Looking ahead:

Challenges and Changes in Cough management

Woo-Jung Song, MD, PhD

Associate Professor, Asan Medical Center

University of Ulsan College of Medicine

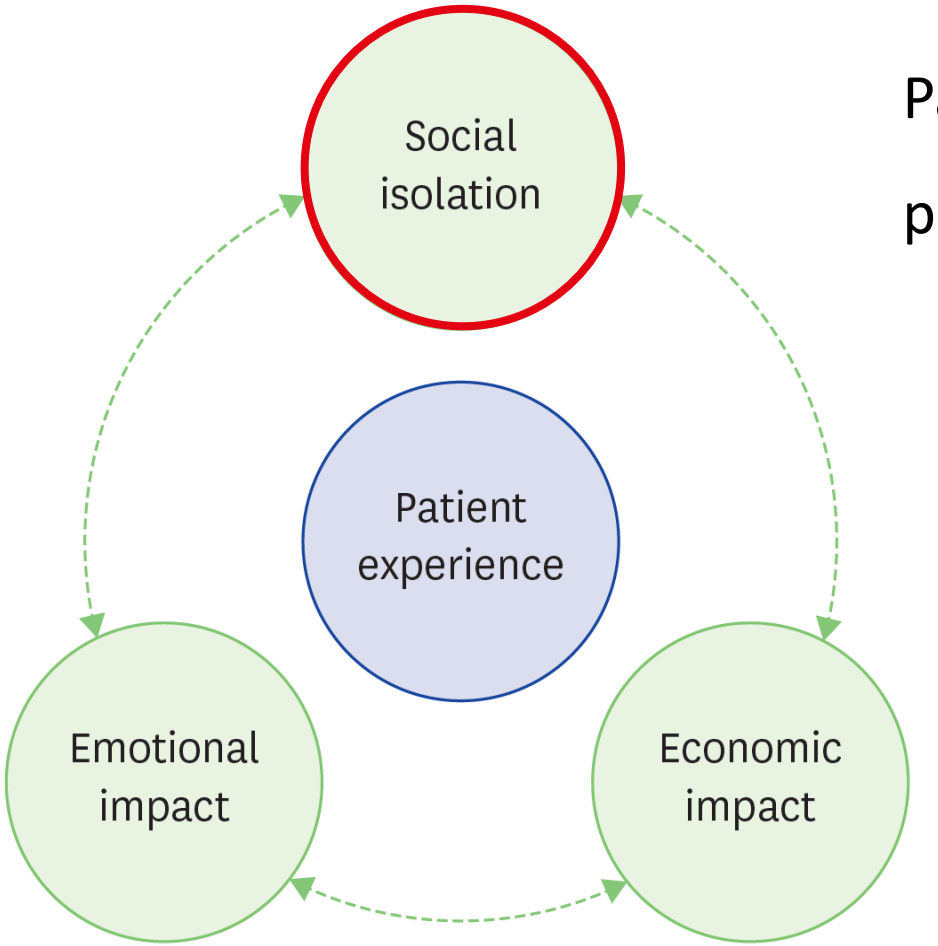
Seoul, Korea

ASAN Medical Center

Overview

- Burden of cough
- Challenges in clinical practice and knowledge gaps in research
- New ways of thinking about and treating chronic cough
- Future directions in cough management

Burden of chronic cough: Cough as a social problem



Patients get stigmatized against due to coughing, particularly since the COVID-19 pandemics began.

"Since it is difficult for me to control my cough, I should avoid public places... it's comfortable just to stay at home alone."

"It's alright if I don't talk when I meet my friends, but if I have to talk, I just start coughing. It shrinks me."

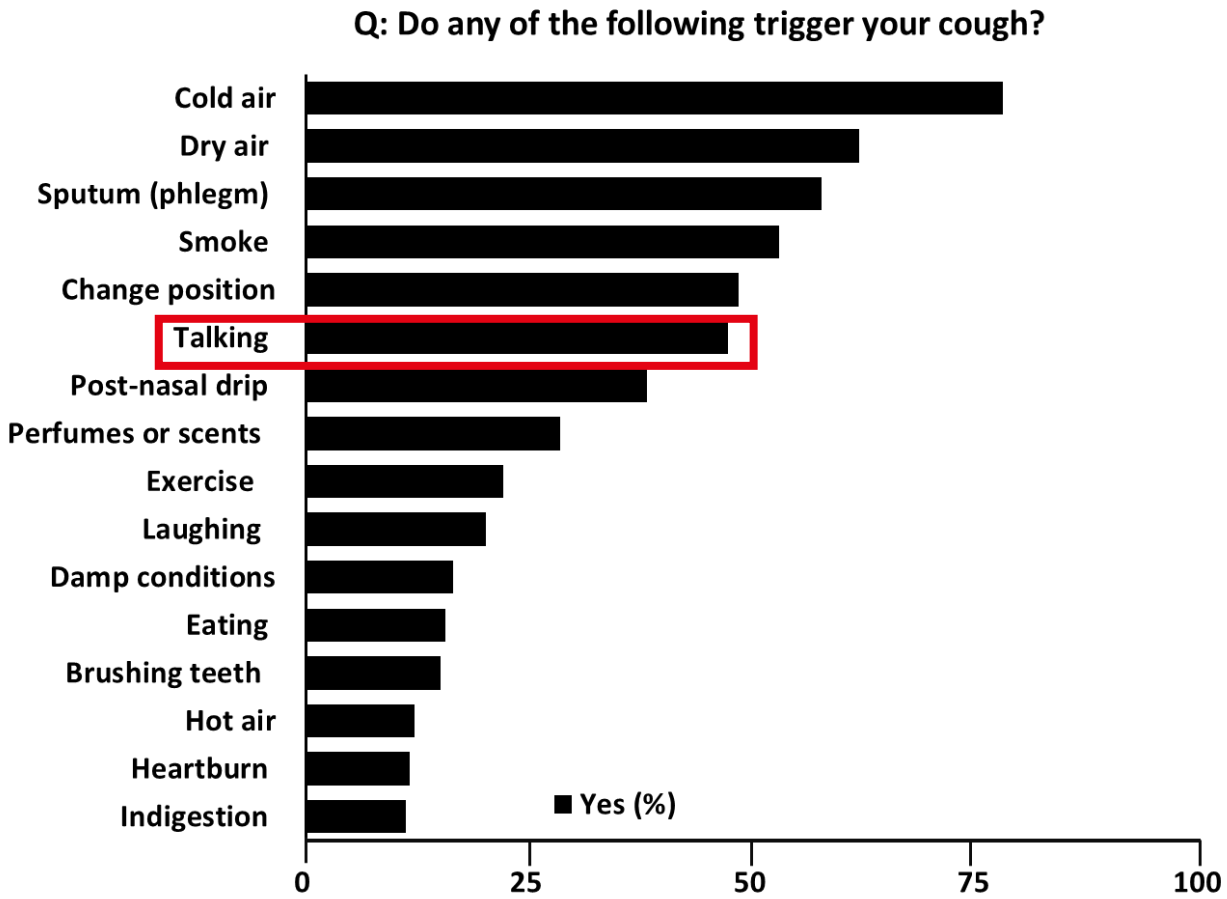
Won HK et al. *Asia Pacific Allergy 2021*

Why Coughers are in trouble?

- Cough cannot be controlled:

Why Coughers are in trouble?

- Cough is triggered by many different trivial or environmental stimuli (such as talking):

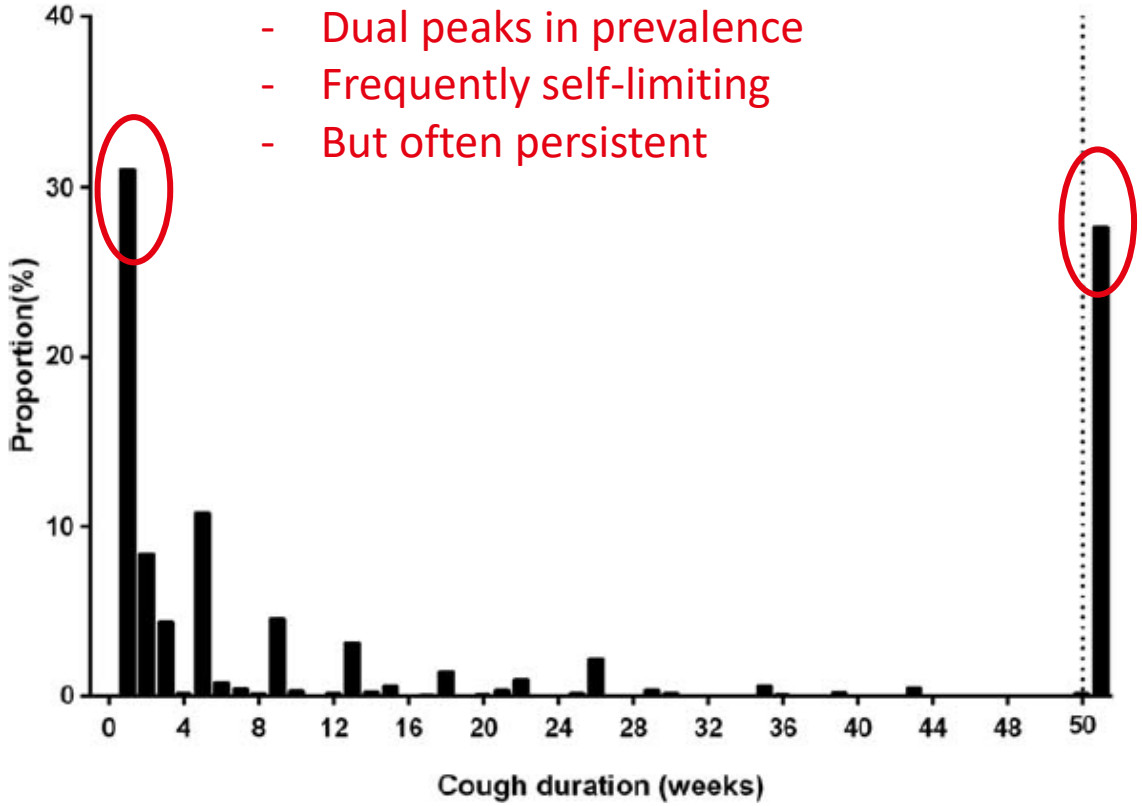


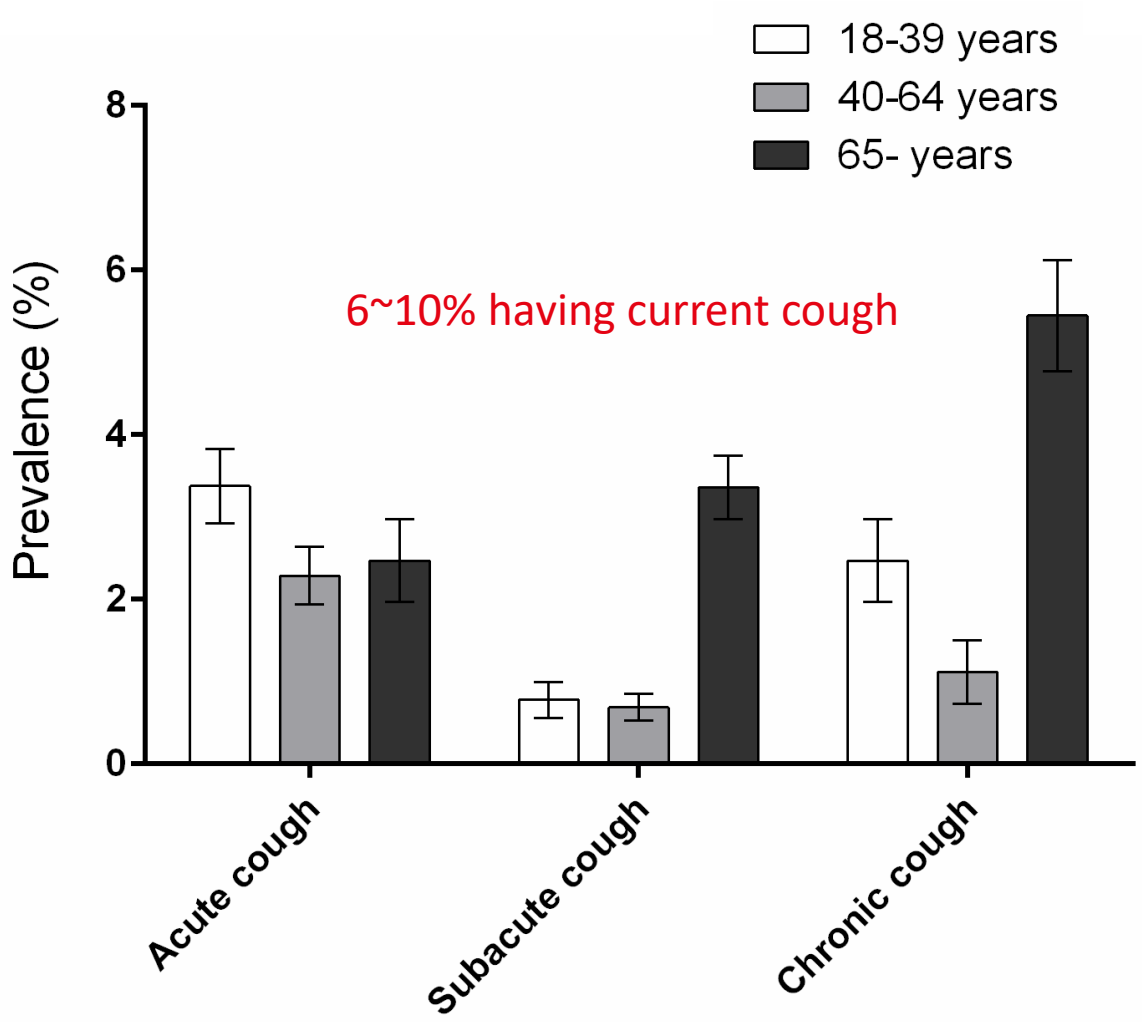
Won HK, Kang SY et al. *Allergy Asthma Immunol Res 2019*

Point prevalence and epidemiological characteristics of chronic cough in the general adult population

The Korean National Health and Nutrition Examination Survey 2010–2012

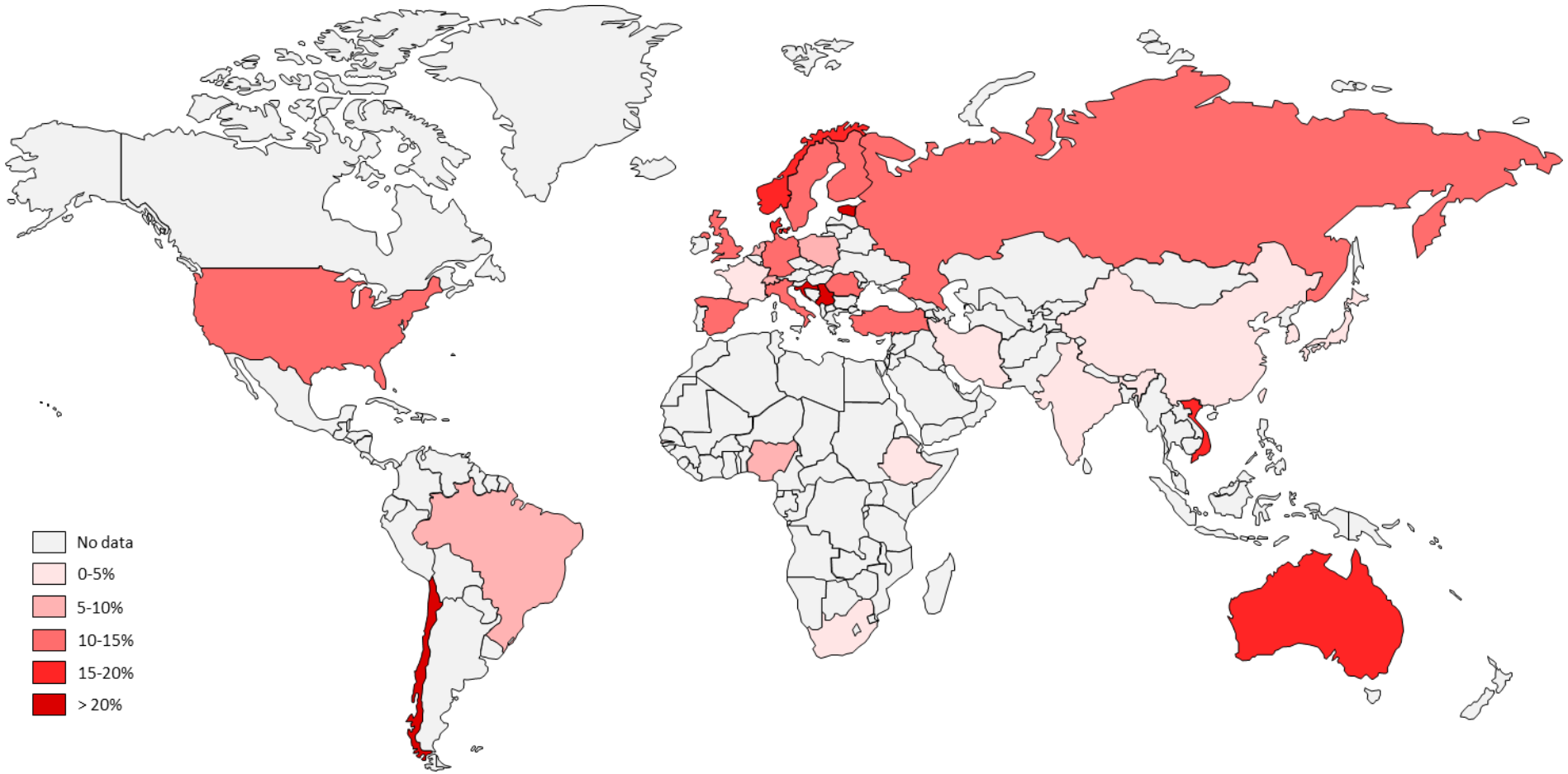
acute / subacute / chronic
- Dual peaks in prevalence
- Frequently self-limiting
- But often persistent





