



Decoding the impact of the placebo response in clinical trials for chronic cough

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The impact of the placebo response in clinical trials for cough medications and potential solutions to address this problem. <https://bit.ly/3R6XSXz>

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Abstract

Chronic cough is a prevalent and challenging condition, with limited treatment options available. The interpretation of clinical trial results for antitussive drugs is complicated by the presence of the placebo response, which can confound outcomes and impede regulatory approval. This review aims to explore the impact of the placebo response on clinical trials for cough medications and elucidate the underlying mechanisms involved. The multifaceted nature of antitussive effects, including pharmacological, psychological/neurobiological and nonspecific effects, is discussed. Additionally, potential solutions to address the placebo response in future cough medication development, such as strategic study design, appropriate choice of end-points and meticulous patient selection, are proposed. More progress to harness this issue is urgently needed.

Introduction

Chronic cough (CC) is a common condition that affects approximately 10% of adults in the general population [1]. It has long been considered a consequence of various diseases and divided into distinct categories, such as upper airway cough syndrome, cough variant asthma, eosinophilic bronchitis and gastro-oesophageal reflux disease-associated cough. However, this classification was made based on previous diagnostic assumptions or targeted therapy orientation, and in 20–46% of CC patients, cough persists despite guideline-based treatment [2]. The synonymous terms “refractory chronic cough” (RCC) and “unexplained chronic cough” (UCC) are currently used to describe these patients [3]. During the last decade, CC has increasingly been realised as a distinct disease given its unique demographic profile with a female predominance in most populations [4]. Cough reflex hypersensitivity has been extensively investigated and seen as the underlying mechanism of CC. It is characterised by vagal hypersensitivity and is now termed “cough hypersensitivity syndrome” [5]. Functional brain imaging has revealed striking similarities between CC and other aversive sensory modalities, such as chronic pain, indicating analogous underlying mechanisms [6, 7]. Realising that CC is a neuronal disorder, numerous studies have been looking at neurons as a target and seeking agents to reduce this vagal hypersensitivity; the transient receptor potential (TRP) channel family is a good example. TRP vanilloid-1 and vanilloid-4 receptors were implicated to be involved in activating afferent nerves inducing cough in preclinical studies; however, the drugs clinically tested against these targets showed no antitussive efficacy [8, 9]. To date, antitussive drugs, whether over the counter or prescribed, are all off label use, such as neuromodulators (e.g. gabapentin [10], baclofen [11], pregabalin [12] and amitriptyline [13]) and low-dose morphine [14]. In a real-world setting, neuromodulators did not improve the capsaicin sensitivity in responsive RCC patients and nearly a third of patients did not respond to neuromodulators [15]. In a randomised placebo-controlled trial, low-dose morphine demonstrated antitussive efficacy in around a third of RCC patients and reduced 24-h cough frequency by 71.8% in responders compared with placebo in another study [16, 17]. However, the utilisation of morphine is subject to restrictions in certain countries [18]. Speech therapy also showed



therapeutic potential in some placebo-controlled clinical trials; however, it could be argued that the healthy lifestyle education in the placebo arm did not represent a true placebo [19, 20]. Thus, the current therapeutic options for CC are limited. Several novel agents that modulate ionotropic P2X₃ receptor [21], neurokinin-1 receptor [22, 23] and γ -aminobutyric acid type B receptor [24] have shown promise in phase II studies. Among the various developments, the P2X₃ antagonist, gefapixant, has shown the most rapid progress, with two pivotal global phase III clinical trials, COUGH-1 and COUGH-2, completed in 2020 [25]. However, this multi-billion-dollar development was recently rejected by the US Food and Drug Administration (FDA) because it was perceived to lack clinically significant efficacy over a large placebo response in the control arm in phase III trials [26]. This review aims to explore the potential mechanisms of this response and provide up-to-date information on how the placebo effect may confound the interpretation of outcomes in clinical trials on cough and the development of new antitussives.

What is a placebo?

