LIVE WEBINAR

Placebo Responses in Refractory Chronic Cough: Reasons & Potential Solutions

Tuesday 11 February
3 - 4pm GMT

Presented by
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Canada Research Chair in Chronic Cough

Placebo Responses in Refractory Chronic Cough; *Reasons, Potential Solutions and Ethics*

11th February 2025, Vitalograph Webinar

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Disclosures

- Funding: *ERS Respire 3 Fellowship Award*, *BMA James Trust Award, North West Lung Centre Charity (Manchester), NIHR CRF Manchester, Merck MSD, AstraZeneca, GSK, Trevi Therapeutics, Genentech, Bayer, Bellus*
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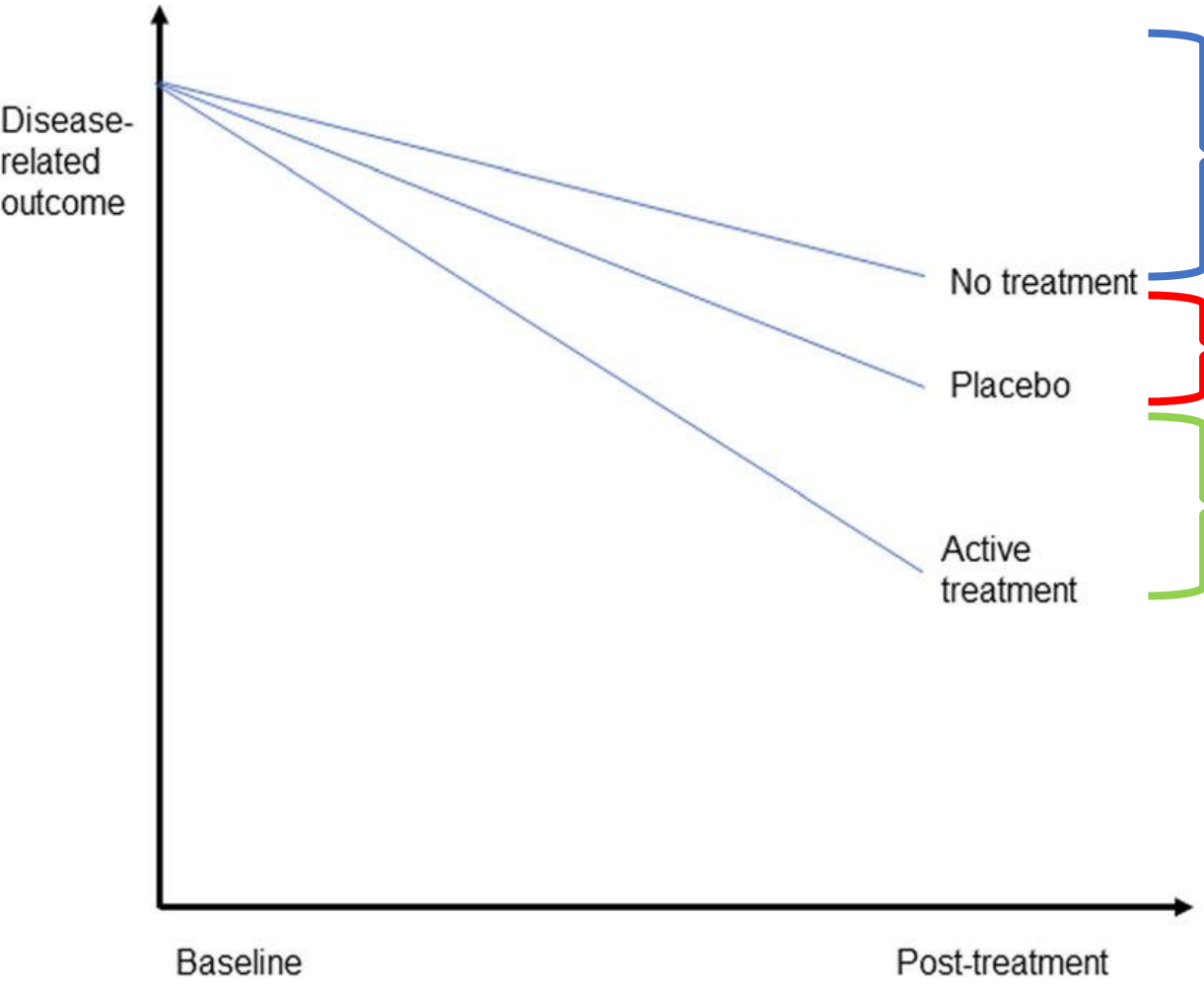
- Speaker Fees: AstraZeneca, GSK, Merck MSD, Sanofi
- Task Force Committees: *Chronic Cough (ERS), Asthma Diagnosis and Management (ERS), NEUROCOUGH (ERS CRC)*
- Employment: *McMaster University*


Relatively New Phenomenon in RCC
Impacts Efficacy in Clinical Trials
Drug Development
Mechanisms Unclear
Magnitude and Pattern Varies
Clinical Practice?
Why?

Learning Objectives

1. What is the Placebo Response
2. Mechanisms of Placebo Response: Lessons from Chronic Pain
3. Lessons from trials in RCC
4. Alternative Study Designs
5. Ethical Considerations

Placebo Response ≠ Placebo Effects



Natural History,
High Baseline Score, Regression to the Mean
Patient-Physician Interactions and Biases
Co-Interventions
Hawthorne Effect

Placebo Effect: Neurobiological and Psychological effects of expectancies, reward, conditioning

Drug/Intervention Effects

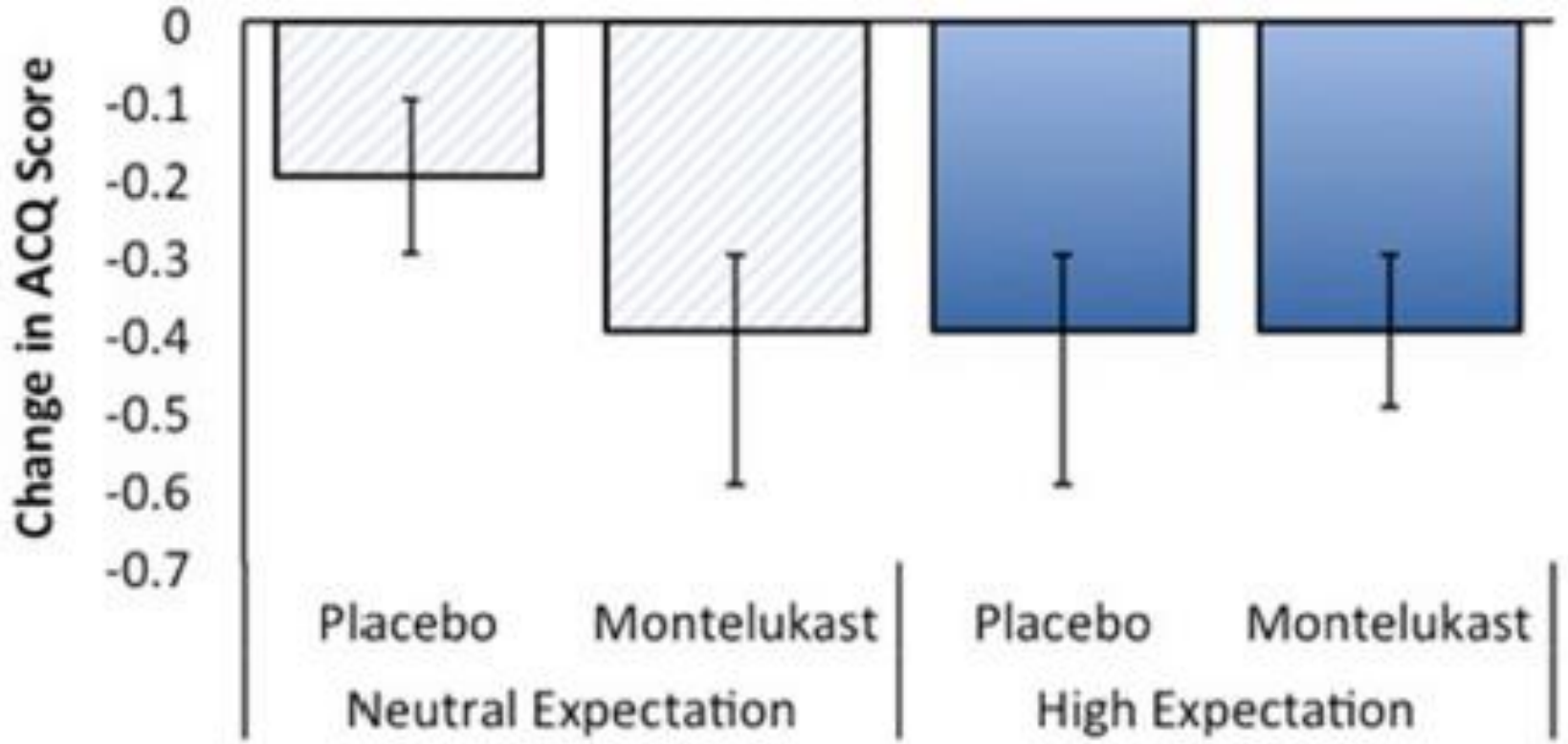
PLACEBO RESPONSE

What are treatment contextual effects?