Kang MG et al. *Medicine (Baltimore) 2017*

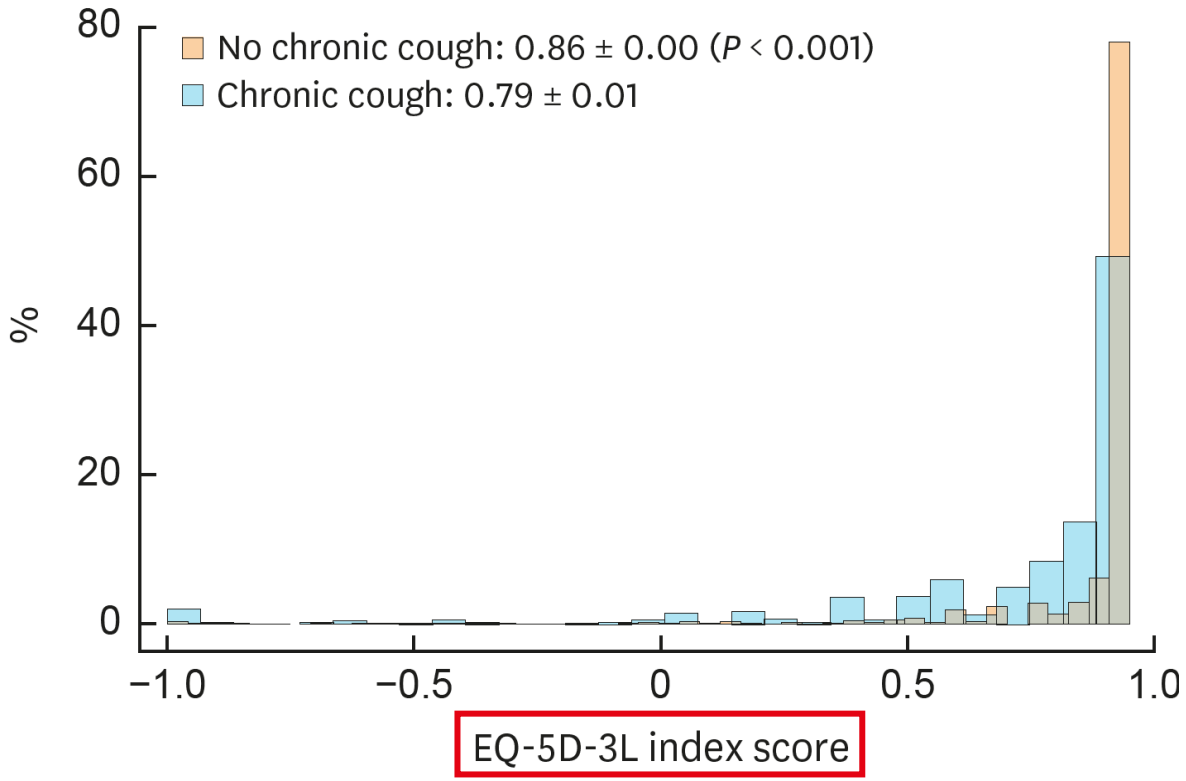
Chronic cough: prevalence

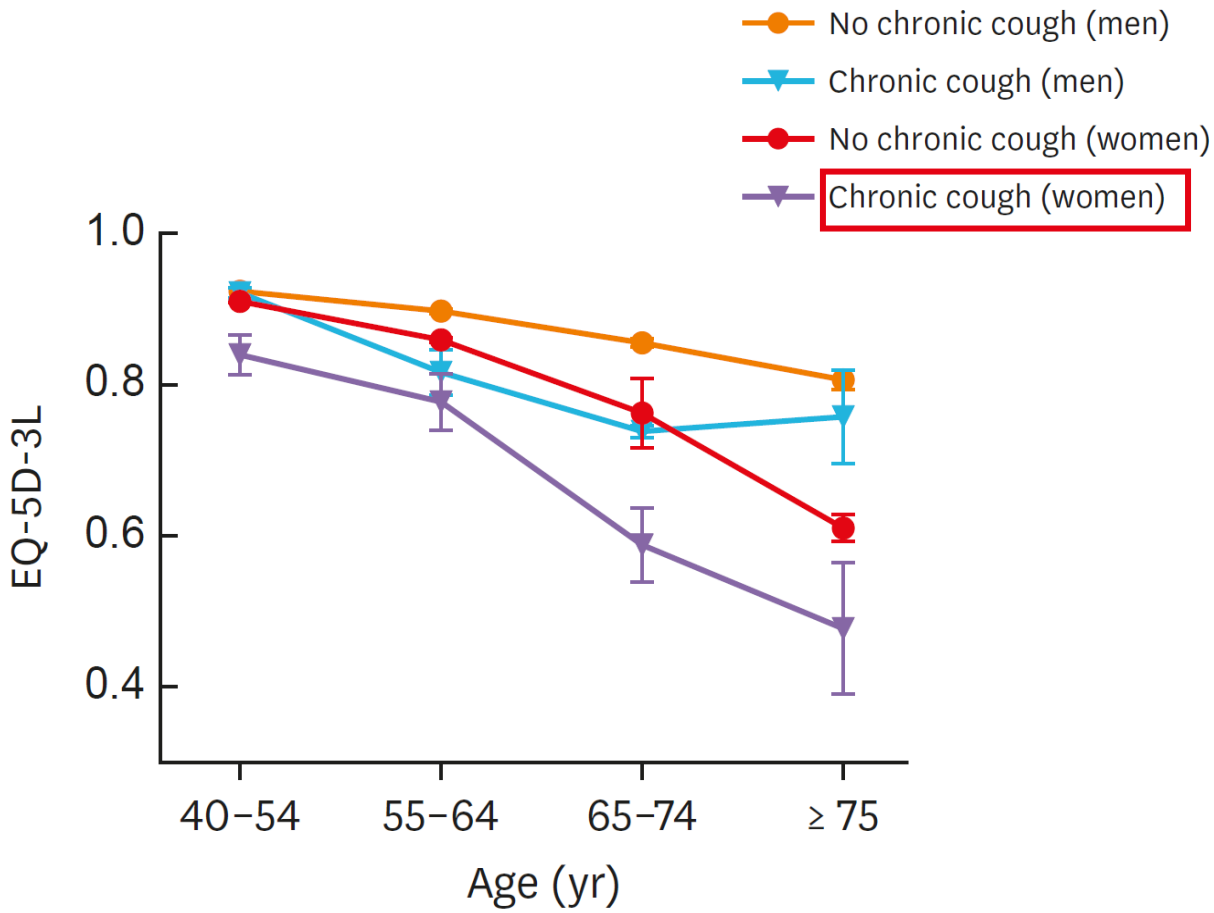


- Meta-analysis of 90 studies during last 3 decades (576,839 subjects)
- Global pooled prevalence: 9.6% (7.6-11.7%, I^2=99%)
- Asia: 4.4% (95% CI 1.8–7.4%) from 22 studies

Song WJ et al. *Eur Respir J 2015*

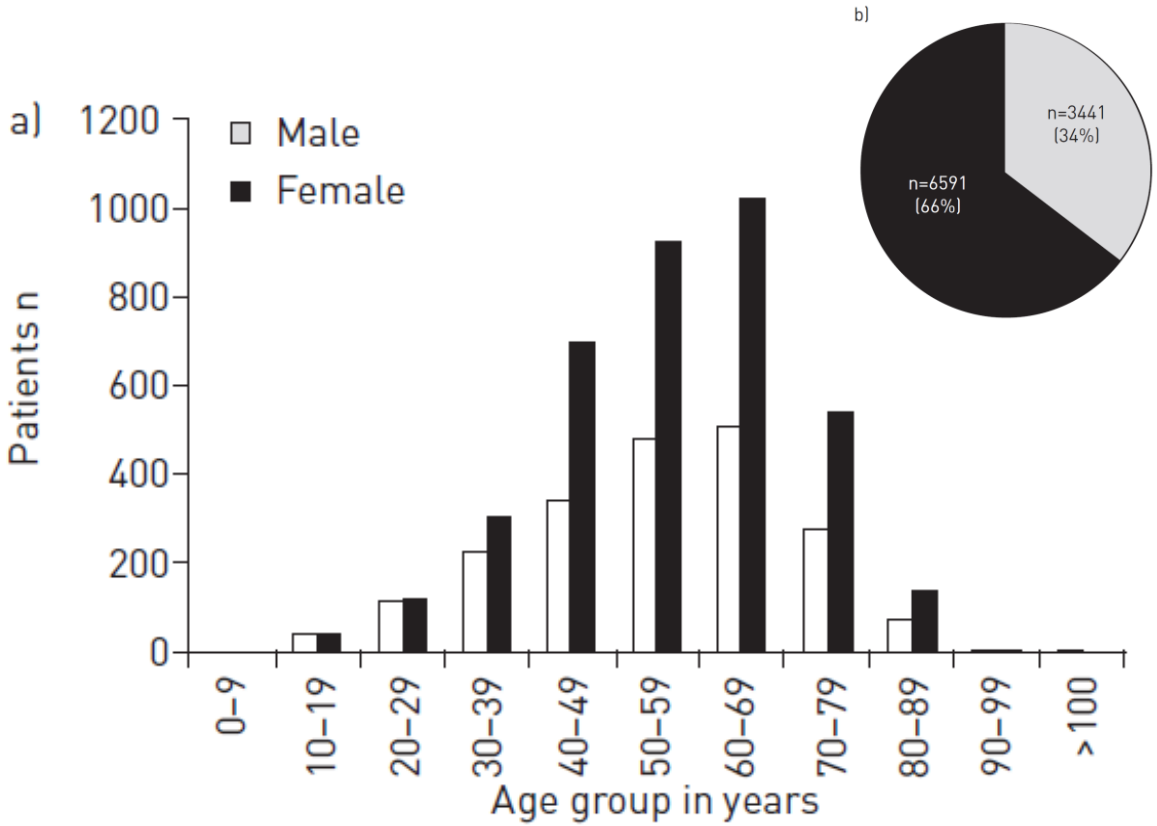
Impact of Chronic Cough on Health-Related Quality of Life in the Korean Adult General Population: The Korean National Health and Nutrition Examination Survey 2010–2016

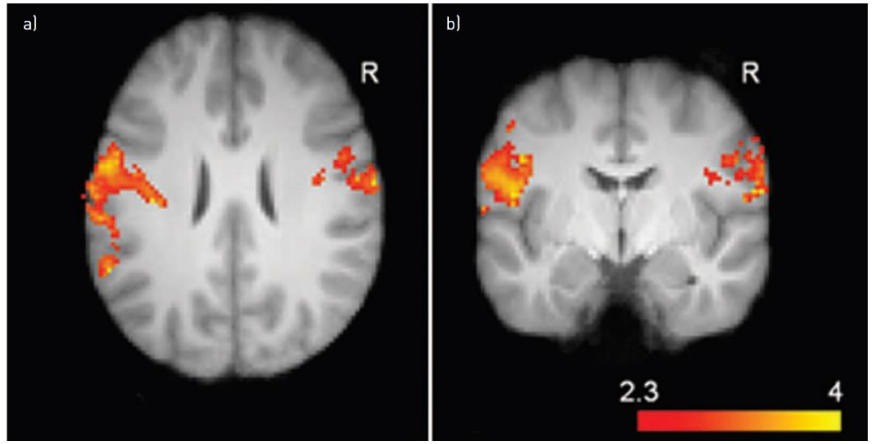


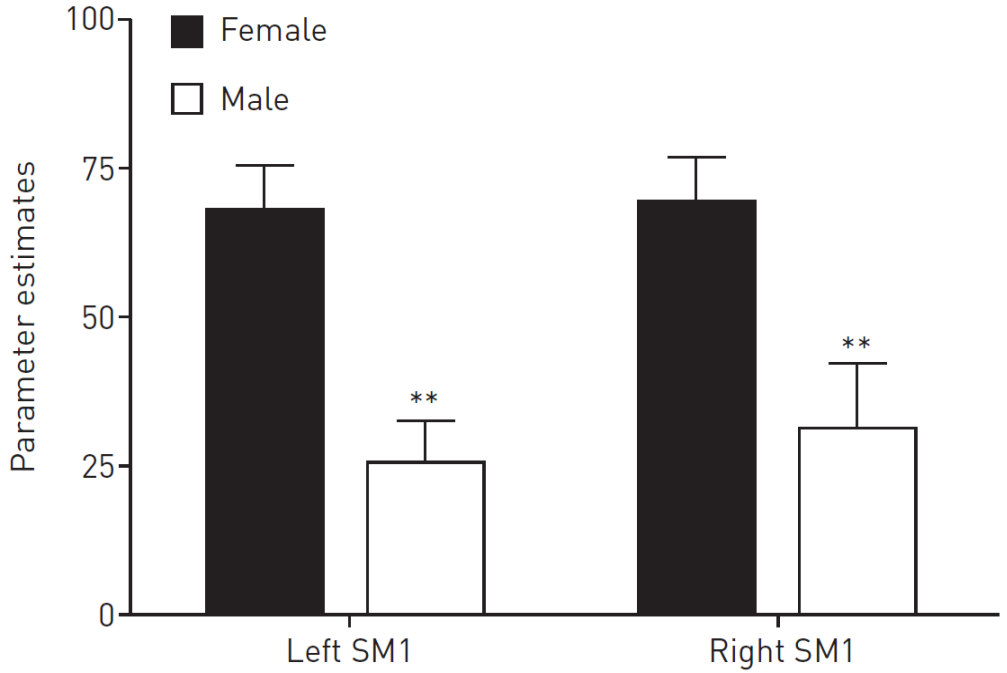


Won HK et al. *Allergy Asthma Immunol Res 2020*

Why women are more susceptible to cough?







Regional brain responses during capsaicin inhalation

Morice AH et al. *Eur Respir J 2014*

Prevalence of stress urinary incontinence in women presenting for evaluation of chronic cough

TABLE 1 Female chronic cough patients with and without urinary stress incontinence

Baseline characteristics

Characteristic	Total cohort	Patients with stress incontinence	Patients without stress incontinence	p-value
Subjects n	210	133	77	
Age	61 (49–70)	61 (51–71)	61 (40–69)	0.112
Duration of chronic cough months	18 (8–60)	18 (8–60)	16 (8–60)	0.959
Body mass index	28 (24–32)	28 (25–34)	26 (23–31)	0.002¶

Multivariable analysis: significant predictors of urinary stress incontinence#

Characteristic	AUC (95% CI)	OR (95% CI)	p-value
Age	0.57 (0.48–0.65)	1.02 (1.00–1.04)	0.028¶
Body mass index	0.63 (0.55–0.71)	1.08 (1.03–1.14)	0.002¶

Data are presented as median (interquartile ranges) and compared using Mann–Whitney U test for non-normally distributed data, unless otherwise stated. #: variables entered into the model were age, body mass index and duration of chronic cough (months); ¶: denotes statistical significance at $p<0.05$.