The concept of placebos has undergone significant evolution over time, adapting to different contexts and perspectives. The term “placebo” is originally derived from the Latin expression “I shall please”. In 1785, “placebo” first appeared in a medical dictionary, later becoming associated with a “make-believe medicine” or a substance with no therapeutic properties [27]. The perception of placebo treatment among scientists turned negative in the 1950s. In 1962, the FDA mandated that all new drugs must be proven “safe and effective” prior to marketing, leading to the widespread use of placebos as an inert comparator in randomised controlled clinical trials. This method of evaluating new drugs was based on a drug–placebo additivity assumption that the placebo response is believed to be roughly equivalent in the active-drug and placebo arms. Today, most prospective new drugs must surpass the placebo arm in two independent pivotal trials (or one pivotal trial with a high degree of statistical evidence) to win regulatory approval [28]. However, the default additivity model is not always correct [29].

To understand the interaction between placebos and treatment effect, it is important to discuss the conceptual distinction between “placebo effect” and “placebo response” (also called a perceived placebo effect containing the true placebo effect). This was first highlighted by Edzard Ernst in 1995 [30] and has been well described in the recent expert consensus guidelines on placebo terminology [31, 32]. The placebo response refers to all health changes after the administration of an inert treatment, including those factors related to a medical condition such as natural disease recovery and regression towards the mean, while the placebo effect specifically refers to changes attributed to neurobiological or psychological factors. The same concept applies to the nocebo effect, in which brain–body responses to contextual information contribute to negative outcomes even in the absence of the active ingredient. A systematic review reported the evidence of interaction between active drug and placebo, which can at times be synergistic or antagonistic [33, 34]. For example, the total treatment response may be less than the active response plus placebo response, especially in individuals exhibiting a high placebo response, thereby underestimating the actual efficacy of the active drug, although in more cases, individuals with a high placebo response also show a high drug response [35]. Some conditions that are more defined by symptoms rather than objective pathophysiology, and are sensitive to the placebo effect, usually in perceived disorders such as neuropathic pain, negative emotion, irritable bowel syndrome (IBS) and coughing [33]. Subjective outcomes are typically preferred for measuring the severity of these conditions, and a placebo can show a 65–85% response compared to active drugs [36]. This situation has been most often investigated in pain where it shows benefits in a manner reversible by opioid antagonists [37, 38]. The placebo response is a gift for patients but poses challenges for pharmaceutical companies trying to prove the efficacy of pain-relieving drugs, as it has been found to be highly significant in pain studies.

Placebo in shaping the clinical response in cough studies

The powerful placebo response also exists in cough studies and steals the spotlight in recent clinical trials for new antitussive medications. Table 1 provides a summary of the design and key efficacy findings of several drugs with expected genuine pharmacological effects. The placebo alone can achieve a cough reduction of over 60%, and in cases of acute cough, this percentage can reach up to 85% [36]. The most typical example wherein the benefit was greatly covered by the placebo is gefapixant [57]. Gefapixant was approved by Japanese and European regulatory authorities, indicated for adults with RCC or UCC, on the evidence of both subjective and objective responses. However, it was deemed to lack substantial evidence of treatment effectiveness and faced a second FDA rejection recently with a vote of 12:1 because only objective evidence (24-h cough counts) was considered [58].

The Merck gefapixant programme consisted of two 52-week, randomised, double-blind and placebo-controlled pivotal trials, P027 (COUGH-1) and P030 (COUGH-2), in adults diagnosed with RCC/UCC.

TABLE 1 Summary of the design and results of the typical clinical trials (not including transient receptor potential vanilloid (TRPV)1 and TRPV4 antagonists)