These features combine to make up the treatment context and are the 'active ingredients' of placebo effects

Wager and Atlas, Nature Reviews Neuroscience 2015

Changing Expectations



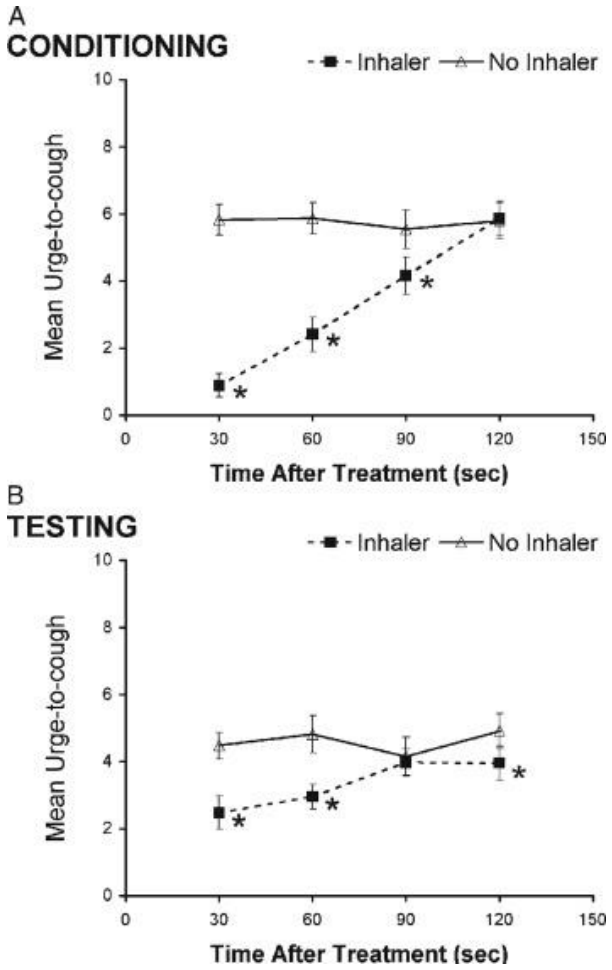
Managing Expectations is an important feature of clinical trial designs and consenting process:

Minimise or keep the potential drug effects neutral

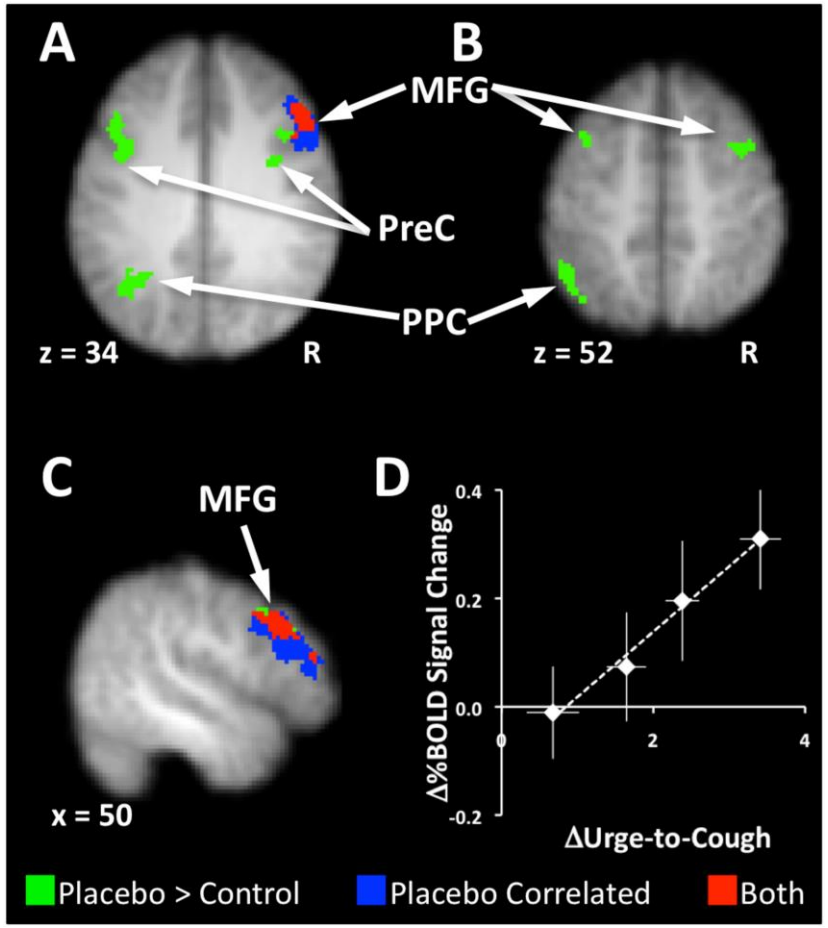
Wise et al, JACI 2009

What are the Neuronal Mechanisms of the Placebo Effect in Cough?

Conditioning lowers urge to cough sensations



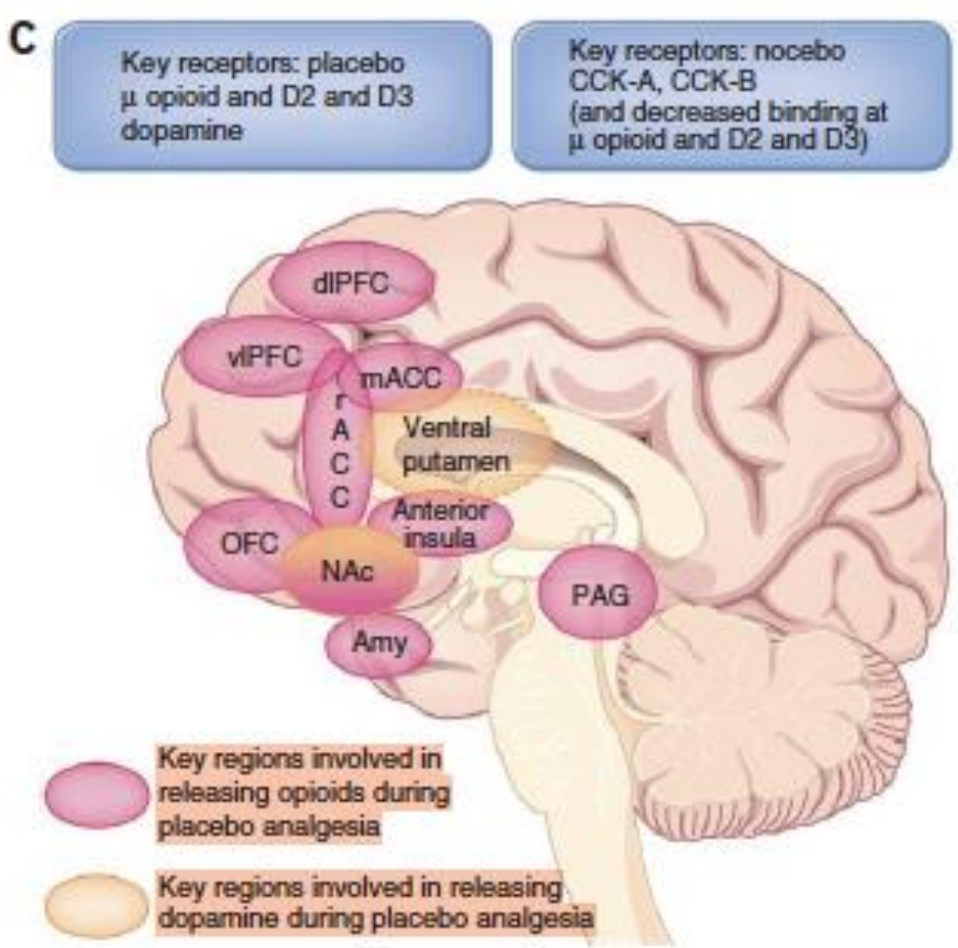
Leech et al, Chest 2012



Leech et al, AJRCCM 2013

"we showed that when participants believed that they were receiving an antitussive treatment, brain activity was increased in regions of the prefrontal and parietal cortices that may represent important components of the placebo suppression network."

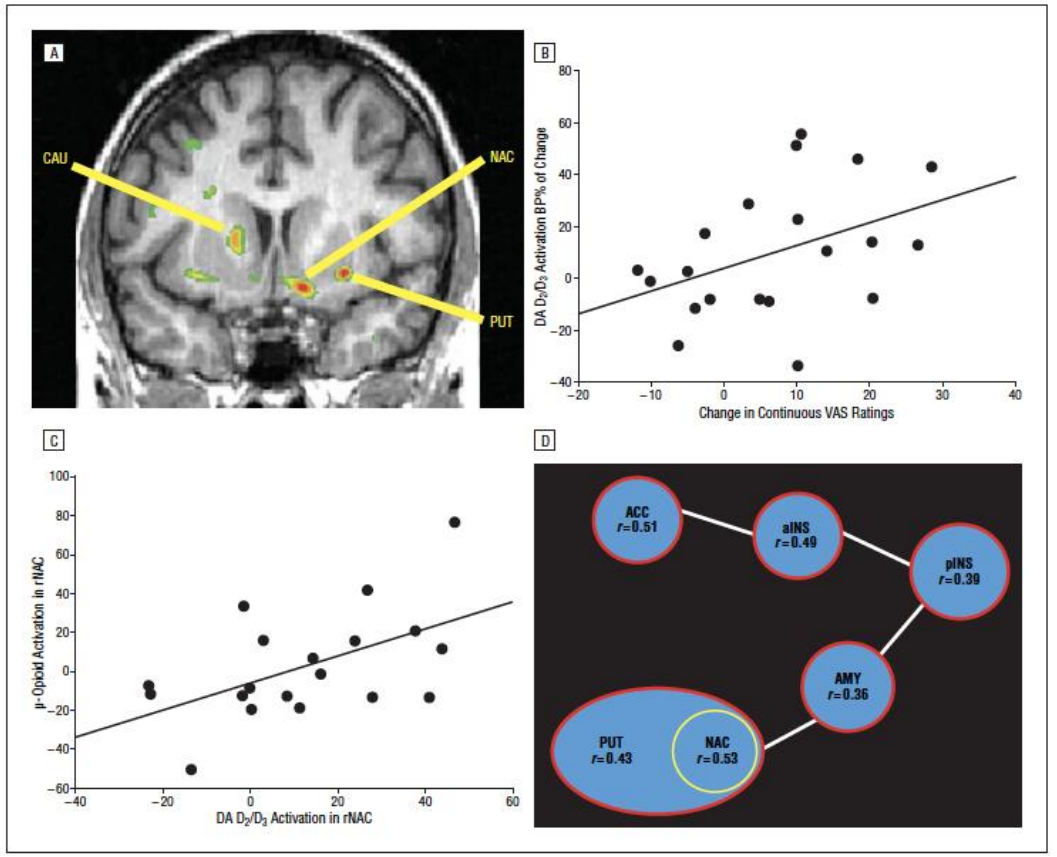
Top-Down Mechanisms in Placebo Analgesia

