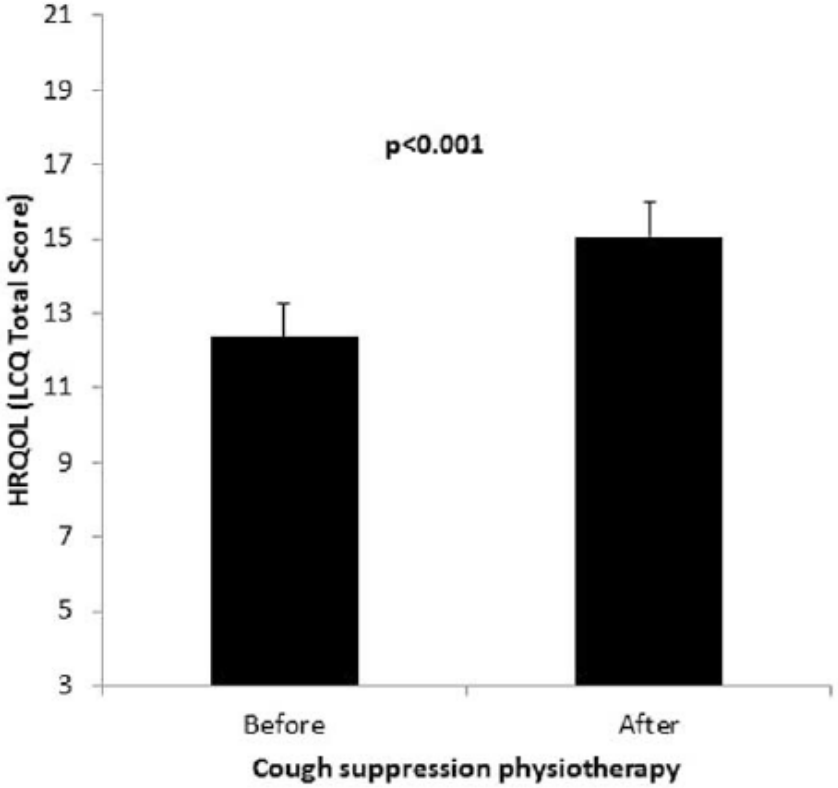
General assessment

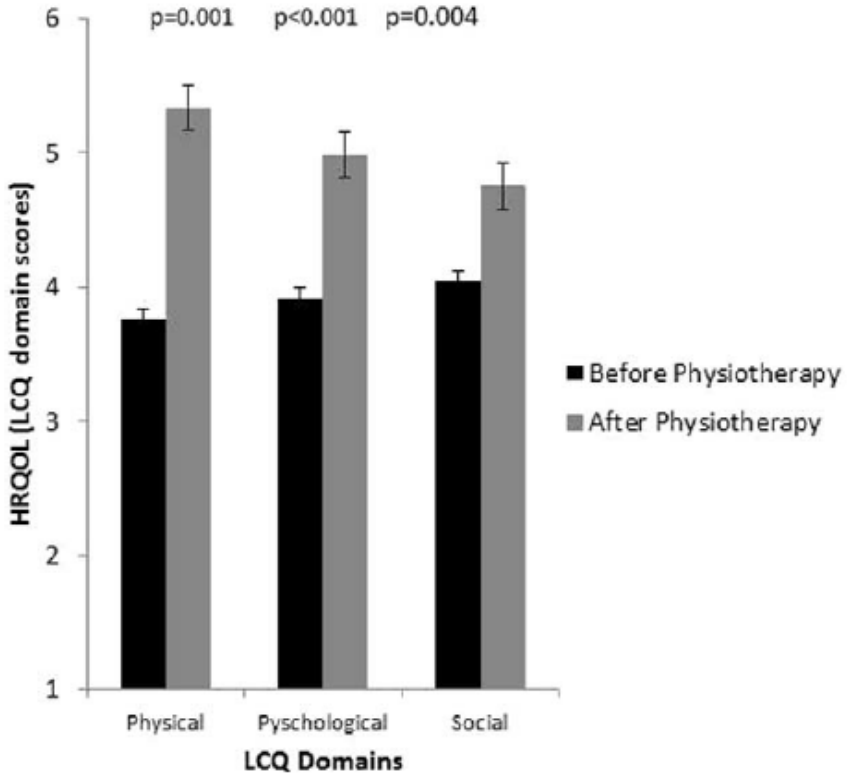
Education and lifestyle advice:

Physiotherapy: A strategy was prescribed to suppress the urge and control cough using distraction (drinking water, chewing gum or sucking sweets or lollies) and substituting the cough with a swallow or relaxed throat breathing (dropping/relaxing shoulders).

Breathing pattern retraining and vocal hygiene:

Reinforcement


21
19
17
15
13
11
9
7
5
3
HRQOL (LCQ Total Score)
p<0.001
Before
After
Cough suppression physiotherapy


6
5
4
3
2
1
HRQOL (LCQ domain scores)
p=0.001
p<0.001
p=0.004
Physical
Pyschological
Social
LCQ Domains
Before Physiotherapy
After Physiotherapy

En résumé

• IPP	• Seulement si RGO
• Macrolides	• Seulement asthme et BPCO
• Pregabaline	• Oui (1 RCT)
• Gabapentine	• Oui (1RCT)
• Capsaicine	• Faisabilité ?
• P2X3 antagonistes	• Oui, mais effets IIaires
• Physiothérapie	• Oui, mais comment ?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