Registration no.	Phase	Design	Population	Dosing	Treatment duration	Primary (otherwise secondary) efficacy end-point	Sample size (n; randomisation ratio)	Results over control group at PEP	Placebo group
Gefapixant (MK7264/AF219, P2X3 antagonist)									
NCT04193202 [39]	IIIb	RCT	ROCC	45 mg twice daily <i>versus</i> placebo	12 weeks	Change from baseline in the LCQ total score at week 12	419; 1:1	OR (95% CI): 0.75 (0.06–1.44)*	+31.77%
NCT04193176 [40, 41]	IIIb	RCT	Women with cSUI	45 mg twice daily <i>versus</i> placebo	12 weeks	Percentage change from baseline in average daily cough-induced SUI episodes at week 12	376; 1:1	–11.67%*	–41.09%
NCT03449134 (P027) [25]	III	RCT	RCC/UCC	45 and 15 mg twice daily <i>versus</i> placebo	52 weeks	Model-based GMR of 24-h objective coughs per hour at week 12 from baseline	732; 1:1:1	45 mg: –18.45%*	–54.82%
NCT03449147 (P030) [25]	III	RCT	RCC/UCC	45 and 15 mg twice daily <i>versus</i> placebo	52 weeks	Model-based GMR of 24-h objective coughs per hour at week 24 from baseline	1317; 1:1:1	45 mg: –14.64%*	–58.06%
NCT02612610 [42]	IIb	RCT	RCC	7.5, 20 and 50 mg twice daily <i>versus</i> placebo	12 weeks	Change in ACF at week 12 from baseline	253; 1:1:1:1	50 mg: –37.0%*	–34.06%
NCT02349425 [43]	II	RCT and crossover	RCC	7.5–200 mg twice daily <i>versus</i> placebo	16 days gefapixant plus 16 days placebo	ACF on day 4 of each dose from baseline	59; 1:1	50–200 mg: –41.2% to –57.1%* 7.5–50 mg: –14.7% to –55.9% (15, 30, 50 mg*)	+3.4% to +29.2%
NCT01432730 [21]	II	RCT and crossover	RCC	600 mg twice daily <i>versus</i> placebo	2 weeks	Change from baseline in daytime objective cough frequency	24; 1:1	–75.1%*	–33.4%
Camlipixant (BLU5937, P2X3 antagonist)									
NCT04678206 (SOOTHE) [44, 45]	IIb	RCT	RCC	12.5, 50 and 200 mg twice daily <i>versus</i> placebo	4 weeks	Placebo-adjusted change from baseline in 24 h cough frequency	310; 1:1:1:1	12.5 mg: –21.1% [#] 50 mg: –34.4%* 200 mg: –34.2%*	–28%
Filapixant (BAY1902607, P2X3 antagonist)									
NCT03535168 [46]	I/IIa	RCT and crossover	RCC	20, 80, 150 and 250 mg twice daily <i>versus</i> placebo	Each dose for 4 days with a 3-day washout and then crossover	The 24-h cough frequency on day 4 of each dosing step	23; 1:1	20 mg: +3.0% [#] 8 mg: –17.3%* 150 mg: –27.7%* 250 mg: –37.2%*	–6.3%

Continued

TABLE 1 Continued

Registration no.	Phase	Design	Population	Dosing	Treatment duration	Primary (otherwise secondary) efficacy end-point	Sample size (n; randomisation ratio)	Results over control group at PEP	Placebo group
Sivopixant (S-600918, P2X3 antagonist)									
NCT04110054 [47]	Ib	RCT	RCC	50, 150 and 300 mg once daily <i>versus</i> placebo	4 weeks	Placebo-adjusted percentage change from baseline in 24-h cough frequency per hour at week 4	406; 1:1:1:1	50 mg: +13.17% [#] 150 mg: −1.77% [#] 300 mg: −12.47% [#]	−60.38%
jRCT2080223969 [48]	Ila	RCT and crossover	RCC/UCC	150 mg once daily <i>versus</i> placebo	2 weeks	Placebo-adjusted percentage change from baseline in daytime cough frequency per hour at week 2	31; 1:1	−31.6% [#]	−33%
Morphine [16, 49]									
	IV	RCT and crossover	CC	5 mg twice daily <i>versus</i> placebo	Placebo 4 weeks and morphine 4 weeks	Change in LCQ	27	+14.81%*	+9.76%
	IV	RCT and crossover	RCC	5–10 mg twice daily <i>versus</i> placebo	Morphine 5–7 days and placebo 5–7 days	Baseline-adjusted total 24-h cough frequency at end of the treatment	22	−71.8%*	−5.24%
Lesogaberan (GABA_B receptor agonist)									
EudraCT2014–005074–11 [24]	II	RCT and crossover	RCC	120 mg twice daily <i>versus</i> placebo	Lesogaberan 2 weeks and placebo 2 weeks	Placebo-adjusted 24-h cough frequency during treatment	22; 1:1	−26.1% [#]	+15.9%
Theobromine, (BC1036, PDE inhibitor)									
NCT01656668 [50]	III	RCT	Persistent cough	300 mg twice daily <i>versus</i> placebo	2 weeks	Baseline-adjusted total LCQ score at day 14	289; 1:1	Mean±SD 2.4±3.5 <i>versus</i> 2.2±3.0 [#]	2.2±3.0
AX-8 (TRPM8 agonist)									
NCT04866563 [51, 52]	II	RCT+crossover	RCC/UCC	40 mg twice daily <i>versus</i> placebo	AX-8 2 weeks+ placebo 2 weeks	Change from baseline in objective 8-hour cough frequency on day 1	51	2 h: −44% <i>versus</i> −18%* 4 h: −35% <i>versus</i> −20%* 8 h: p=0.4	−18% to −20%
GRC17536 (TRPA1 antagonist)									
EudraCT2013-002728-17 [53]	Ila	RCT	RCC	10 mg twice daily <i>versus</i> placebo	4 weeks	Placebo-adjusted change in log 24 h cough frequency from baseline at day 28	52; 1:1	Mean±SD −0.2±0.397 <i>versus</i> −0.21±0.479 [#]	−0.21±0.479