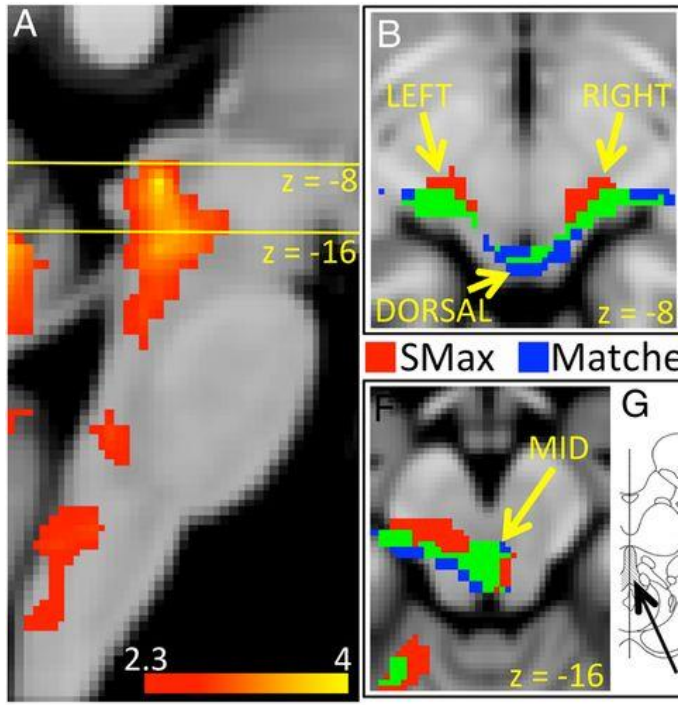


Irene Tracey, Nature Medicine, 2010

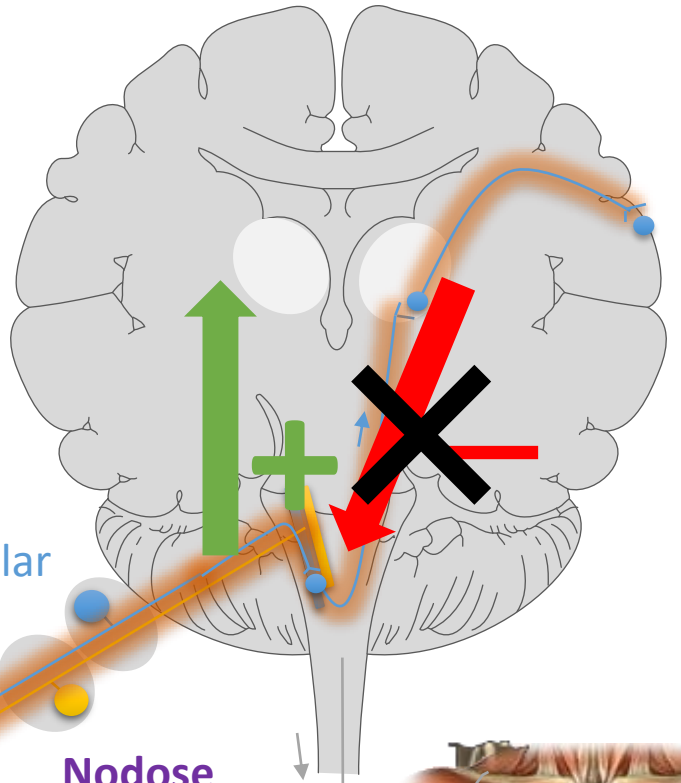
Placebo and Nocebo Effects Are Defined by Opposite Opioid and Dopaminergic Responses

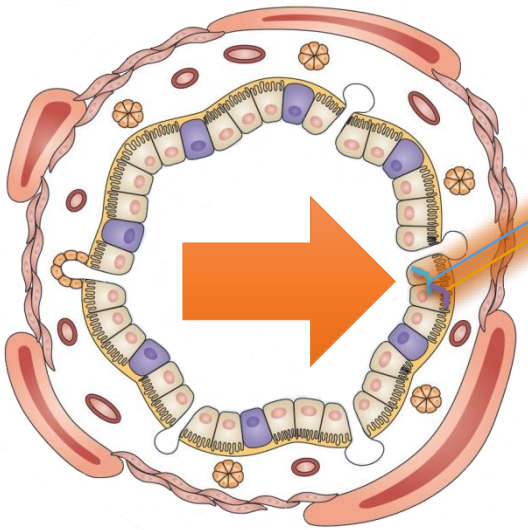
David J. Scott, BS; Christian S. Stohler, DDS, PhD; Christine M. Egnatuk, BS; Heng Wang, PhD; Robert A. Koeppe, PhD; Jon-Kar Zubieta, MD, PhD



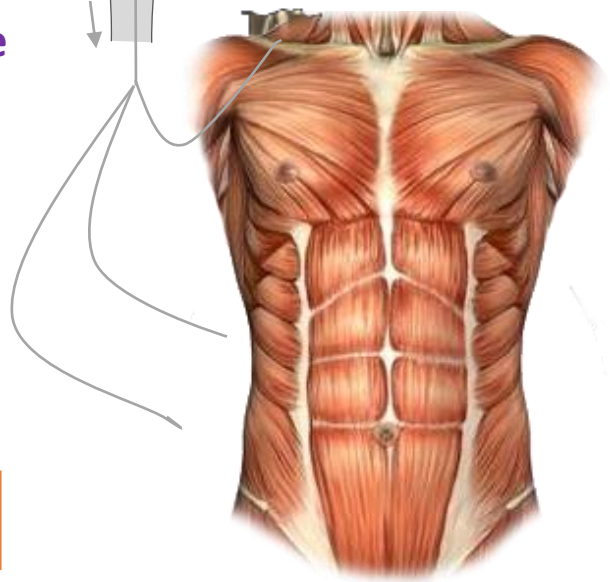


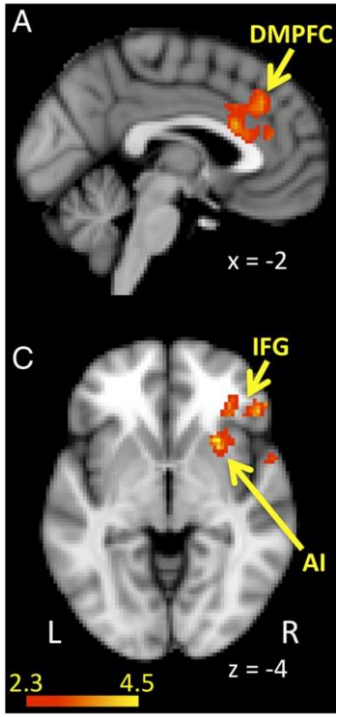
Increased Activity





COUGH





Decreased Activity

Chronic Cough and Chronic Pain share similar mechanisms and likely more amenable to the Placebo Effect…

Ayaka Ando et al. Thorax 2016;71:323-329

Lessons from Clinical Trials in Refractory Chronic Cough

Earlier RCC did not show significant placebo responses

Transient receptor potential vanilloid 1 (TRPV1) antagonism in patients with refractory chronic cough: A double-blind randomized controlled trial

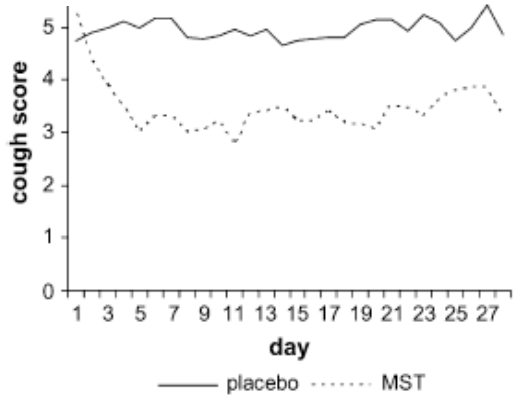
Saifudin Khalid, MB BS, PhD,[a] Robert Murdoch, BSc, PhD,[b] Amy Newlands, BSc, MSc,[b] Kevin Smart, BSc, PhD,[b] Angela Kelsall, BSc, PhD,[a] Kimberley Holt, BSc,[a] Rachel Dockry, BSc, MSc,[a] Ashley Woodcock, MB ChB, MD,[a] and Jaclyn A. Smith, MB ChB, PhD[a] *Manchester and Stevenage, United Kingdom*

XEN-D0501, a Novel Transient Receptor Potential Vanilloid 1 Antagonist, Does Not Reduce Cough in Patients with Refractory Cough

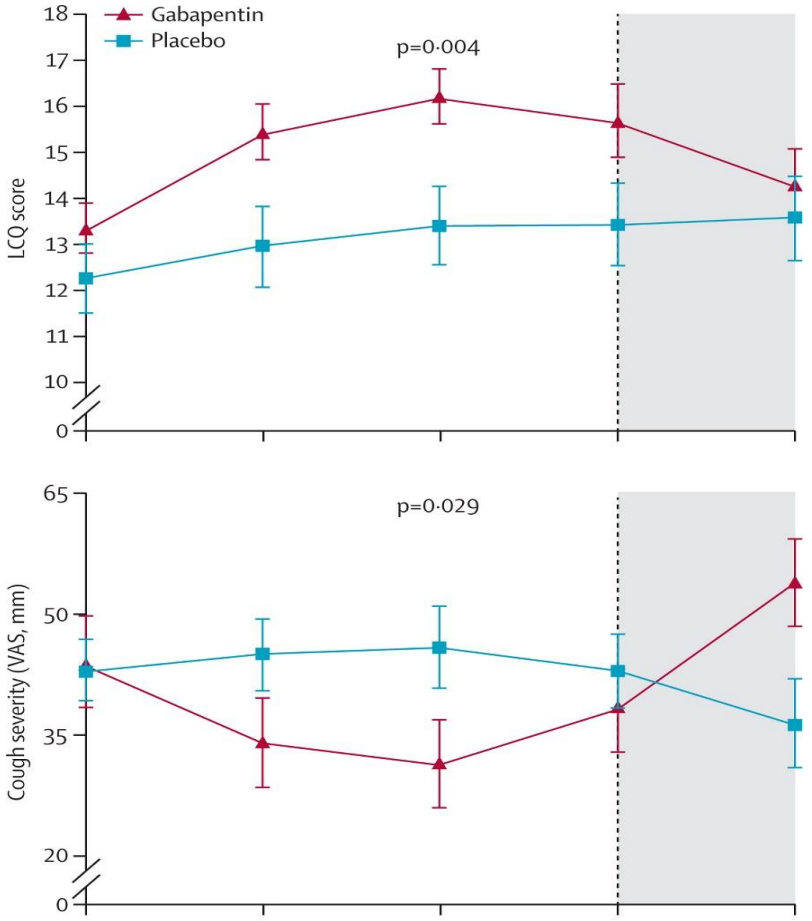
Maria G. Belvisi[1,2], Mark A. Birrell[1], Michael A. Wortley[1], Sarah A. Maher[1], Imran Satia[3], Huda Badri[3], Kimberley Holt[3], Patrick Round[4], Lorcan McGarvey[5], John Ford[4], and Jaclyn A. Smith[3]