Dicpinigaitis P. *ERS Open Res 2021*

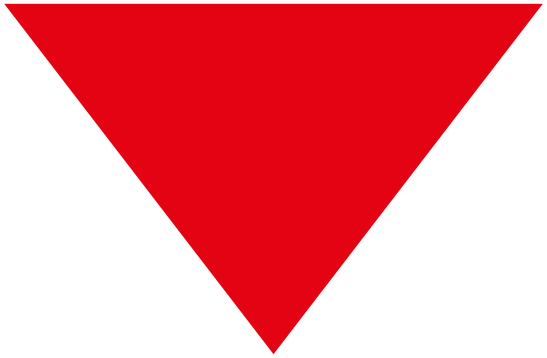
Contemporary approach to patients with cough

- Cough duration

  < 3 weeks (acute)

  3-8 weeks (subacute)

  > 8 weeks (chronic)



- Different chances of self remission
- Different risk factors/endotypes

Acute cough or bronchitis

- The American College of Chest Physicians (ACCP) guideline advises against the use of antitussive drugs in upper respiratory infection (Bolser et al. Chest 2006).

Acute cough or bronchitis – Where are we now?

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold

CHEST Expert Panel Report

Mark A. Malesker, PharmD, FCCP; Priscilla Callahan-Lyon, MD; Belinda Ireland, MD; Richard S. Irwin, MD; Master FCCP; on behalf of the CHEST Expert Cough Panel

Conclusions

Unfortunately, there has been little change in the treatment choices for cough due to the common cold since publication of the 2006 CHEST cough guidelines.

- acetylcysteine, carbocysteine, decongestants/antihistamines, NSAIDs, honey, zinc, and OTC medications

Chest 2017

Pharmacologic and Nonpharmacologic Treatment for Acute Cough Associated With the Common Cold

CHEST Expert Panel Report

Mark A. Malesker, PharmD, FCCP; Priscilla Callahan-Lyon, MD; Belinda Ireland, MD; Richard S. Irwin, MD; Master FCCP; on behalf of the CHEST Expert Cough Panel

- 1. For adult and pediatric patients with cough due to the common cold, we suggest against the use of over the counter cough and cold medicines until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

- 2. In adult patients with cough due to the common cold, we suggest against the use of nonsteroidal anti-inflammatory agents until they have been shown to make cough less severe or resolve sooner (Ungraded Consensus-Based Statement).

Chest 2017

JAMA | Clinical Trial

Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults With Acute Lower Respiratory Tract Infection

A Randomized Clinical Trial

DESIGN, SETTING, AND PARTICIPANTS Multicenter, placebo-controlled, randomized trial (July 2013 to final follow-up October 2014) conducted in 54 family practices in England among 401 adults with acute cough and at least 1 lower respiratory tract symptom not requiring immediate antibiotic treatment and with no history of chronic pulmonary disease or use of asthma medication in the past 5 years.

INTERVENTIONS Two 20-mg prednisolone tablets (n = 199) or matched placebo (n = 202) once daily for 5 days.

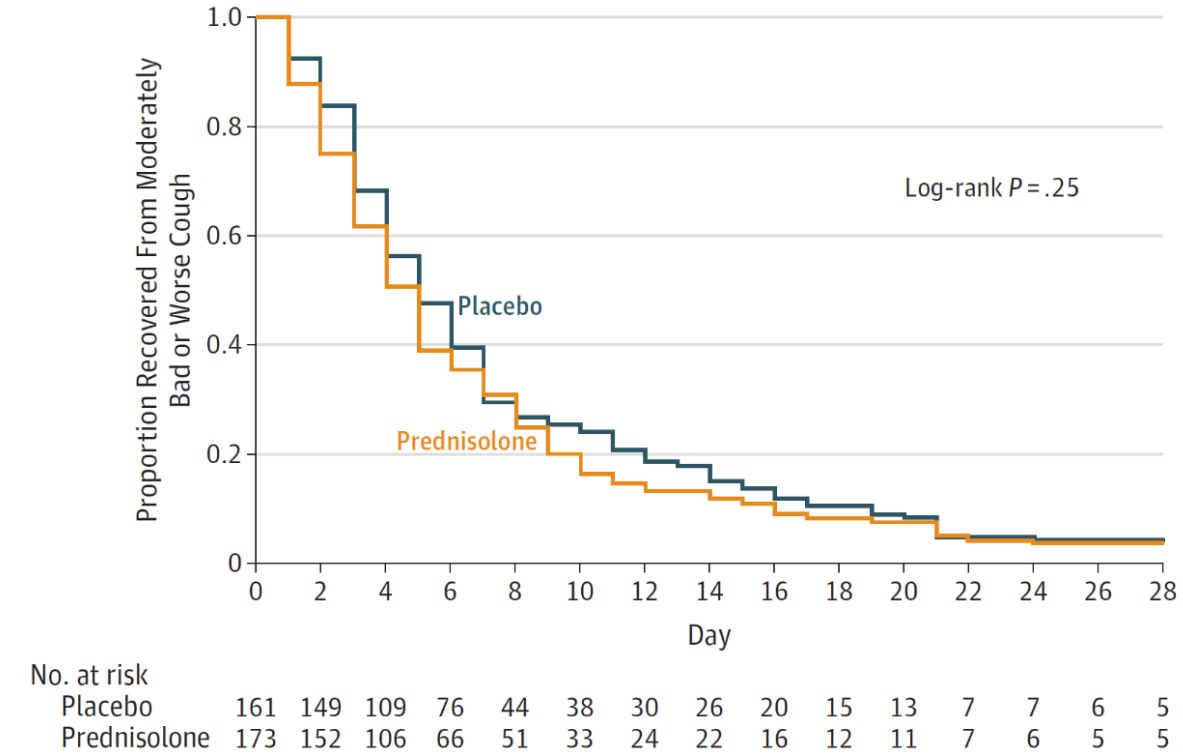
JAMA. 2017 Aug 22;318(8):721-730.

JAMA | Clinical Trial

Effect of Oral Prednisolone on Symptom Duration and Severity in Nonasthmatic Adults With Acute Lower Respiratory Tract Infection

A Randomized Clinical Trial

Figure 2. Kaplan-Meier Analysis of Time to Recovery From Moderately Bad or Worse Cough

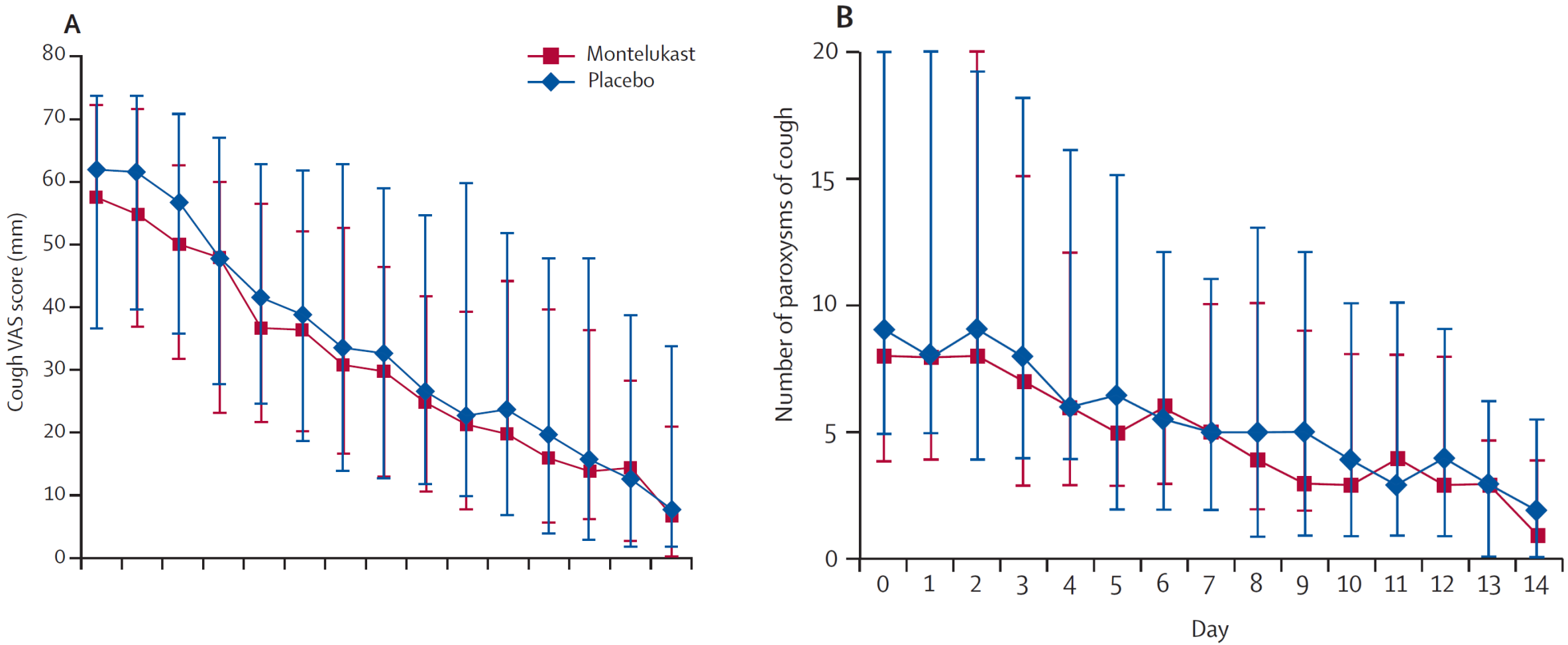


The median duration of follow-up for recovery from moderately bad or worse cough was 5 days (interquartile range, 3-8 days) in the prednisolone group and 5 days (interquartile range, 3-10 days) in the placebo group.

JAMA. 2017 Aug 22;318(8):721-730.

Montelukast for postinfectious cough in adults: a double-blind randomised placebo-controlled trial

Kay Wang, Surinder S Birring, Kathryn Taylor, Norman K Fry, Alastair D Hay, Michael Moore, Jing Jin, Rafael Perera, Andrew Farmer, Paul Little, Timothy G Harrison, David Mant, Anthony Harnden

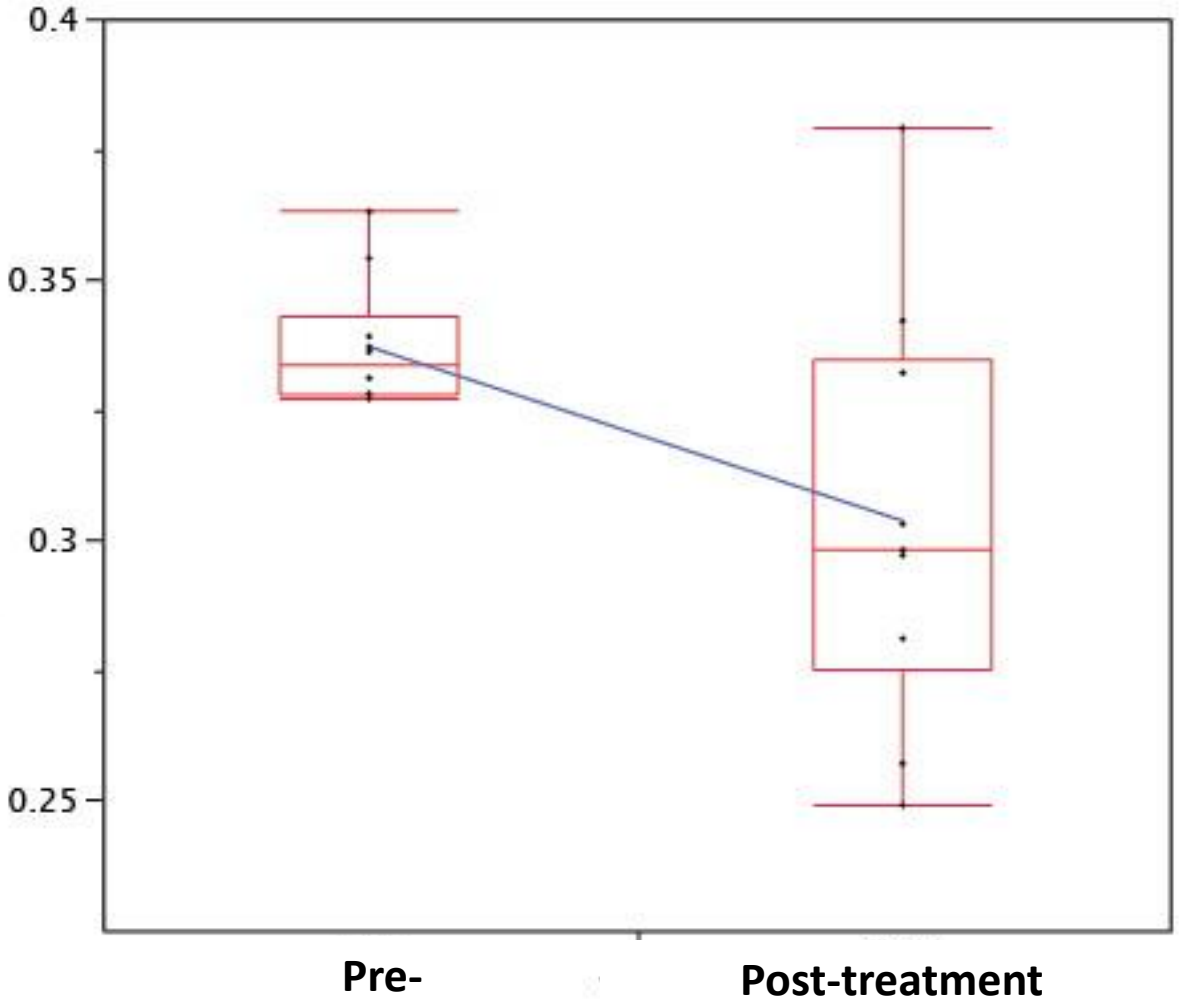


Wang K et al. Lancet Respir Med. 2014 Jan;2(1):35-43.

Why many drugs are not effective?

- Methodological challenges in RCTs in acute cough
- Poor understanding of cough neurobiology

Regression to the mean: a methodological challenge



"Time cures."

Present in all types of cough

More evident in acute cough

Larger sample sizes are required

Endpoints should be sophisticated

in acute cough trials

Expectation bias?