Continued

TABLE 1 Continued

Registration no.	Phase	Design	Population	Dosing	Treatment duration	Primary (otherwise secondary) efficacy end-point	Sample size (n; randomisation ratio)	Results over control group at PEP	Placebo group
ADX-629 (anti-RASP)									
NCT05392192 [54]	II	RCT and crossover	RCC/UCC	300 mg twice daily <i>versus</i> placebo	ADX-629 2 weeks and placebo 2 weeks	Change from baseline in ACF after 2-week treatment period	51; 1:1	p=0.01	NR
Bradanicline ($\alpha 7$ receptor agonist)									
NCT03622216 [55]	II	RCT and crossover	RCC	50, 75, 150 mg <i>versus</i> placebo	Bradanicline 21 days and placebo 21 days	Awake coughs per hour at days 7, 14, 21, 43, 50 and 57	46; 1:1	p>0.05	NR
Serlopitant (MTI-110, NK1 antagonist)									
NCT03282591 [56]	II	RCT	RCC	5 mg once daily <i>versus</i> placebo	12 weeks	Placebo-adjusted change in 24-h objective cough frequency (log normalised percentage change)	185	+31%	54% experienced a $\geq 30\%$ cough reduction
Orvepitant (NK1 antagonist)									
NCT02993822 (VOLCANO-2) [23]	IIb	RCT	RCC/UCC	10, 20 and 30 mg once daily <i>versus</i> placebo	12 weeks	Change from baseline to week 12 in ACF	315	p>0.05	NR
2014-003947-36 (VOLCANO-1) [22]	II	Open label	RCC	30 mg once daily	4 weeks	Change from baseline in daytime cough frequency at week 4	13	−26%*	NA
ACF: awake cough frequency; CC: chronic cough; cSUI: cough-induced stress urinary incontinence; GABA _B : γ -aminobutyric acid type B; GMR: geometric mean ratio; LCQ: Leicester Cough Questionnaire; NA: not applicable; NK1: neurokinin 1; NR: not reported; PDE: phosphodiesterase; PEP: primary end-point; RASP: reactive aldehyde species; RCC: refractory CC; RCT: randomised controlled trial; ROCC: recent-onset CC for ≤ 12 months and a diagnosis of RCC/UCC; TRPA1: TRP cation channel subfamily A member 1; TRPM8: TRP melastatin subtype 8; UCC: unexplained CC. *: p<0.05; #: p \geq 0.05.									

Both trials compared gefapixant 45 mg twice daily and 15 mg twice daily to placebo twice daily. The mean change from baseline in the natural log-transformed cough frequency at weeks 12 in P027 and 24 in P030, respectively, was analysed as the primary end-point, compared with placebo. Cough frequency was measured using the VitaloJAK cough counting system, which calculated the number of cough events over a 24-h period divided by the total duration of recording (minimum 20 h). The prespecified primary analysis used mixed model repeated measures, a longitudinal analysis of covariance. Merck only sought approval for the 45-mg dosage, as the 15-mg cohort did not demonstrate a statistically significant reduction in cough frequency compared with placebo [59].