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

Nicole M Ryan, Surinder S Birring, Peter G Gibson

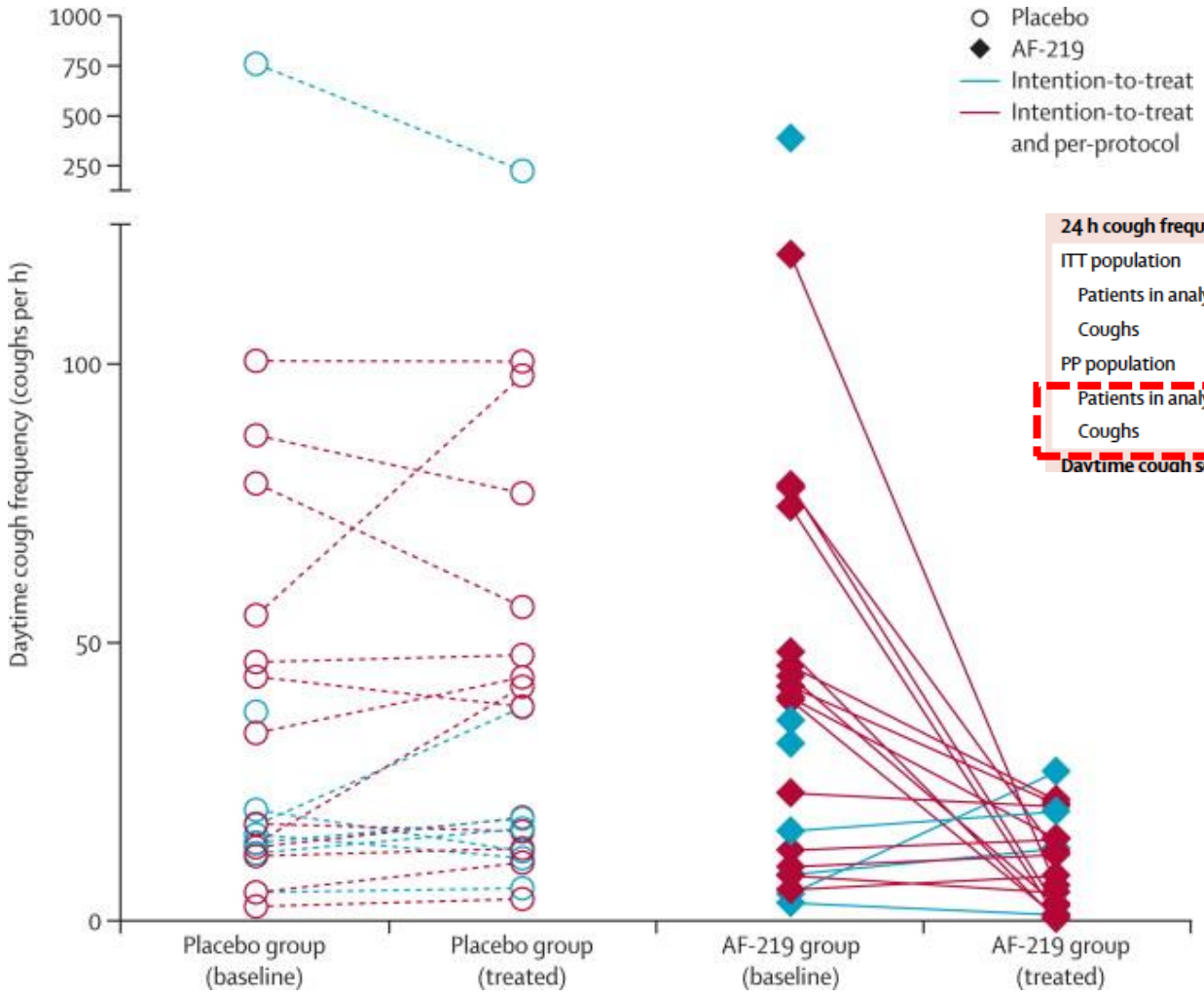


Morice et al AJRCCM 2007



Lancet 2012; 380: 1583–89

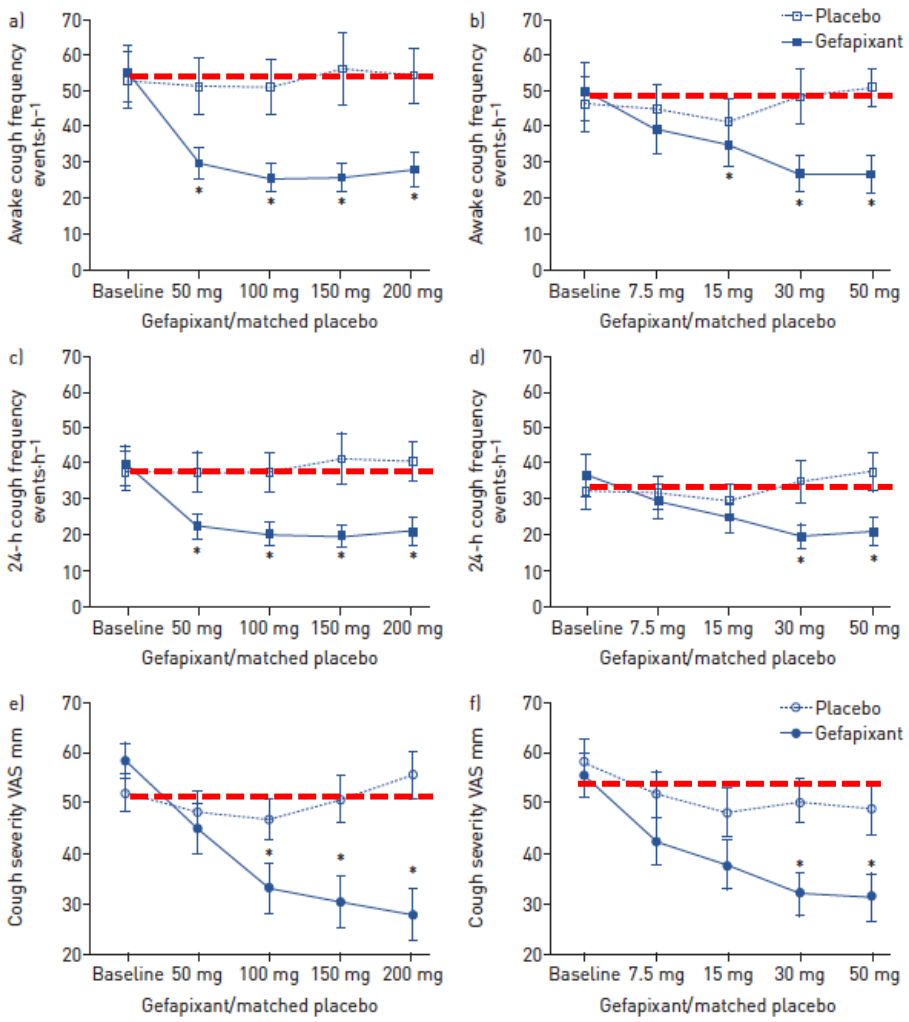
Gefapixant Phase 2a: First Positive Study!



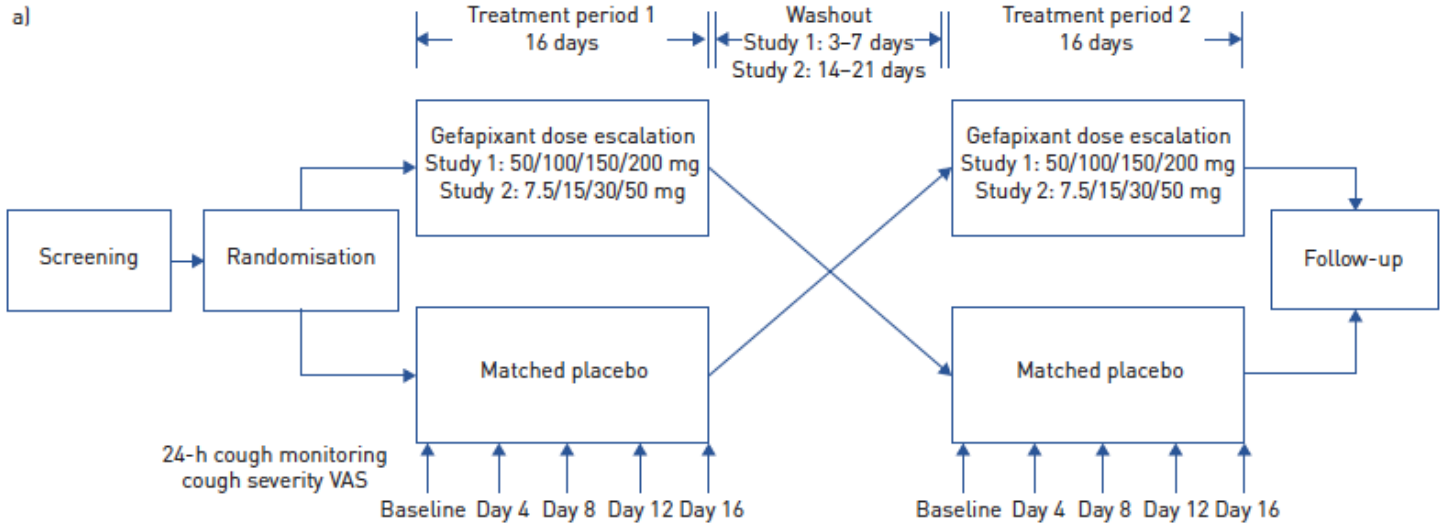
24 h cough frequency						
ITT population						
Patients in analysis	18	18	20	20	..	..
Coughs	26·63 (22·63)	7·74 (6·02)	44·70 (105·16)	28·85 (31·17)	−74% (−87 to −46)	0·001
PP population						
Patients in analysis	12	12	12	12	..	..
Coughs	33·24 (24·13)	6·96 (5·63)	28·42 (22·46)	30·44 (22·29)	−89% (−97 to −67)	0·001
Daytime cough severity VAS						