Proof-of-concept: no placebo effects

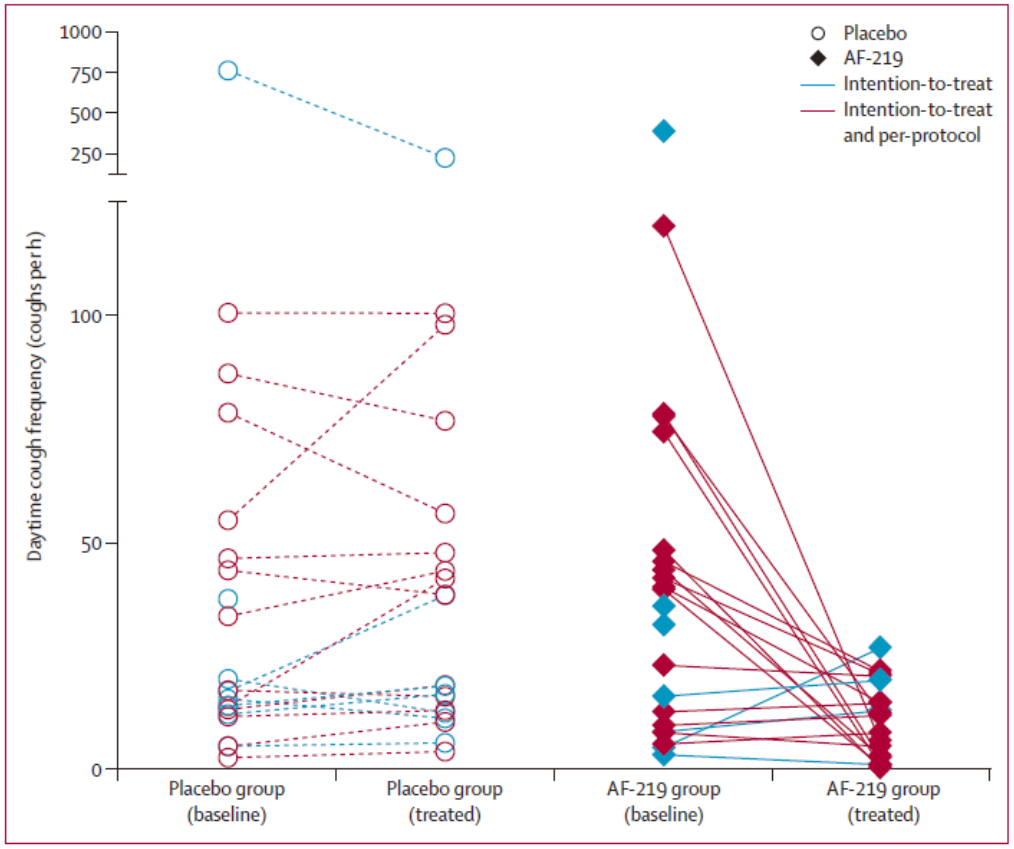
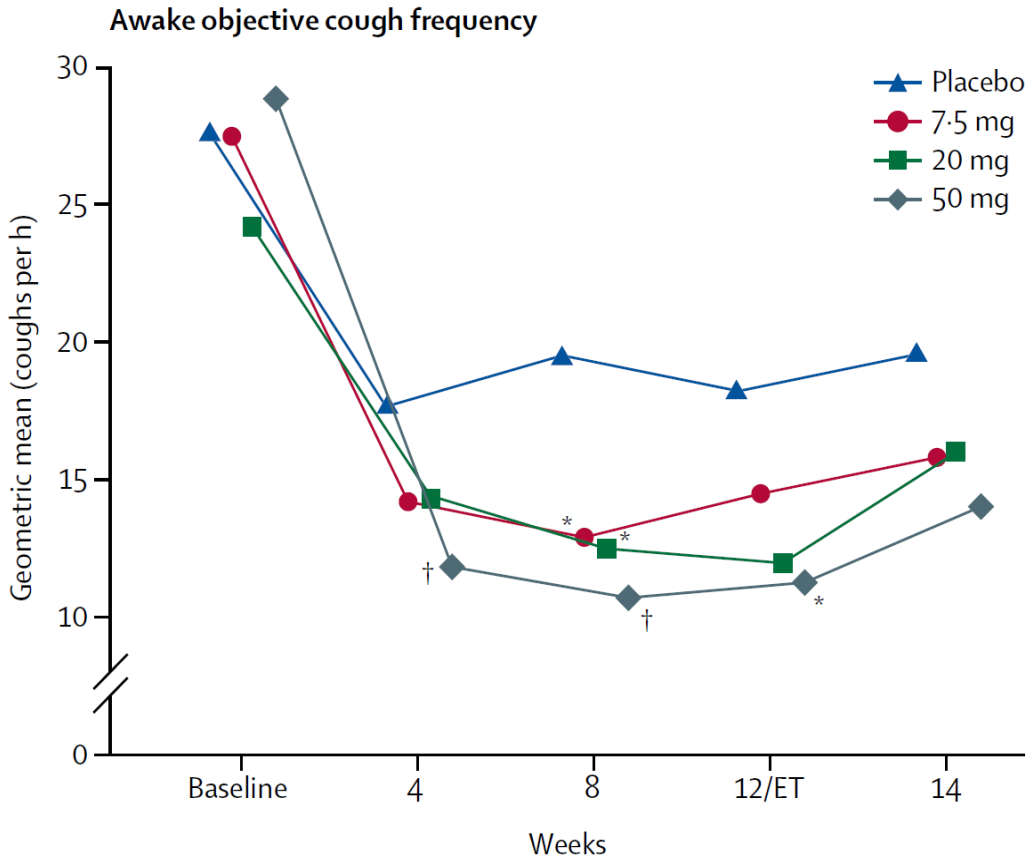


Figure 2: **Changes in objective daytime cough frequency from baseline to end of the treatment period**
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al. *Lancet* 2015

Phase 2b: substantial placebo effects



Smith et al. *Lancet Respir Med 2020*

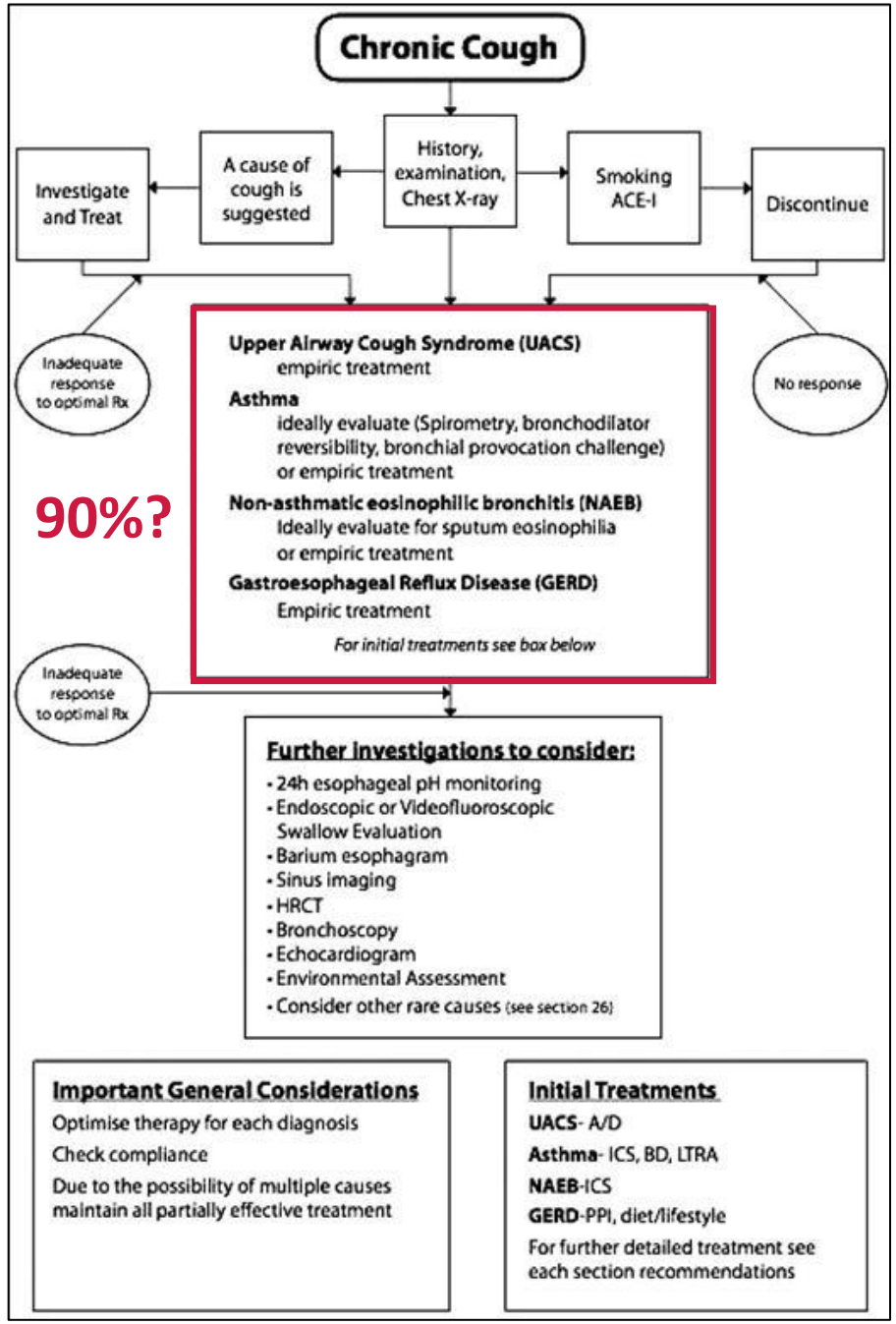
Why RCT evidence is important in chronic cough?

- Cough can wax and wane over time.
- Cough is frequently self-limiting (= regression to the mean).
- Cough is prone to placebo effects.
- Thus, improvement in observational studies may not indicate true treatment effects.
- This is why RCTs are necessary to confirm a drug treatment efficacy in cough.

Pitfalls in observational studies

- The diagnostic yields of anatomic diagnostic protocols may have been overestimated, particularly for UACS or GERD, where the use of objective tests is limited.

  (= cough in some of these patients may indeed have improved spontaneously).

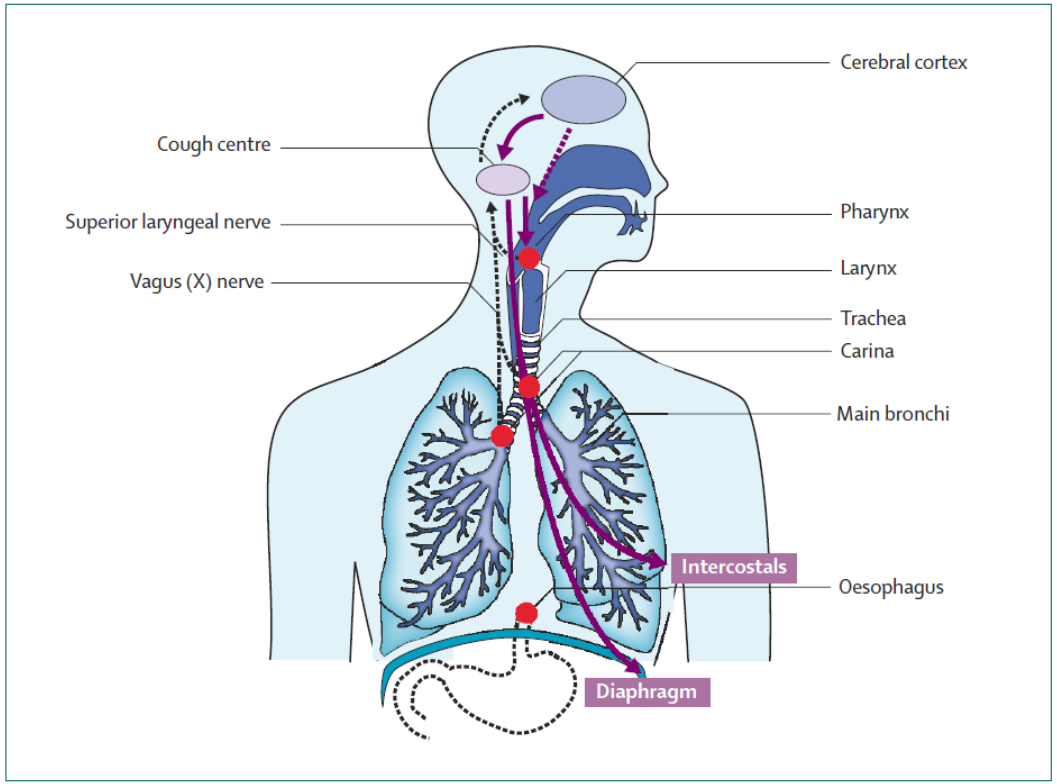


Irwin R et al. ACCP guideline. *Chest 2006*

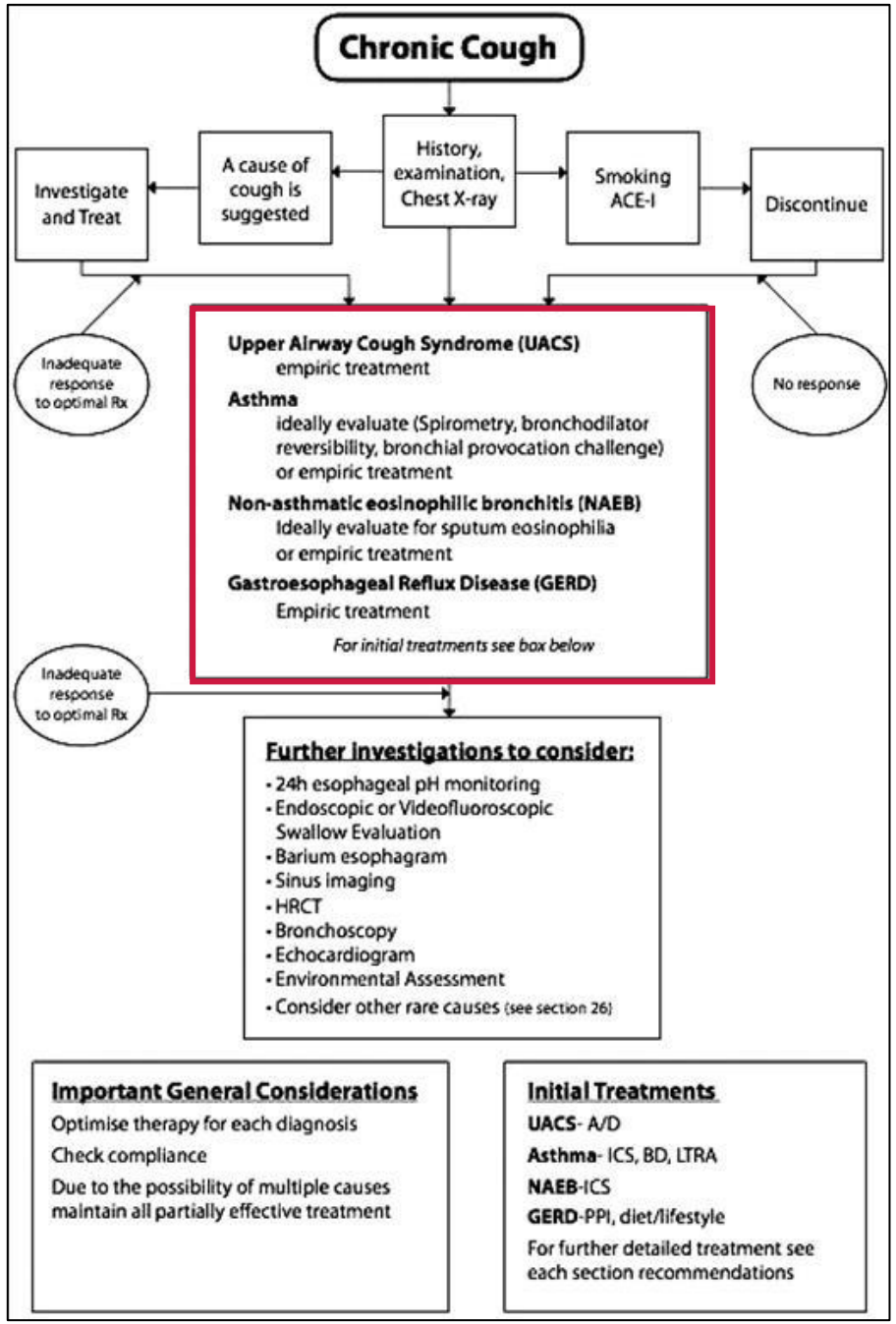
Poor understanding of cough neurobiology

- Lack of proper experimental models
- Inter-species differences in cough pathophysiology
- Difficulty to study human nerve tissues directly

Chronic cough management: key principles



Anatomic diagnostic protocols based on
the neuro-anatomy of cough reflex pathways
: to find and treat causes of cough



Chung KF et al. *Lancet* 2008; Irwin R et al. ACCP guideline. *Chest 2006*

Challenges in clinics

- Diagnostic algorithms are often difficult to follow (e.g., induced sputum).
- Cough causes are not clearly explained in many patients.
- Treatment responses do not always confirm specific causes or true treatment effects.