Abdulqawi et al, Lancet. 2015 Mar 28;385(9974):1198-205

Phase 2a – Placebo Group is stable



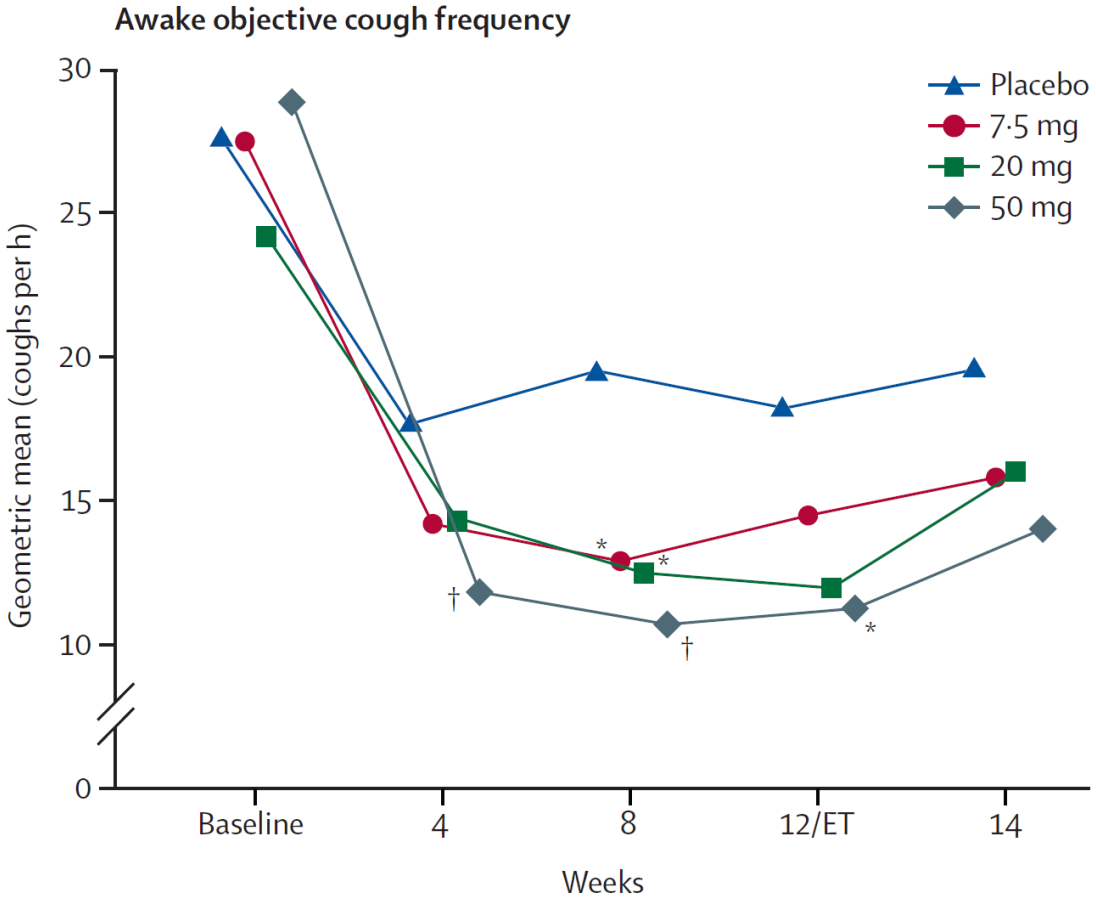
12 Sites in the US only
29 patients in study 1
30 patients in study 2



% change over placebo ranged from
41% - 57% in study 1
15%-56% in study 2

Smith et al, ERJ. 2019

Phase 2b – first signs of large placebo response



35% reduction placebo response

37% reduction over placebo

57% reduction from baseline

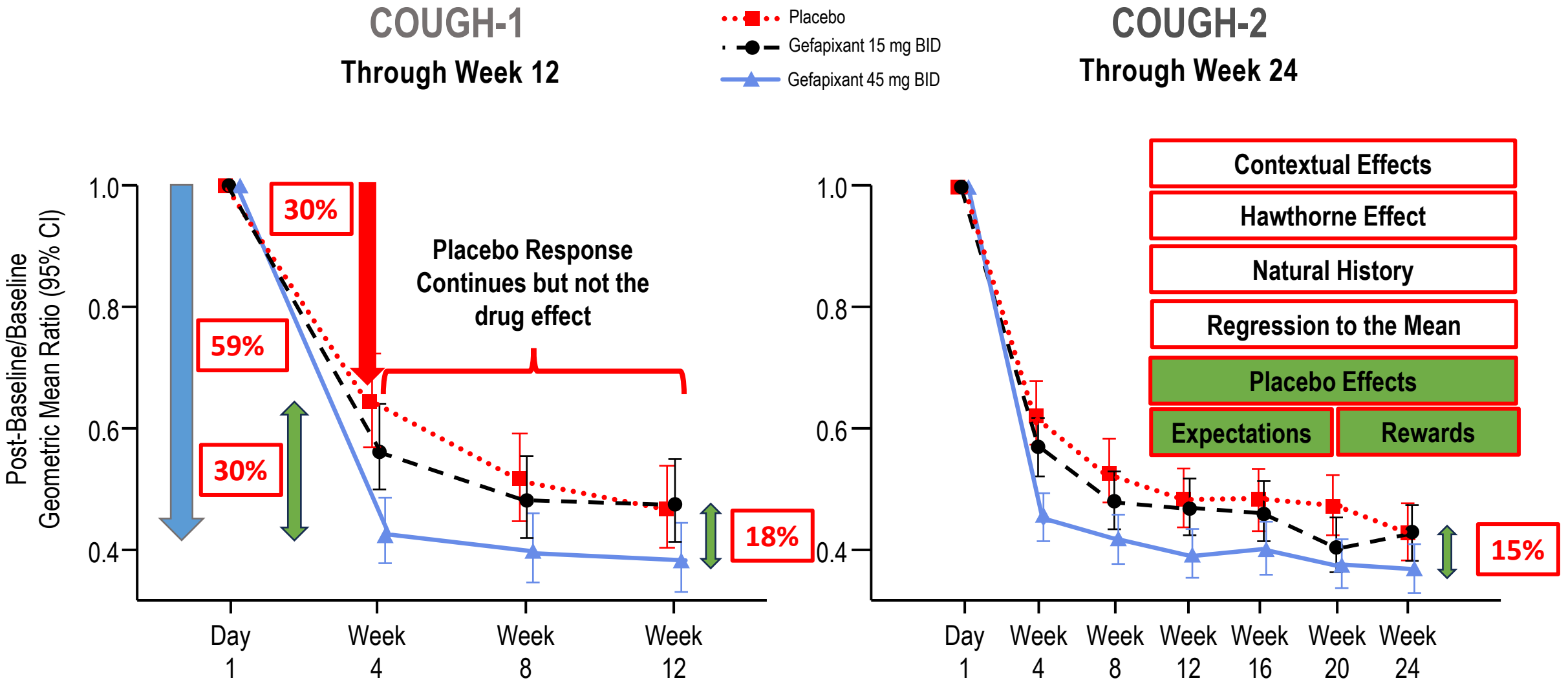
44 sites in the US and UK: Pulmonologist and allergists.

NOTE: Baseline awake cough frequency around 28-30 coughs/hr.

24-hr cough frequency around 20 cough/hr

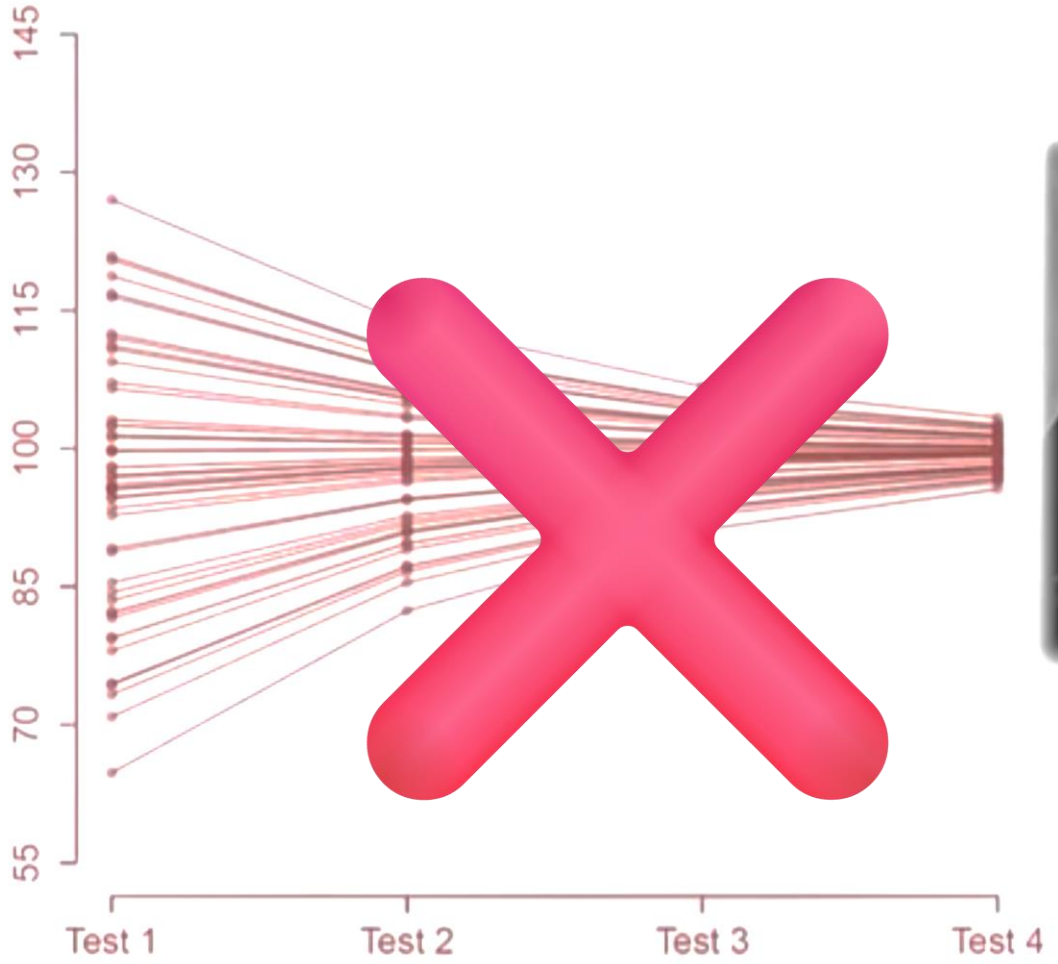
Smith et al Lancet Resp 2020

Gefapixant, Phase 3 Data



McGarvey et al Lancet 2022

What is not Regression to the Mean (RTM)?