  - First-generation H1RAs: affecting both upper airways and CNS

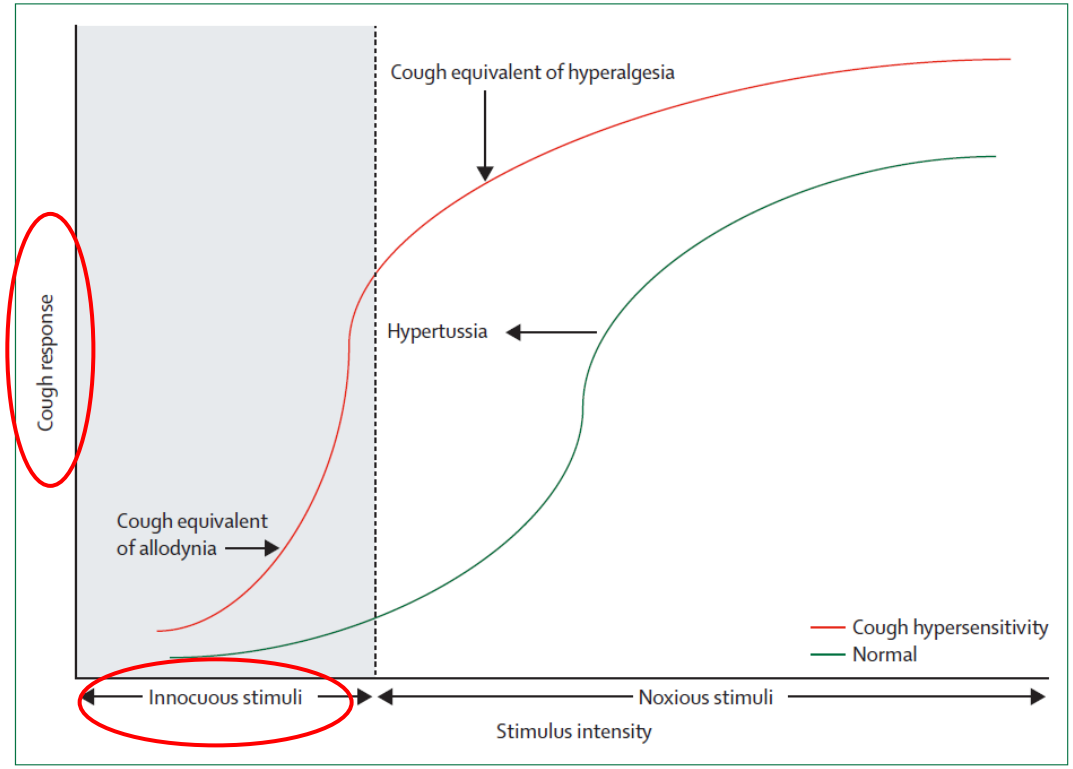
  - In any long-term drug treatments: spontaneous improvement or regression to the mean effect

- About 10%-20% patients remain refractory.

The concept of Cough Hypersensitivity Syndrome proposed

- ERS Taskforce report in 2014: defining chronic cough as a distinct clinical syndrome
- Characterized by troublesome coughing often triggered by low levels of thermal, mechanical or chemical exposure

- Umbrella term encompassing cough phenotypes
  - refractory cough
  - asthmatic or eosinophilic cough
  - upper airway cough syndrome
  - reflux cough…



Chung KF et al. *Lancet Resp Med 2013*

Chronic cough ≈ a disordered fire alarm (that is too sensitive)

- Both have intrinsically protective roles.
- Managing chronic cough ≈ fixing the fire alarm (= normalization of alarming function)
- Three types of approaches:

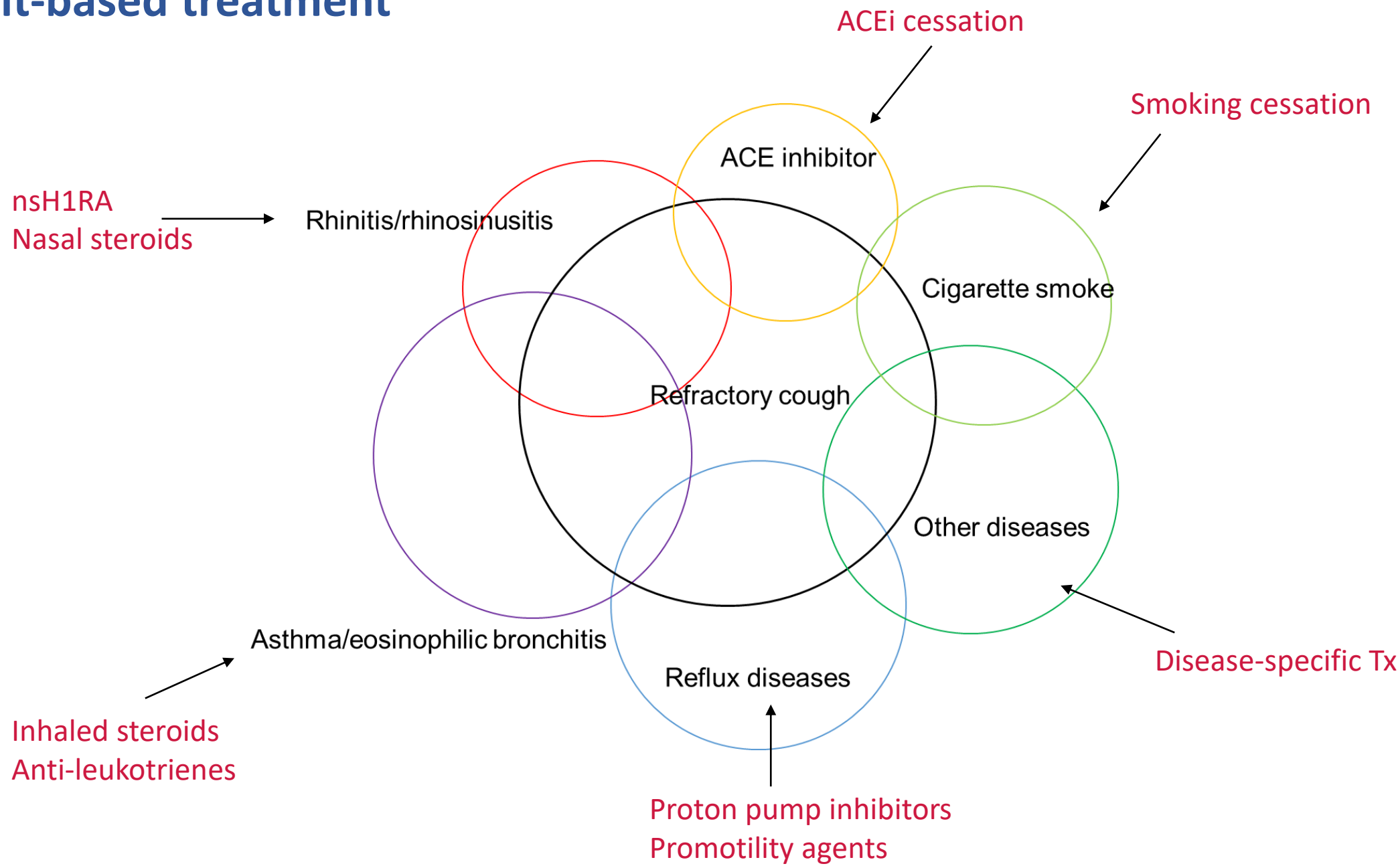
1. Removing triggers or stimuli (treating eosinophilic bronchitis, acid reflux…)
2. Controlling hyper-excitability in the reflex circuit (with anti-tussives)
3. Restoring suppression function (with speech pathology therapy?)

Routine evaluations at baseline: to find out treatable traits

- Cough duration: > 8 weeks? (adults)
- History taking: allergic rhinitis, asthma, or acid reflux (heartburn)?
- Drug-induced cough? (ACE inhibitor…)
- Current smoker?
- Underlying pulmonary disease? (chest X-rays)
- Airway obstruction? (spirometry)
- Eosinophilic inflammation? (induced sputum, FeNO, blood eosinophil count)

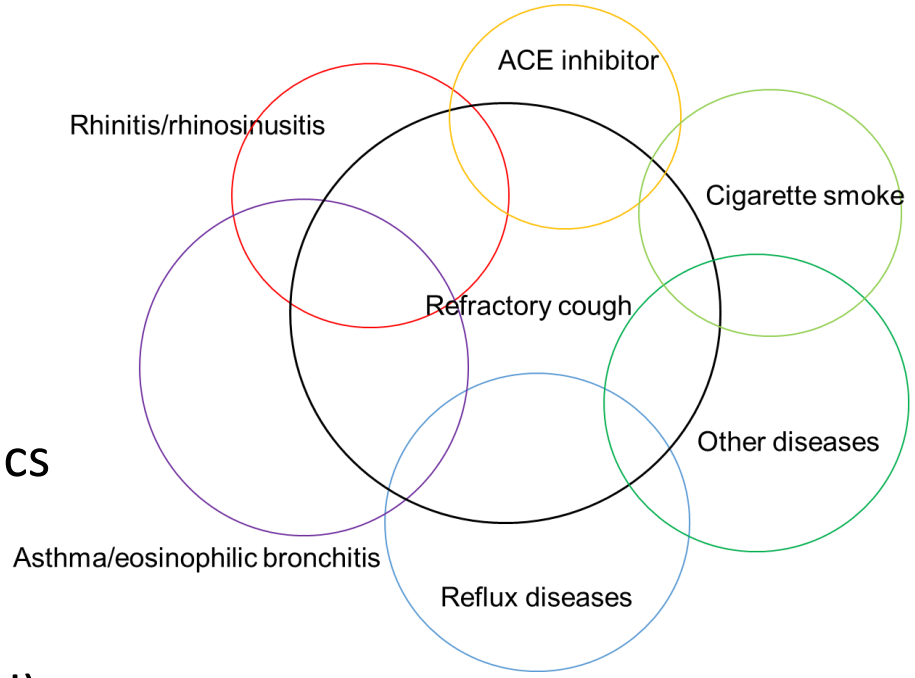
→ To identify treatable traits (or reversible factors) in chronic cough

Trait-based treatment



Patients who are refractory to treatments

- Refractory or unexplained chronic cough (RUCC)



- 5%~40% of chronic cough patients at specialist cough clinics
- Clinical profile
  - More likely to be older women (aged around 60 years old)
  - More hypersensitive to environmental or mechanical triggers (cough hypersensitivity)
  - More sensitive throat (laryngeal hypersensitivity)

Treatments with RCT evidence in RUCC

- Non-pharmacological treatment

  - Speech pathology or language therapy: safe and effective, but not yet available in many countries

- Pharmacological treatment

  - Low-dose SR morphine

  - Gabapentin and pregabalin

Morice AH et al. *Eur Respir J 2020*

Opioids in RUCC

- One RCT published

  P: 27 patients with RUCC

  I: Low-dose SR morphine (5 mg bid) for 4 weeks

  C: Placebo for 4 weeks

  O: Cough-specific-QoL and severity score

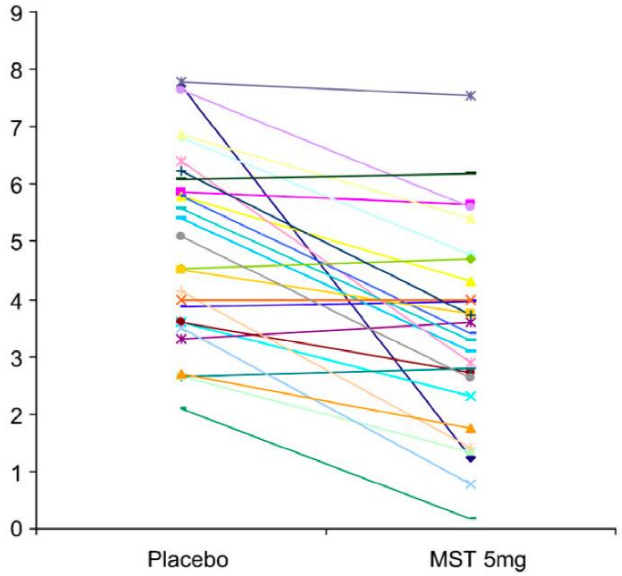


Figure 1. Daily cough severity scores on a scale of 0 to 9. MST = slow-release morphine sulfate.

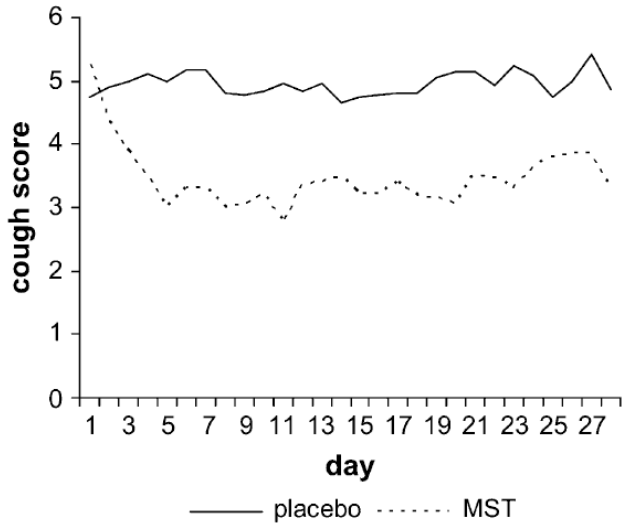


Figure 2. Mean of daily diary cough scores.

TABLE 1. ANALYSIS OF VARIANCE–TUKEY *POST HOC* TEST FOR MULTIPLE COMPARISONS ON SUBDOMAINS OF THE LEICESTER COUGH QUESTIONNAIRE

LCQ Domain	Mean Value at Baseline	Mean value for Placebo	Mean value for Morphine	95% Confidence Interval		
				Baseline vs. Placebo	Baseline vs. Morphine	Placebo vs. Morphine
Physical	4.0	4.8	5.3	−1.3 to –0.3, $p < 0.01$	−1.8 to −0.8, $p < 0.01$	−1.1 to −4.3, $p < 0.04$
Psychological	4.1	4.6	5.1	−1.0 to −0.1, $p = 0.1$	−1.6 to −0.5, $p < 0.01$	−1.1 to −3.9, $p < 0.04$
Social	3.7	4.2	5.1	−1.4 to 0.3, $p = 0.03$	−2.2 to −0.5, $p < 0.01$	−1.7 to −3.0, $p < 0.05$

Side effects: constipation (40%)

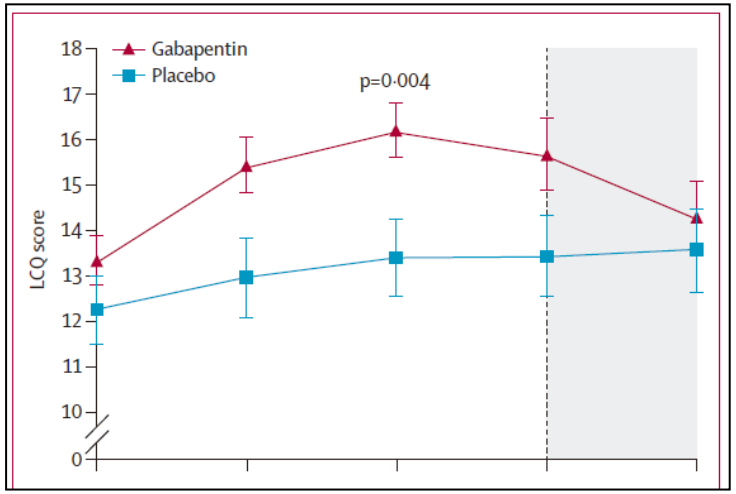
and drowsiness (25%)

Long-term safety and regulatory concern

Only codeine is used in many countries

Morice AH et al. *Am J Respir Crit Care Med* 2007

Gabapentin and pregabalin in RUCC



- Two RCTs

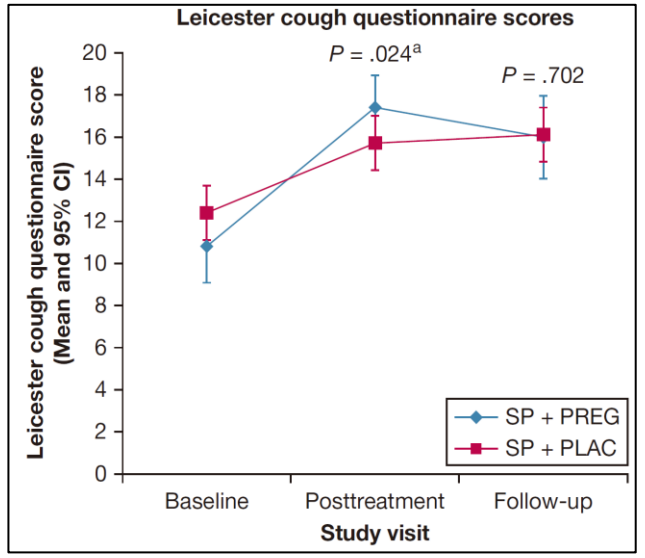
  - gabapentin (up to 1800 mg per day) vs. placebo for 8 weeks

  - pregabalin (300 mg daily) + speech pathology therapy vs. placebo + speech pathology therapy

- More effective in improving subjective cough outcomes (cough-specific QoL)

  Less effective in reducing objective cough frequency

- Frequent side effects: dizziness, blurred vision, cognitive changes



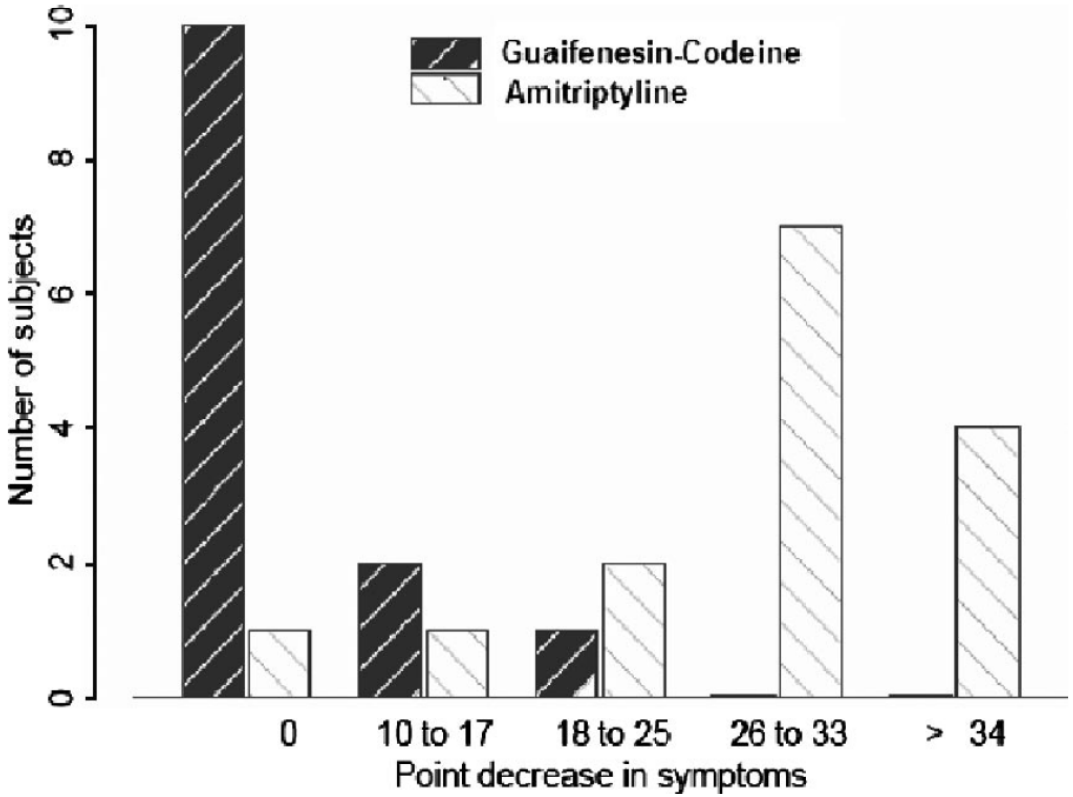
Ryan N et al. *Lancet 2012*; Vertigan AE et al. *Chest 2016*

Amitriptyline

Effectiveness of Amitriptyline Versus Cough Suppressants in the Treatment of Chronic Cough Resulting From Postviral Vagal Neuropathy

TABLE II.
Patient Demographics.

N = 28	Amitriptyline (N = 15; 7 female)	Codeine/Guaifenesin (N = 13; 8 female)
Median age	54.6 years	49.7 years
Median duration of cough	15.1 months	11.4 months
History of nasal allergy	2	3



Jeyakumar A et al. *Laryngoscope 2006*

Amitriptyline

Long-term Follow-up of Amitriptyline Treatment for Idiopathic Cough

TABLE II.
Results at Initial Clinical Follow-up at Mean of 2.6 Months After Starting Amitriptyline (N = 36).

Result	No.	%
Still taking medication	32	89%
Daily dosage		
0 mg	4	11%
1–20 mg daily	17	47%
21–40 mg daily	12	33%
>40 mg daily	3	8%
Cough improved	33	92%
Cough improved ≥50%	24	67%
Reported side effects	6	17%

- True response rate: ?

Ryan M et al. *Laryngoscope 2016*

Idiopathic chronic productive cough and response to open-label macrolide therapy: An observational study

MATTHEW J. MARTIN,[1] HELEN LEE,[1] CARLY CLAYTON,[1] KATE POINTON,[2] IRSHAD SOOMRO,[3] DOMINICK E. SHAW[1] AND TIM W. HARRISON[1]

- Chronic productive cough patients
  who had not smoked for ≥10 years with a <20 pack-year smoking history
  and if initial investigations found no cause for their symptoms

- 12 weeks of low-dose azithromycin (250 mg thrice weekly)

Table 2 Changes in primary and secondary outcome measures for whole cohort (n = 29) with azithromycin treatment

	V1	V4	V1 – V4 difference	Significance (P)	V5	V1 – V5 difference	Significance (P)
LCQ score	11.5 (3)	17.8 (5.9)	6.3	**<0.00001**	15.9 (8.3)	4.4	**0.0006**
24-h Sputum volume (mL)	7.9 (5.5)	2.1 (7.2)	−5.8	**0.0001**			
FE_{NO} level (ppb)	19 (19.5)	12.5 (12)	−6.5	0.14			
FEV_1 (L)[†]	2.77 (0.99)	2.75 (1.0)	−0.02	0.78			

Martin M et al. *Respirology 2019*

Table 4 Demographics of azithromycin responders versus non-responders

	Responders (post-treatment LCQ > MCID)	Non-responders (post-treatment LCQ < MCID)	
	Frequency (%)	Frequency (%)	Significance (*P*)
Total number included for analysis	22	7	
Mean age (range)	55.5 (25–77)	63.9 (55–70)	0.20
Sex: male	7 (31.8)	5 (71.4)	0.09
Ethnic group			
Black or Black British	1 (4.6)	0 (0)	
White or White British	21 (95.4)	7 (100)	1.0
Smoking history			
Ex-smokers	7 (31.8)	4 (57.1)	
Non-smokers	15 (68.2)	3 (42.9)	0.38
Diagnosis of asthma	11 (50)	6 (85.7)	0.19
On inhaled steroid treatment	11 (50)	6 (85.7)	0.19
History/symptoms of GORD	4 (18.2)	1 (14.3)	1.0
History/symptoms of PNDS	4 (18.2)	2 (28.6)	0.61
Sputum/bronchial wash inflammatory type ($n = 29$)			
Neutrophilic (>61%)	14 (63.6)	1 (14.3)	**<0.001**
Eosinophilic (>3%)	0 (0)	5 (71.4)	
Paucigranulocytic	5 (22.7)	1 (14.3)	
Missing sample	3 (13.6)	0 (0)	
	Mean (SD)	Mean (SD)	Significance (*P*)
ICS dose (BDP equivalent μg)†	800 (800)	900 (800)	0.12
Blood eosinophil count ($\times 10^9$/L)†	0.2 (0.1)	0.4 (0.45)	0.0004
FE_{NO} (ppb)†	18 (17)	19 (37.5)	0.68
FEV_1 (% predicted)	103.6 (18.8)	73.6 (17.3)	**0.0009**
FEV_1/FVC ratio (%)	78.4 (7)	67.6 (8)	**0.0019**
Baseline (V1) sputum % neutrophils ($n = 26$)	73.2 (21.9)	46.8 (34.2)	0.06
Baseline (V1) sputum % eosinophils ($n = 26$)	0.5 (0.75)	13.7 (24.8)	**0.03**

Patients with sputum eosinophilia or airflow obstruction are likely to be non-responders

Martin M et al. *Respirology 2019*

Unmet clinical needs in RUCC management

- Current drugs used as anti-tussives (opioids, gabapentin, or pregabalin)

  - not originally developed for cough management

  - only effective in less than half of patients

  - short-term and long-term safety concerns, and regulatory issues

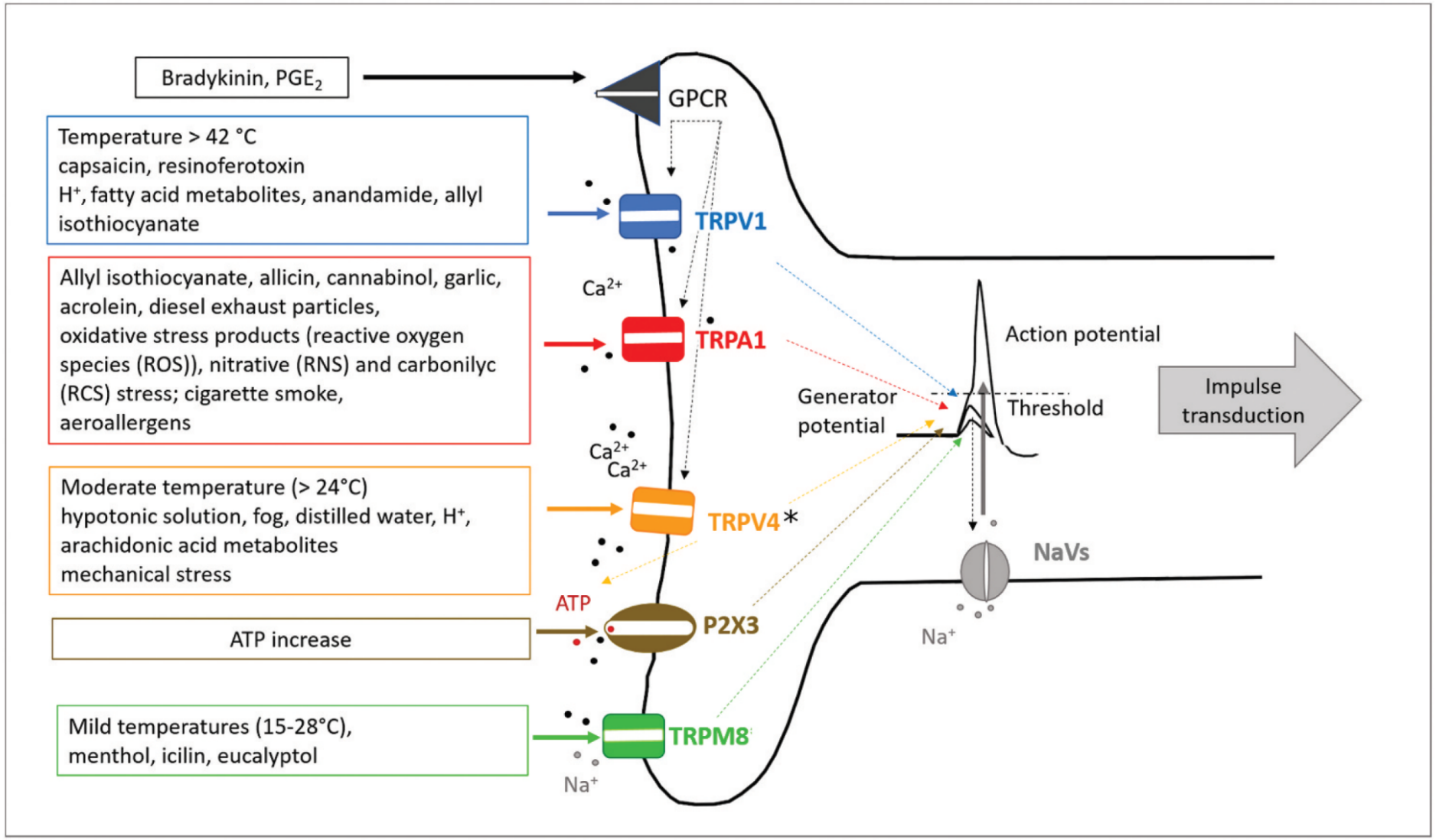
- Patients are long exposed to drugs and investigations that may not be necessary or useful.

- Large burden to patients and society

  - according to a healthcare database study in the US (Zeiger RS et al. JACI Practice 2020),

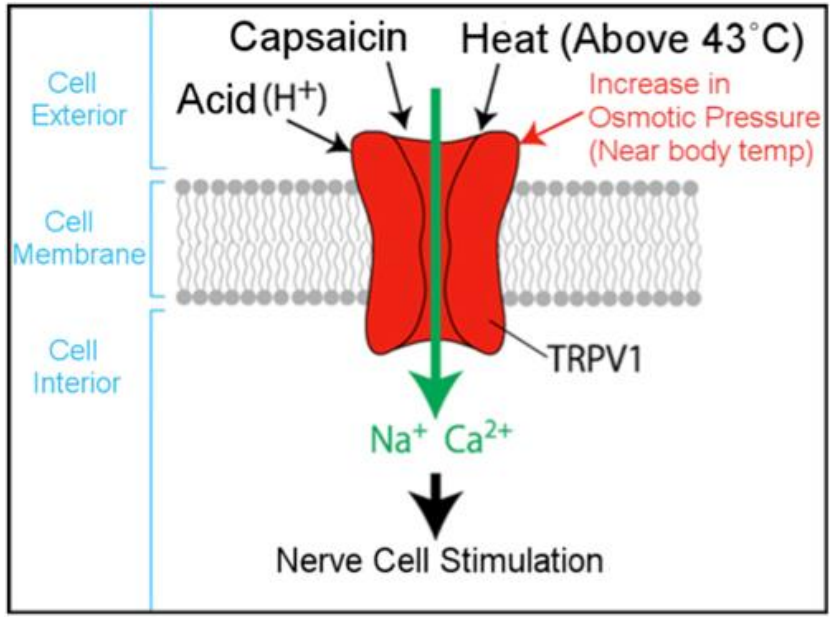
  chest CT scans (21%), PPIs (45%), respiratory antibiotics (72%), steroids (47%), and narcotics including codeine (60%)

Recent advances in understanding afferent nerve cough receptors



Grabczak EM et al. *Exp Rev Respir Med 2020*

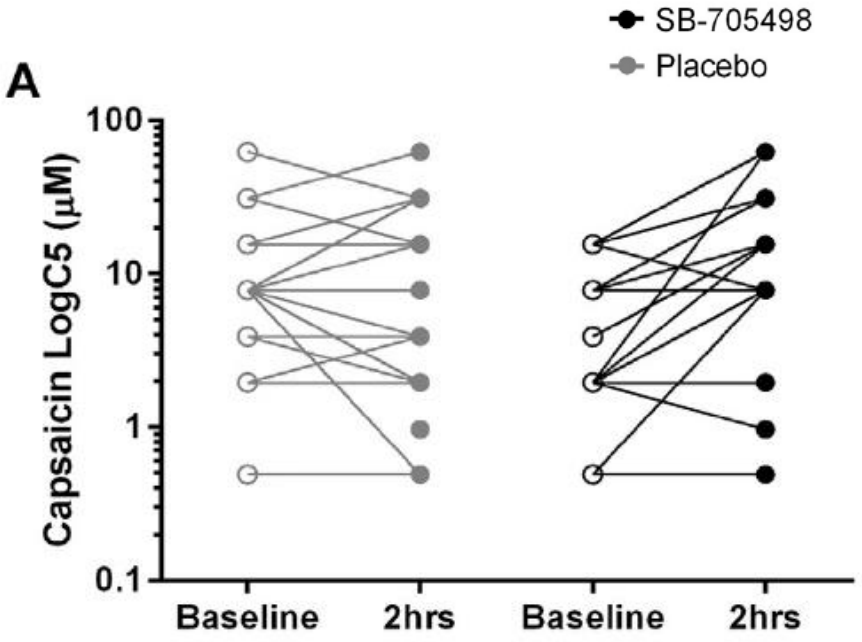
TRPV1: the first target in Refractory or Unexplained Chronic Cough (RUCC)