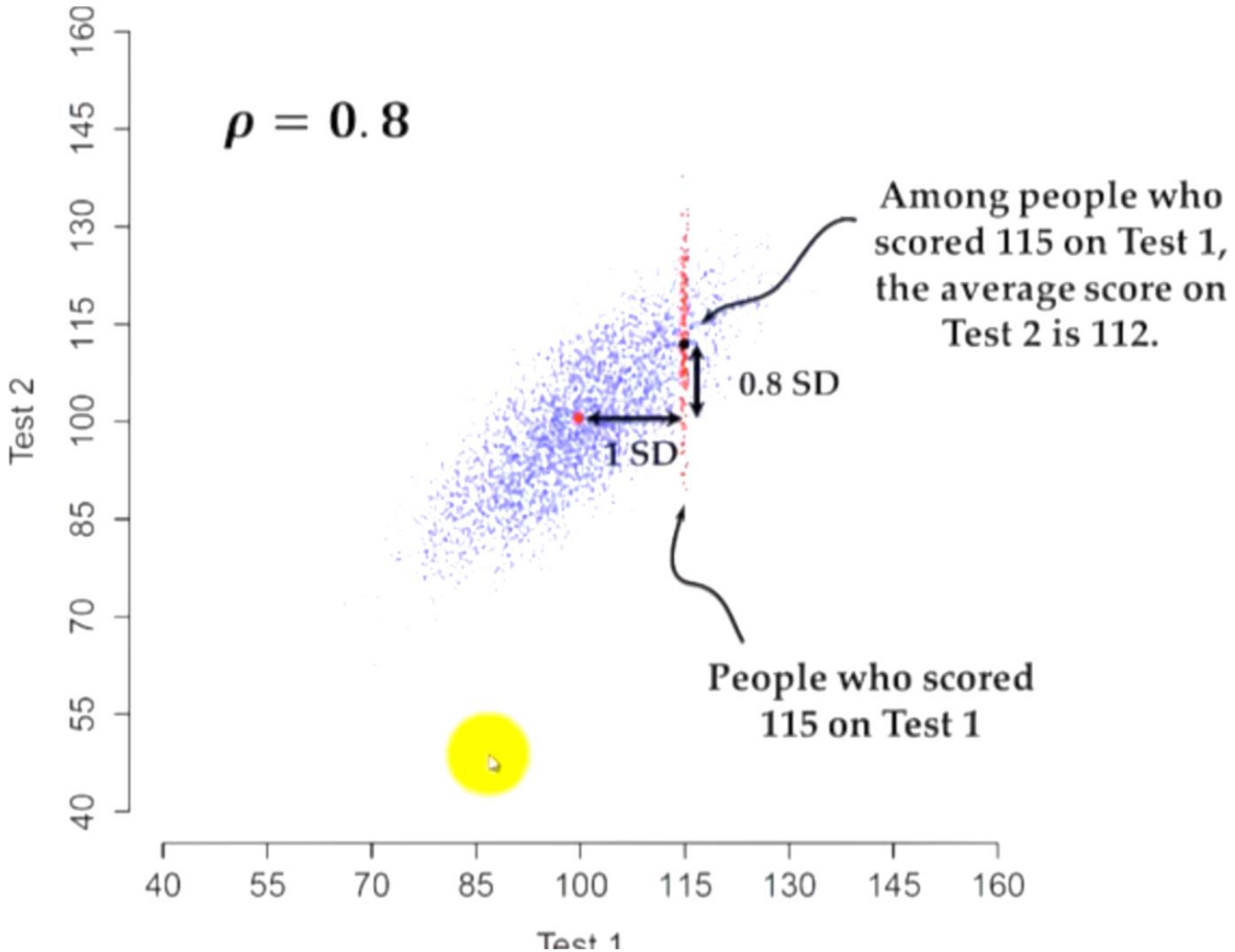
Francis Galton
1822–1911

This would suggest:

1. We are all moving to the GROUP average.
2. Decreased variability over time.
3. RTM is some “Universal Force” making everyone move to the average.

These are NOT true.

RTM occurs when there is an imperfect correlation

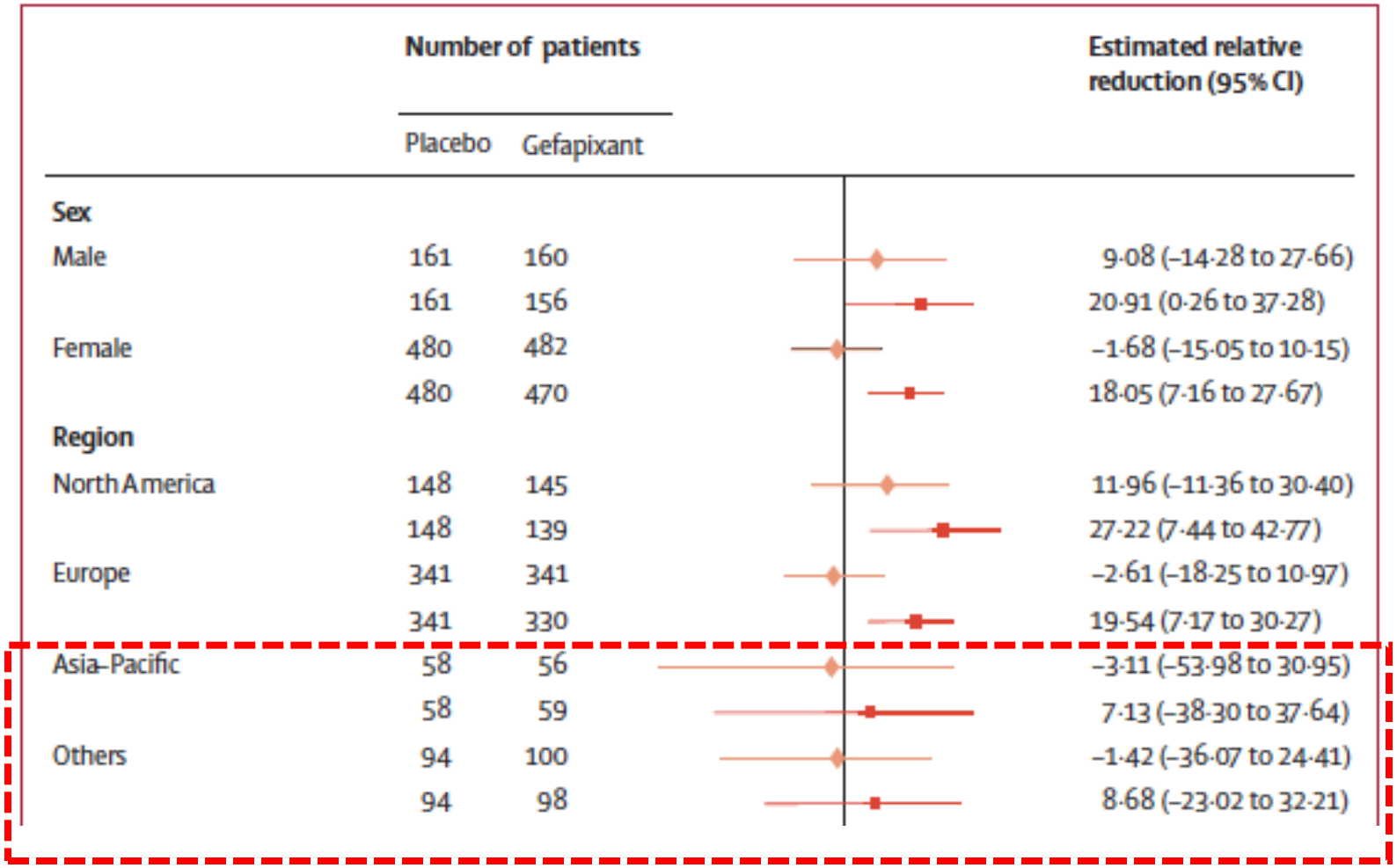


RTM is:

1. Descriptive NOT causal
2. People regress to their INDIVIDUAL mean.
3. Extremes – Low and High will move towards their individual mean.
4. The worse the correlation, the greater the RTM.
5. Does not rule out everyone getting better or worse together, because there may be an intervention.

N.B: football example

Patient/Investigator Selection is important



	Number of patients		Estimated relative reduction (95% CI)
	Placebo	Gefapixant	
Sex			
Male	161	160	9·08 (–14·28 to 27·66)
	161	156	20·91 (0·26 to 37·28)
Female	480	482	–1·68 (–15·05 to 10·15)
	480	470	18·05 (7·16 to 27·67)
Region			
North America	148	145	11·96 (–11·36 to 30·40)
	148	139	27·22 (7·44 to 42·77)
Europe	341	341	–2·61 (–18·25 to 10·97)
	341	330	19·54 (7·17 to 30·27)
Asia–Pacific	58	56	–3·11 (–53·98 to 30·95)
	58	59	7·13 (–38·30 to 37·64)
Others	94	100	–1·42 (–36·07 to 24·41)
	94	98	8·68 (–23·02 to 32·21)

Is this because:

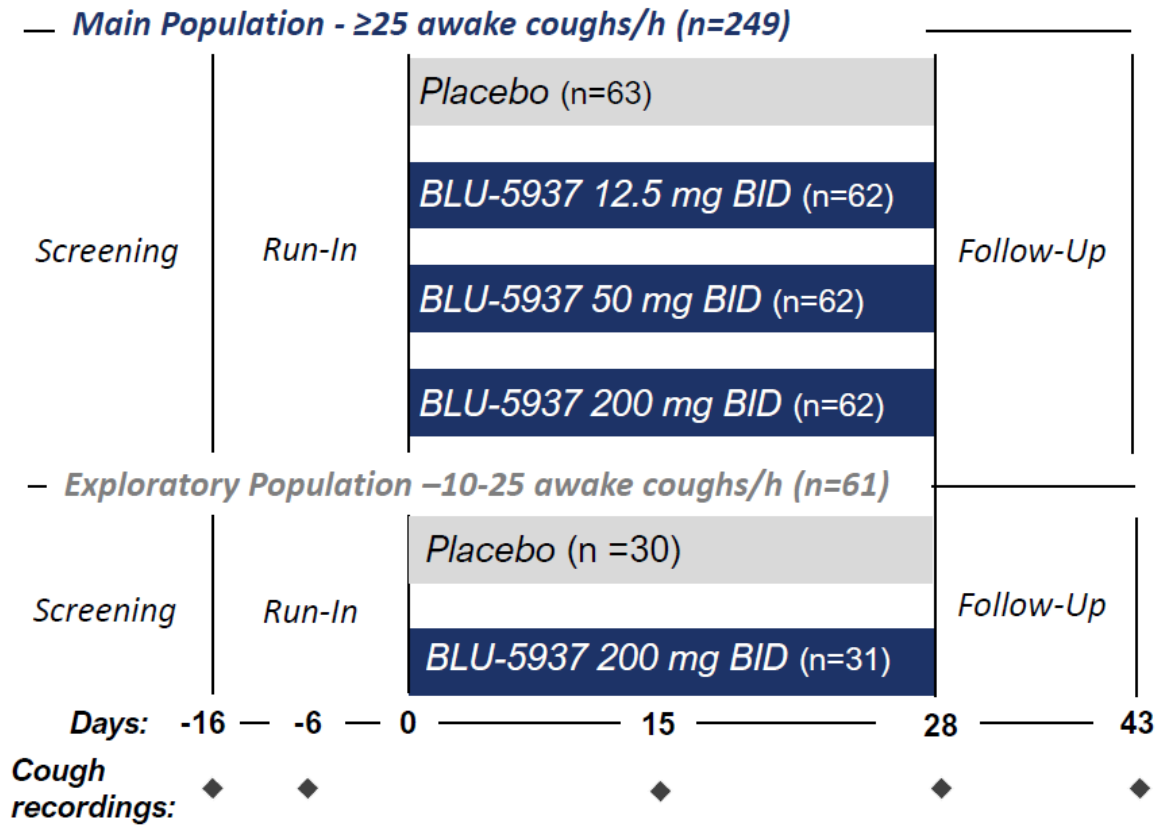
a) Greater placebo response and similar response to gefapixant or

b) Similar 50% placebo response and smaller response to gefapixant.