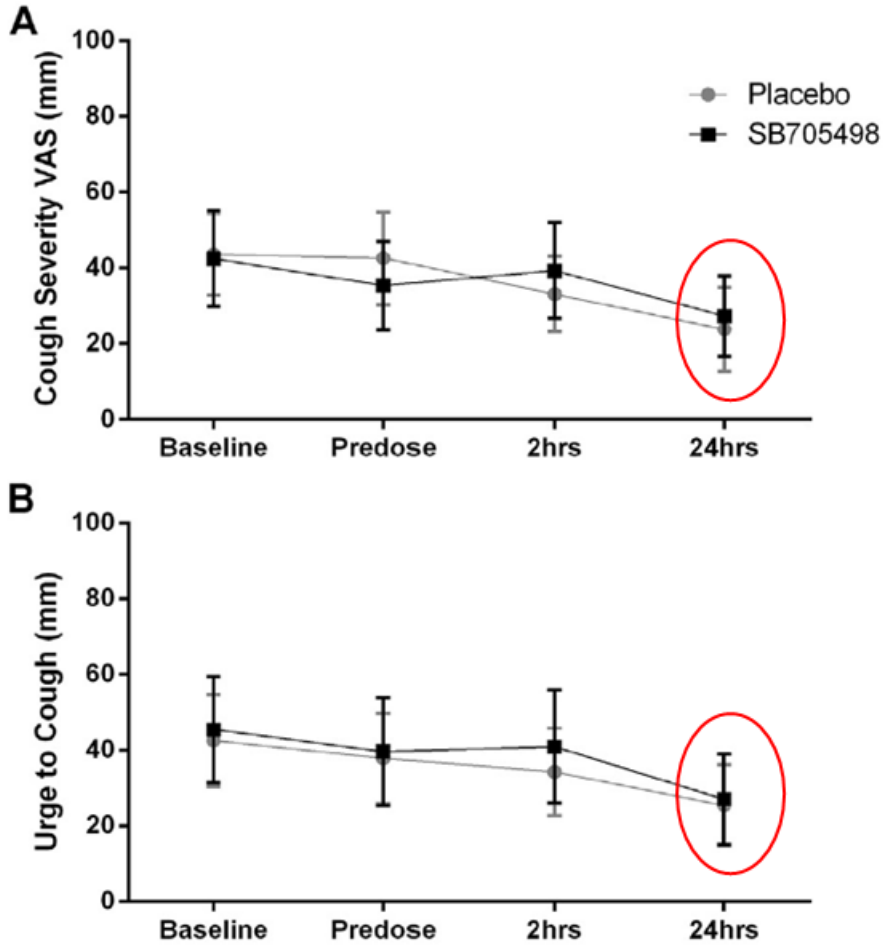
- Chili pepper (capsaicin): well-known tussigen
- TRPV1: sensing capsaicin (1999)

  - sensation of hot temperature, acid, endogenous inflammatory mediators

Failure of TRPV1 antagonist SB-705498



Refractory cough patients (n=21)



Khalid et al. *J Allergy Clin Immunol* 2014

XEN-D0501, a novel TRPV1 Antagonist, does not reduce Cough in Refractory Cough Patients

Maria G. Belvisi[1*], Mark A. Birrell[1], Michael A. Wortley[1], Sarah A. Maher[1], Imran Satia[2], Huda Badri[2], Kimberley Holt[2], Patrick Round[3], Lorcan McGarvey[4], John Ford[3], and Jaclyn A. Smith[2*]

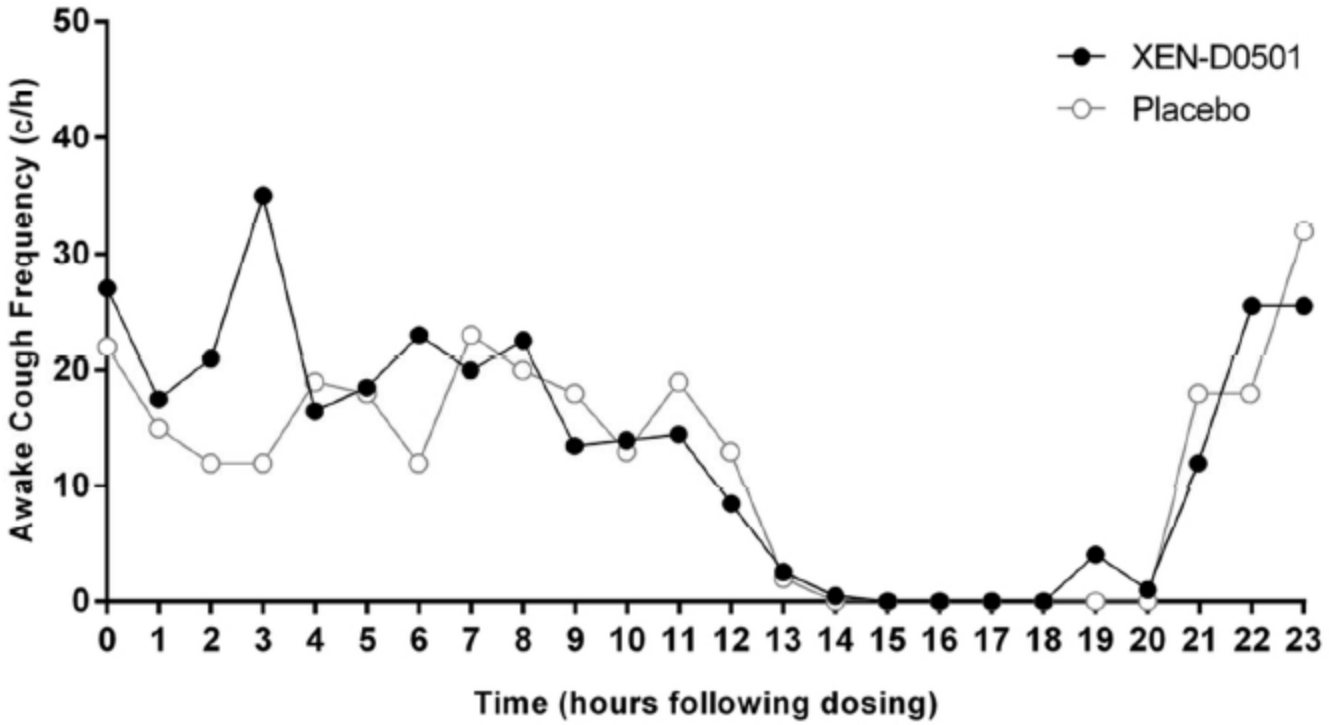
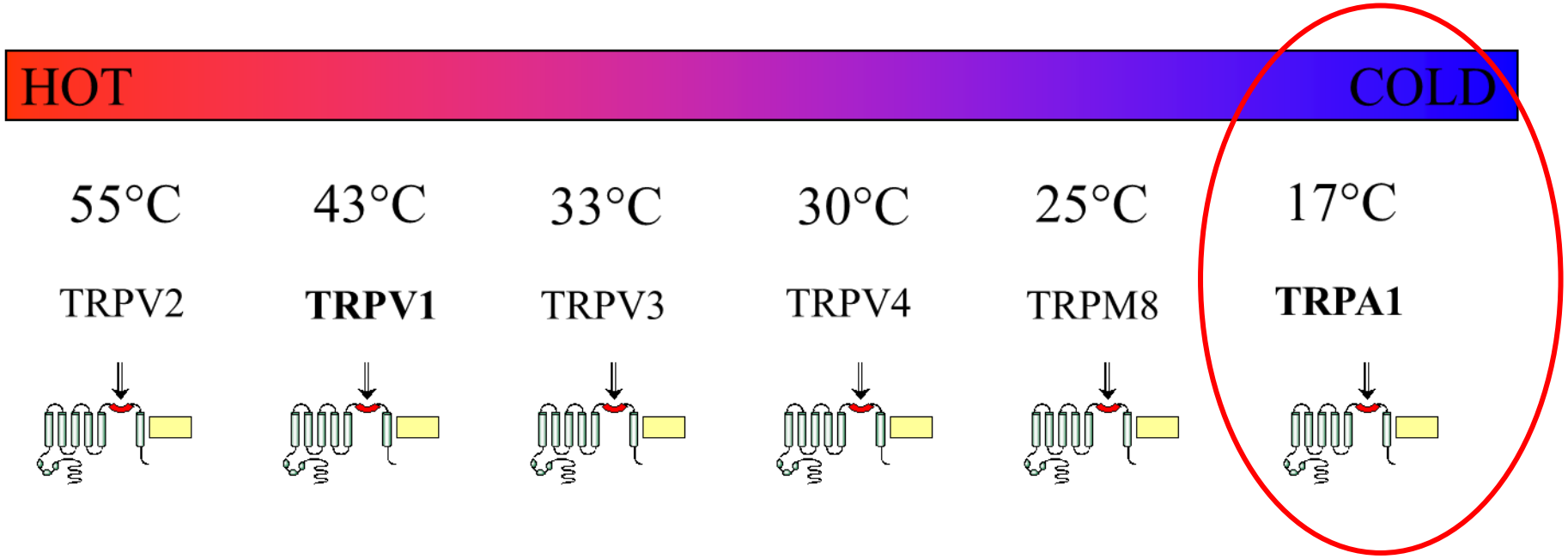


Figure 5. Hourly Cough Frequency. Comparison of cough frequency hour by hour on day 14 of treatment with XEN-0501 compared with placebo; data shown are medians.

Belvisi et al. *Am J Respir Crit Care Med 2017*

TRPA1

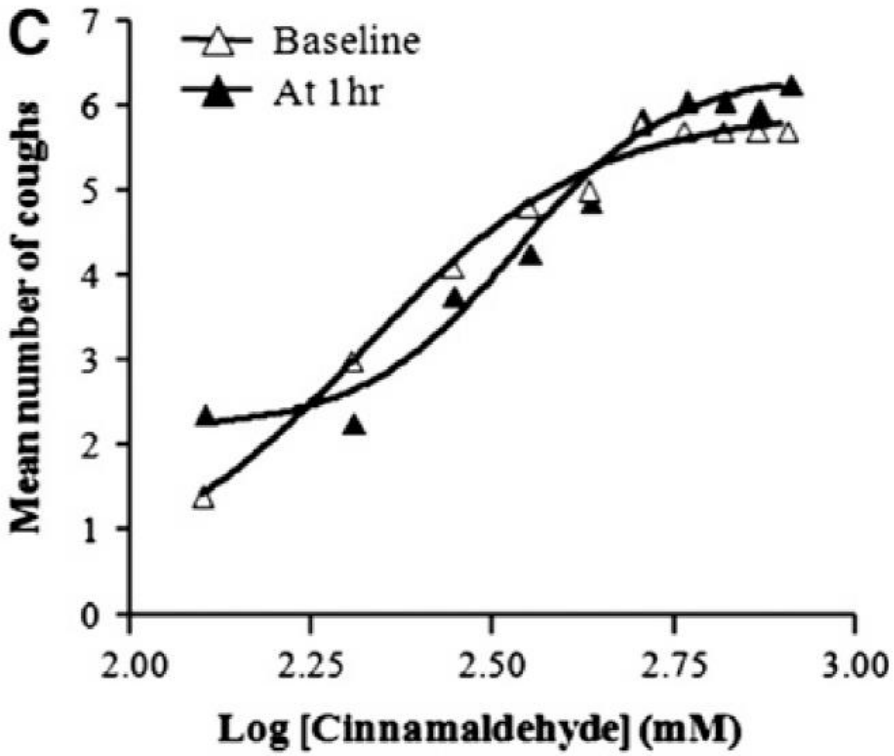


Hot receptor

Cold receptor

Extensive sensitivity to irritant chemicals (acrolein, TDI, smoke, formaldehyde...)

TRPA1: second target



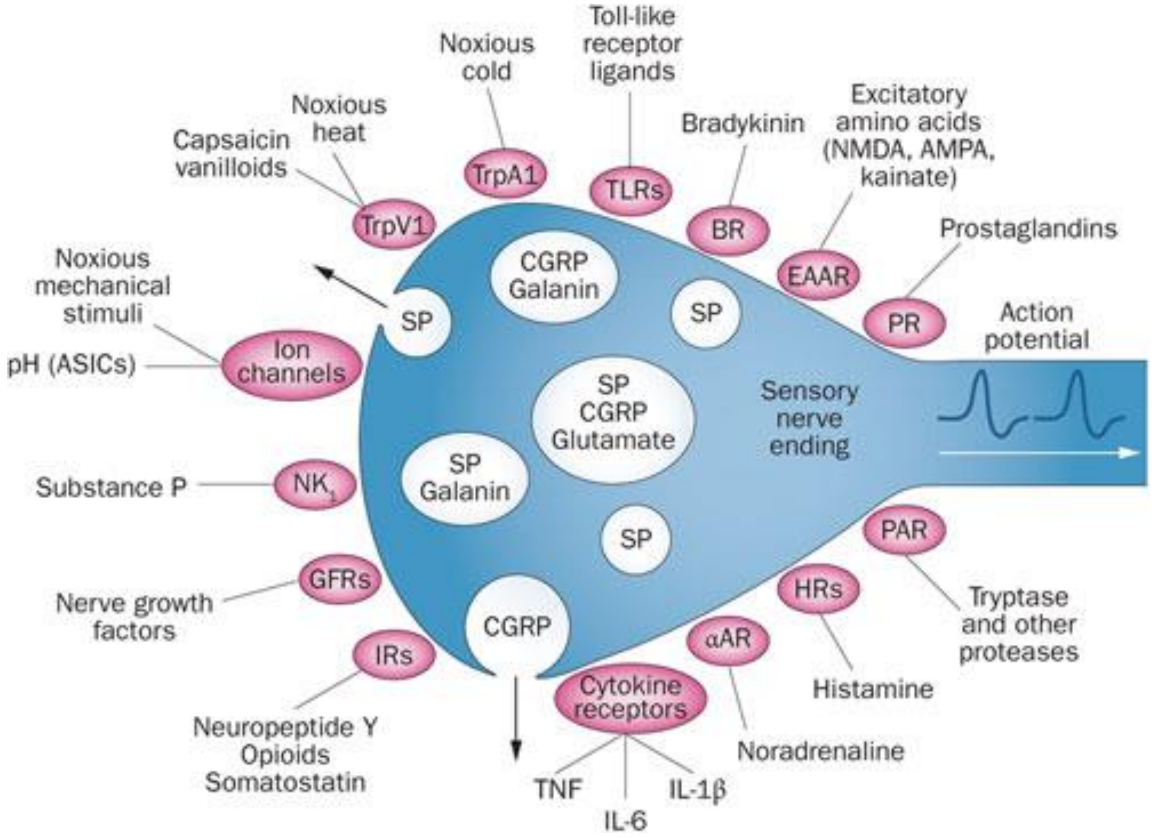
TRPA1 as cough receptor
in response to various environmental irritants
(smoke, acrolein, AITC…) and also cold air

Birrell et al. *Am J Respir Crit Care Med* 2009

Failures of TRP channel antagonists

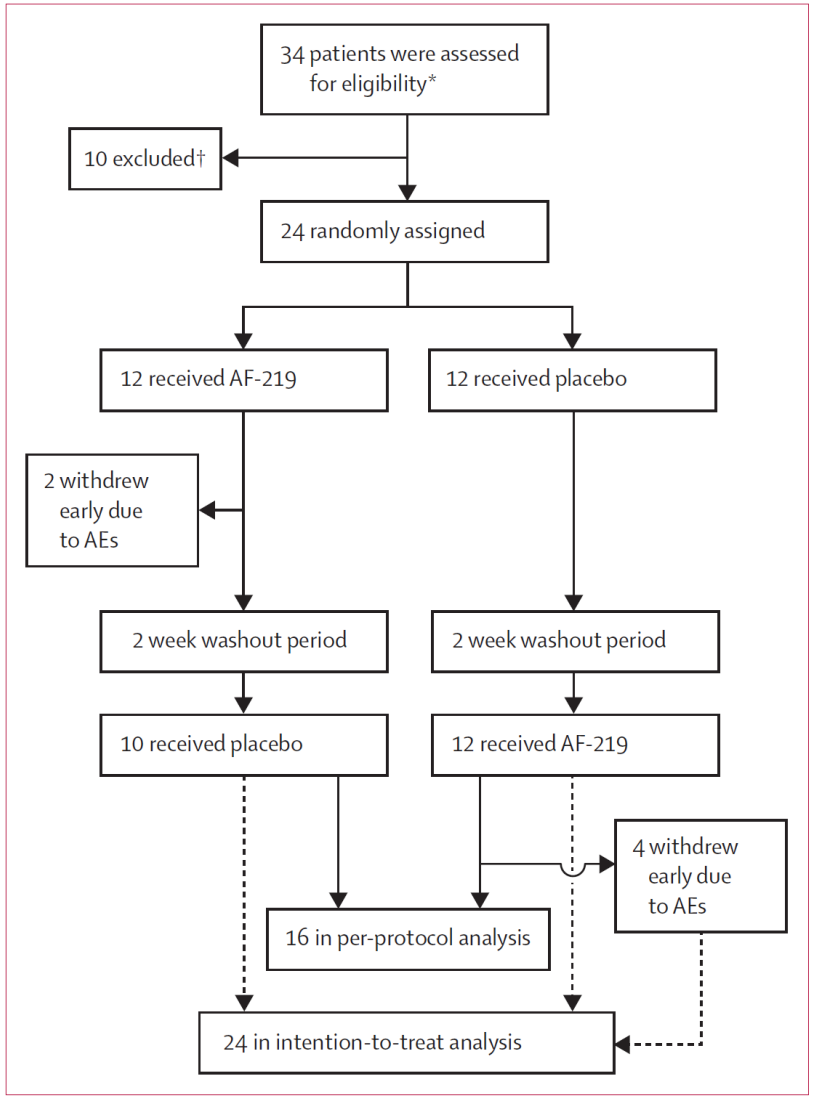
- Targeting a single receptor at peripheral levels

  could be a move in the wrong direction?