Newer Study Design

Camlipixant - single blind placebo run-in and high/stable coughs

Randomized, double-blind, 29-day placebo-controlled parallel arm study with 3 active doses in 310 subjects



PRIMARY ENDPOINT

Placebo-adjusted change from baseline in 24H cough frequency (Day 28)

SECONDARY ENDPOINTS

Leicester Cough Questionnaire (LCQ)
Cough Severity Visual Analogue Scale (CS-VAS)

MAIN POPULATION

Refractory chronic cough for ≥1 year

Screening / baseline awake cough frequency: ≥25 coughs/h

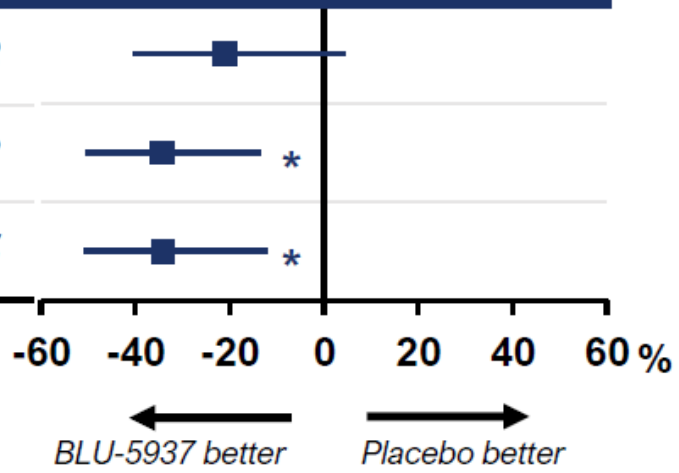
249 participants recruited from
64 North American sites (142 participants)
56 European sites (107 participants)

Single Blind Placebo Run-In can help

Placebo-adjusted 24H cough frequency change from baseline at Day 28

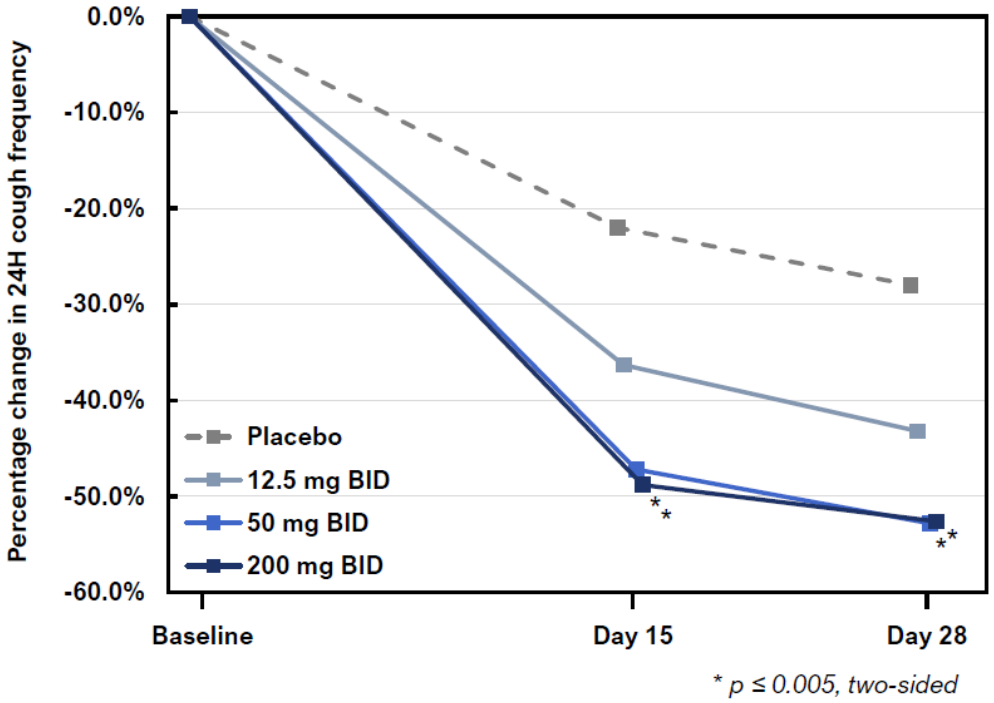
Intent-to-treat analysis; n=249

Dose	Δ	p-value	Mean and 95% CI
12.5 mg	-21.1%	0.098	
50 mg	-34.4%	0.003	*
200 mg	-34.2%	0.005	*