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



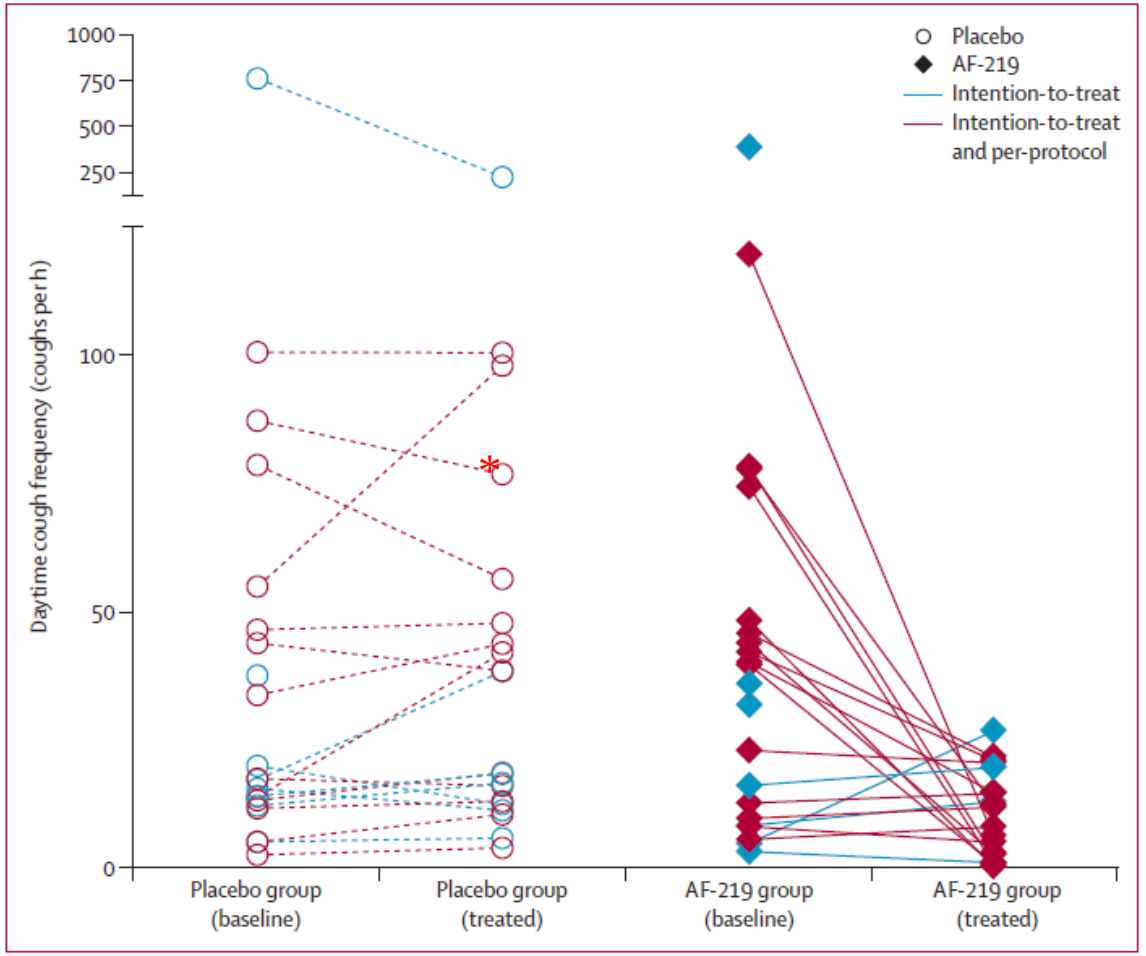
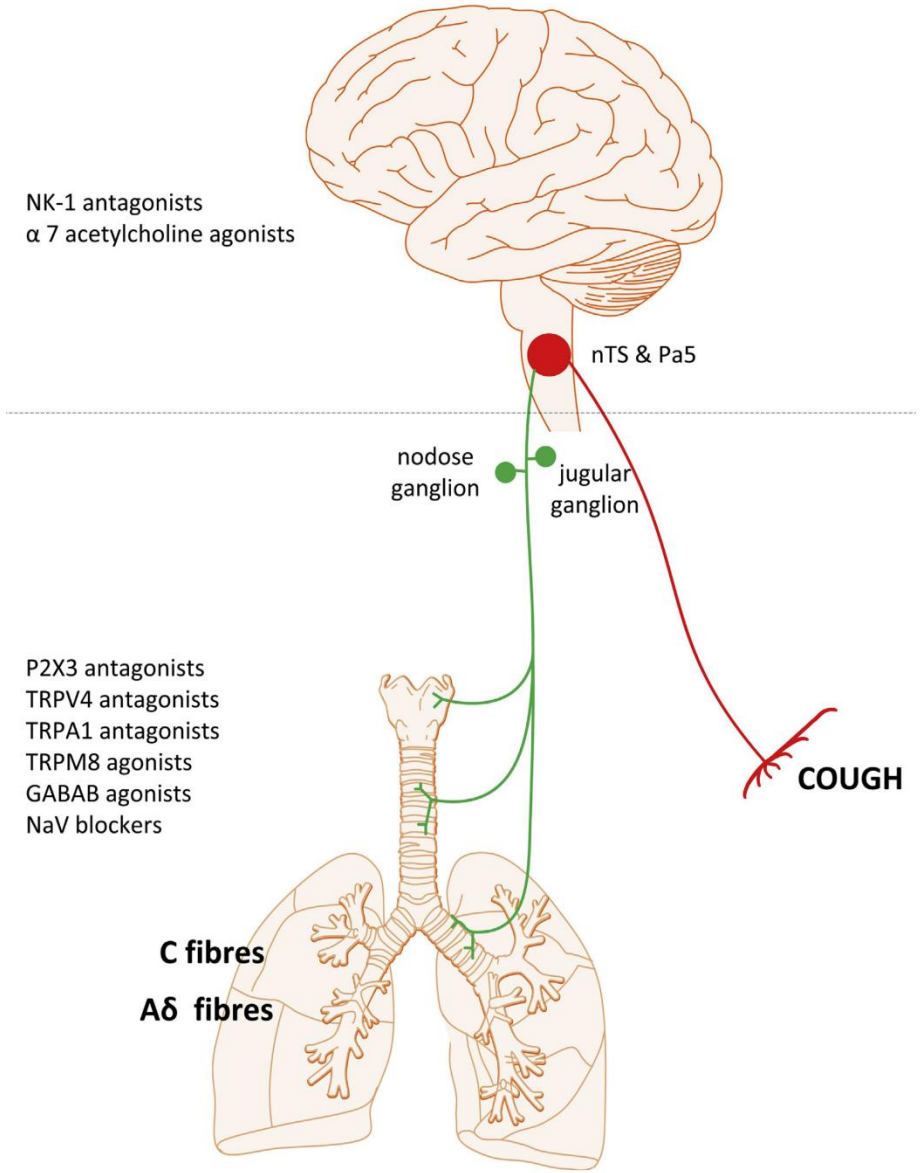
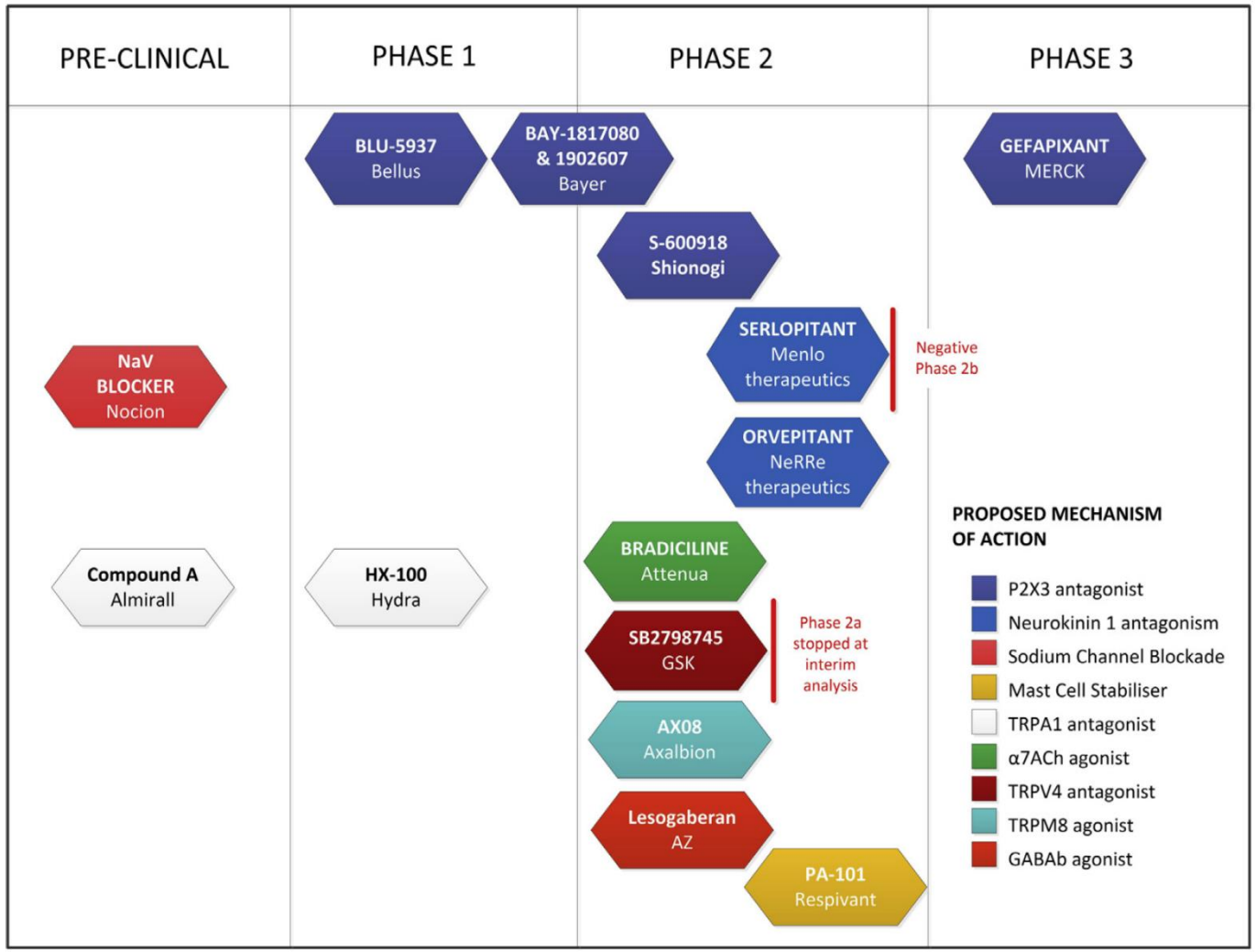


Figure 2: **Changes in objective daytime cough frequency from baseline to end of the treatment period**
Intention-to-treat analysis included the blue and red data points, whereas the per-protocol included data in red only.

Abdulqawi et al. *Lancet* 2015

Future directions – novel antitussives





Smith JA et al. *JACI Practice 2019*

RCTs with anti-tussives in chronic cough

Drug (publication or clinical trial ID)	Phase	Patients		Significant benefit on cough outcome (intervention vs. control)		
		Disease	Number	Frequency	Severity	QoL
Codeine (Smith 2006)	PoC	COPD cough	21	*p*=0.52*	*p*=0.96	
Morphine (Morice 2007)	PoC	CRC	27		Not specified	*p*<0.02*
Morphine (Al-Sheklly 2017†)	PoC	CRC (responder)	22	*p*<0.05*	*p*<0.05	*p*<0.05
Gabapentin (Ryan 2012)	PoC	CRC	62	*p*=0.028	*p*=0.029	*p*=0.004*
Pregabalin (Vertigan 2016)	PoC	CRC	40	*p*=0.671*	*p*=0.002*	*p*=0.024*
Amitriptyline (Jeyakumar 2006††)	PoC	PVVN cough	28			Not specified
TRPV1 antagonist$_a$ (Khalid 2014)	PoC	CRC	21	*p*=0.508*	Not specified	Not specified
TRPV1 antagonist$_b$ (Belvisi 2017)	PoC	CRC	20	*p*=0.41*	Not specified	Not specified
Gefapixant 600 mg (Abdulqawi 2014)	PoC	CRC	24	*p*=0.003*	*p*=0.003	*p*=0.018
Gefapixant 50 mg$_c$ (Smith 2020)	Dose ranging	CRC	30	*p*<0.05*	*p*<0.05	*p*<0.05
Gefapixant 50 mg$_d$ (Smith 2020)	Phase 2b	CRC	253	*p*=0.0027*	*p*=0.0108	*p*=0.0028
Gefapixant 50 mg (NCT02502097†)	PoC	IPF cough	51	*p*=0.07*		
TRPV4 antagonist$_e$ (NCT03372603†)	PoC	CRC	12	Not specified		
Serlopitant (EudraCT 2017-003250-16†)	Phase 2	CRC	185	*p*=0.994*	*p*=0.908	Not specified
Orvepitant (NCT02993822†)	Phase 2b	CRC	315	Not specified*	*p*=0.046	*p*=0.009
Inhaled cromolyn PA101 (Birring 2017)	PoC	IPF cough	24	*p*=0.024*	*p*=0.13	*p*=0.09
Inhaled cromolyn PA101 (Birring 2017)	PoC	CRC	28	*p*=0.31*	*p*=0.92	*p*=0.42
NaV blocker GSK2339345 (Smith 2017)	PoC	CRC	11	Increased*	Not specified	
NaV blocker VRP700 (Satia 2015†)	PoC	IPF cough	20	Increased*	Not specified	

Not measured

p ≥0.05

0.01 ≤ *p* < 0.05

0.001 ≤ *p* < 0.01

p <0.001

TRPV1 antagonist$_a$ = SB-705498

TRPV1 antagonist$_b$ = XEN-0501

Gefapixant 50 mg$_c$ = day 16 data of study 2

Gefapixant 50 mg$_d$ = week 12 data

TRPV4 antagonist$_e$ = GSK2798745

Song WJ and Chung KF. *Expert Opin Pharmacother 2020*

P2X3 antagonists are now over the horizon: for RUCC

- Gefapixant (MSD, previously AF-219) – finished phase 3
- Eliapixant (Bayer) – finished phase 2a
- BLU-5937 (Bellus Health) in phase 2
- Shivopixant (Shionogi) – finished phase 2b

- And more novel therapeutic agents (with specific neuronal targets) on the pipeline

Summary

- Paradigms and managements for cough have evolved to solve unmet clinical needs.
- Initial management

  Identification of treatable traits based on anatomic diagnostic protocols should be the key steps.

  But RCT evidence is lacking in many areas.
- RUCC management

  1) Current practice: A few drugs with RCT evidence may be trialled (opioids, gabapentin).

  2) Unmet needs: These drugs have safety concerns and limited efficacy profile.
- Future directions

  - novel anti-tussive treatments and biomarkers

Thank you!