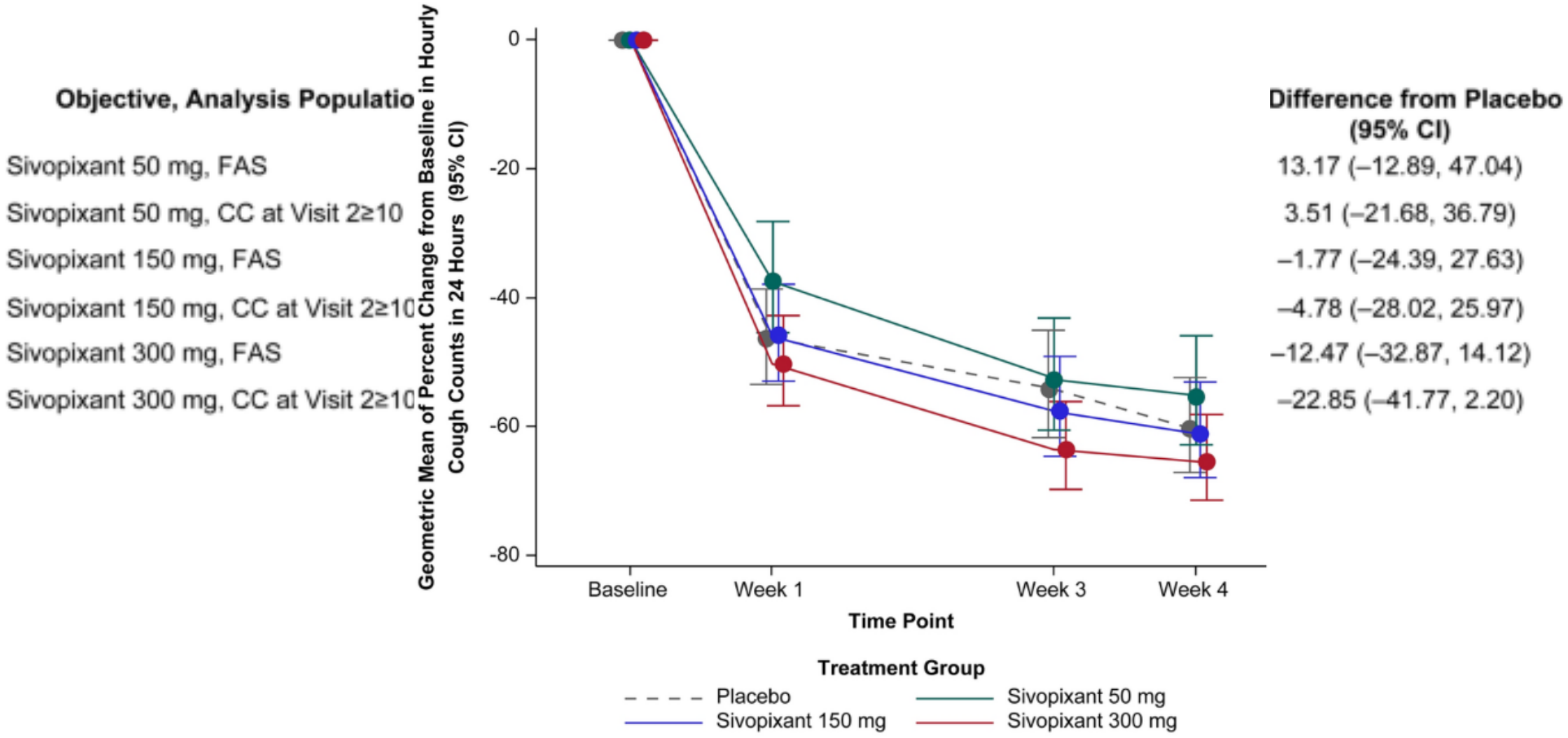
** p ≤ 0.005, two-sided*

Relative change from baseline in 24H cough frequency



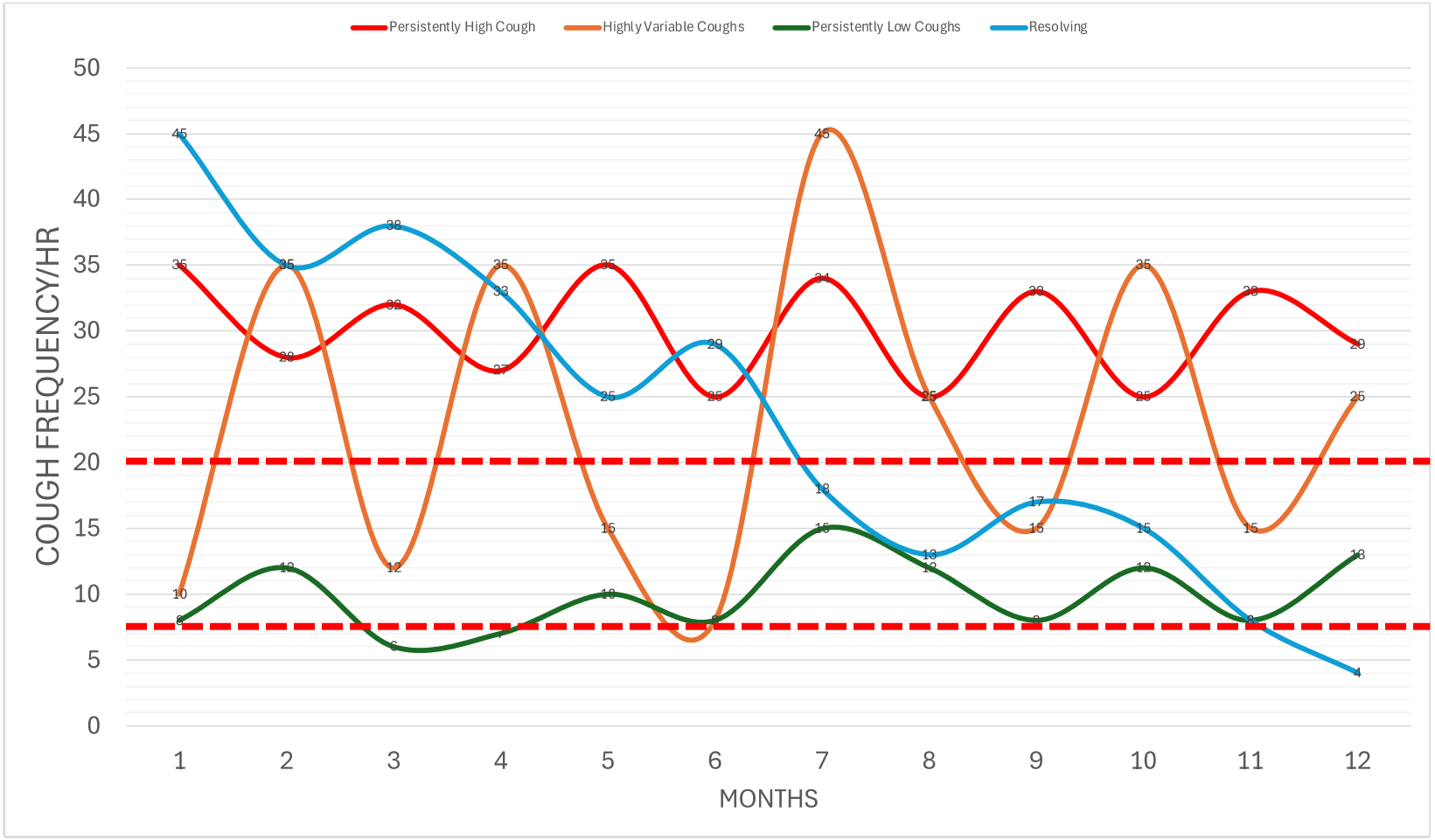
** p ≤ 0.005, two-sided*

Sivopixant Failed, but signal towards benefit in those with coughs>10 at 2 time points



McGarvey et al Lung 2023

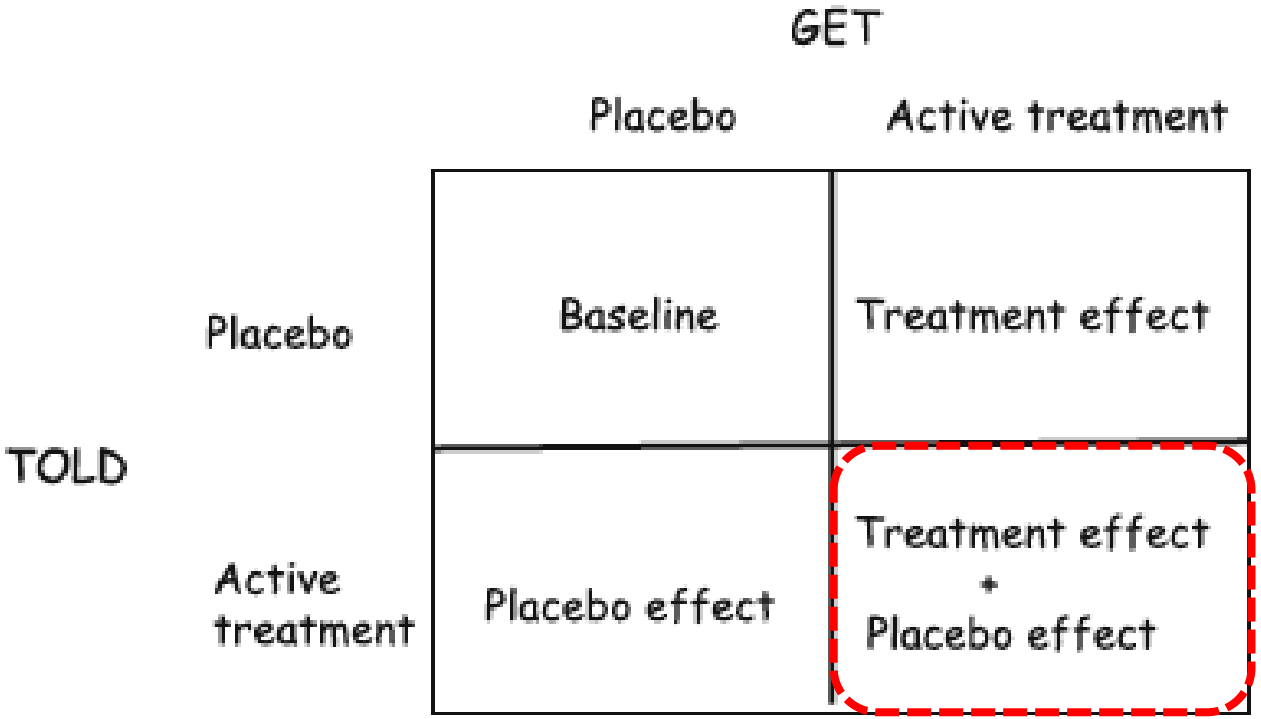
Selecting the right cough patient



CALM-1 and 2 Criteria:
Single Blind Placebo Run In Then…

Cohort	Baseline	Screening
High	**>16**	**>20**
Low	**8-40**	**8-20**
Exploratory	0-16	0-8

Balanced Placebo Design



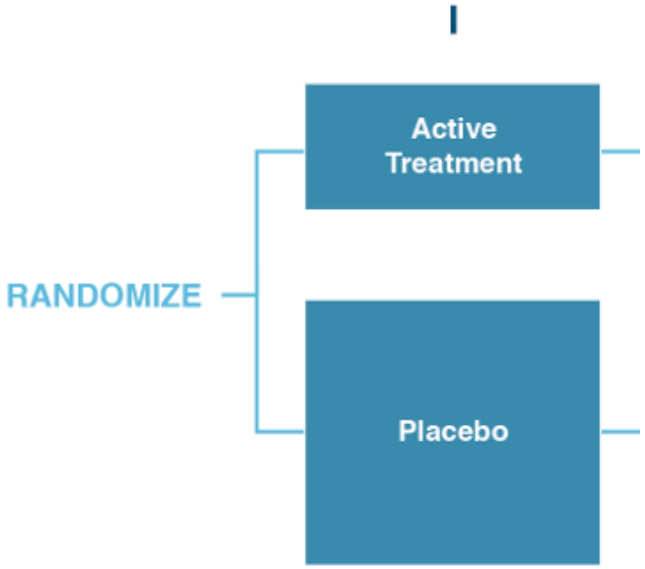
Real life – doctor/patient
Maybe closest to open-label extension

allows investigators to identify the modulations of drug action by verbal suggestion

Note: Involves some deception!

Ross S et al Psychol Rep 10:383–392

Sequential Parallel Comparison Design (SPCD)



Stage 1:
Standard Parallel Group Design (Drug-Placebo Effects are expected to be smaller)

→ Stage 1:
Generate a cohort of placebo non-responders

→ Stage 2:
Drug – Placebo Differences are expected to be greater

How do we apriori define non-responders?
Can lead to very unbalanced treatment/placebo
Complexity of setup, analysis and interpretation
Regulators might not accept

Fava et al 2003

Ethical Conflicts and Dilemma over placebo-controlled studies and deception

The battle of Helsinki

Two troublesome paragraphs in the Declaration of Helsinki are causing a furore over medical research ethics

> Unhappy with revisions made to the DoH between 2000 and 2004, the FDA now refers to the 1989 version of the Declaration, which the WMA itself considers invalid

> Notwithstanding these ethical debates, the discrepancy in guidelines could cause dissonance for researchers…

Aspect	Declaration of Helsinki	ICH/FDA
Use of Placebos When Effective Treatments Exist	Placebo use is limited to cases where no proven intervention exists or withholding treatment does not cause serious harm.	Placebo controls is allowed, even if effective treatments exist.
Scientific Validity vs. Ethical Constraints	**Prioritizes participant welfare over methodological rigor,** favouring active comparators when effective treatments exist.	**Emphasizes scientific rigor and clear efficacy data**, often favouring placebo controls for robust results, especially in subjective conditions.
Post-Trial Access to Treatments	Those receiving placebos, have access to the best proven treatments post-trial.	Post-trial access to treatments is not mandatory.
Ethical Review Requirements	More focus on participant welfare and minimizing harm in placebo-controlled trials.	More leniency on placebo use to ensure methodological robustness.

Wolinsky, EMBO Rep. 2006 Jul;7(7):670–672

Criteria from American Psychological Association 2003

Justification of Deception

- Needs to have significant prospective scientific, educational, or applied value.
- Effective non-deceptive alternative procedures are not feasible.

Harm Avoidance

- Cannot cause physical pain or severe emotional distress.
- Researchers must explain any deception that is an integral feature of the design and conduct of an experiment to participants as early as is feasible, preferably at the conclusion of their participation, but no later than at the conclusion of the data collection.
- Participants should be permitted to withdraw their data if they choose.

Consent

- Provide participants with as much information as possible about the study without compromising the research objectives
- Debriefing session afterwards

Key take home points

1. Placebo responses in RCC are relatively new but large.
2. Complex neuro-psychological reasons for the placebo effects.
3. Multiple reasons for the large placebo response.
4. Selecting patients who do not have a high variability and single blind placebo can be effective at reducing but not eliminating the placebo response.
5. Studying the true placebo effects requires study of a no-treatment control arm or balance placebo design involving some deception.

Thank you to my mentors, collaborators and funding bodies:

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Nermin Diab
Danica Brister
Wafa Hassan

Manchester
Jacky Smith
Huda Badri
Stephen Fowler
Ashley Woodcock
Kim Holt
Rachel Dockry
Shilpi Sen

Funders
European Respiratory Society
NIHR CRF (south and Central)
British Medical Association
Hamilton Academic Health Sciences Office (HAHSO)
Merck
Respiplus
GSK
Bellus Health
Genentech
NSA
Canadian Institutes for Health Research (CIHR)
Vitalograph

www.chronic-cough.ca

Questions?