In both well-controlled pivotal trials of gefapixant, although the results regarding primary end-point compared with baseline were clinically significant, large placebo responses were observed and resulted in a small treatment difference relative to placebo cohort (P027: -17.0% , $p=0.057$; P030: -14.6% , $p=0.03$). The *post hoc* analyses of the absolute cough frequency showed that the median changes in 24-h cough frequency from baseline in gefapixant 45-mg cohorts *versus* placebo were -10.52 *versus* -8.87 at weeks 12 in P027 and -9.83 *versus* -8.71 at weeks 24 in P030, respectively. The results of awake cough frequency were similar to the primary end-point. This was deemed to be a small treatment effect by the FDA. Notably, a significant proportion of gefapixant responders were found to overlap with placebo responders, and the decreased cough frequency and improved quality of life from gefapixant was closely paralleled with the placebo response [39, 60]. The percentage of subjects with a $\geq 30\%$ reduction in cough frequency was only 5% higher in the gefapixant 45-mg group compared with placebo in P027 (69.9% *versus* 65.9% at week 12; $p=0.42$) and 6% higher in P030 (72.9% *versus* 66.9% at week 24; $p=0.08$) [25]. The results for a $\geq 50\%$ reduction in cough frequency from baseline at the primary end-point were 6% and 5% in P027 and P030, respectively. *Post hoc* anchor-based analyses using Patient Global Impression of Change (PGIC), a subjective patient report outcome (PRO) that was the only PRO measure considered reasonable as an anchor scale in both trials, demonstrated a poor correlation with the primary objective end-points ($r=0.32$ for P027 and 0.30 for P030), as the FDA reported, “patients who reported feeling better per the PGIC were not necessarily those patients who were coughing less” [58]. Other subjective PROs also showed a large placebo response, with the Leicester Cough Questionnaire (LCQ) total score increase of ≥ 1.3 points being the only PRO outcome that achieved statistical significance (OR *versus* placebo: 1.4 ; $p=0.04$). In this context, the FDA questioned whether gefapixant offers a therapeutic effect on the feelings of CC patients rather than a placebo response in the recent complete response letter [61]. After all, the small measured absolute differences of PRO end-points from placebo in the total score and the ambiguous interpretation of clinically meaningful improvements did complicate the results, especially when the incidence of up to 65% taste disturbance may have potentially unblinded the patients.

Merck also conducted another two 12-week phase IIIb trials in adult females with stress urinary incontinence and RCC or UCC (P042) [40] and in adults with recent-onset (<12 months) RCC or UCC (P043) [39]. P042 aimed to evaluate the change in all-cause incontinence episodes using an incontinence diary as the primary end-point, alongside an exploratory end-point of change in cough PRO, and did not measure cough frequency [41]. P043 used change from baseline in the LCQ total score at week 12 as the primary end-point without capturing the objective cough frequency, and again, showed a large placebo response with a 0.75 estimated treatment difference from the placebo ($p=0.034$) [39]. Although the percentage of participants with an increase in LCQ total score from baseline ≥ 1.3 points in the gefapixant 45-mg cohort overcame the placebo (80.6% *versus* 67.4% , odds ratio: 2.01), the FDA raised concerns about the responder threshold of PRO outcomes. Thus, in the opinion of the FDA, neither of the trials was fit for purpose to inform regulatory decisions.

Smaller placebo responses were observed in phase II gefapixant trials varying from 3.4% to 34.1% . This pattern mirrored across other antitussive drug programmes. Most compounds under development, as summarised in table 1, were at the phase II stage and showed placebo responses ranging from 5.2% to 33% . Only a phase IIb trial of sivopixant recorded a large placebo response of 60.4% , which may be explained by poor patient selection, expectation bias and relative inexperience of the investigators [47].

Components of antitussive effects

To mitigate the potential confounding of clinical trial results of the placebo response, a comprehensive understanding of the mechanisms underlying the efficacy of cough medication is essential. In addition to the pharmacological effect, the antitussive effects also consist of true placebo and nonspecific effects (figure 1) [62, 65]. These concepts were first introduced to cough research by ECCLES [36, 63, 66].

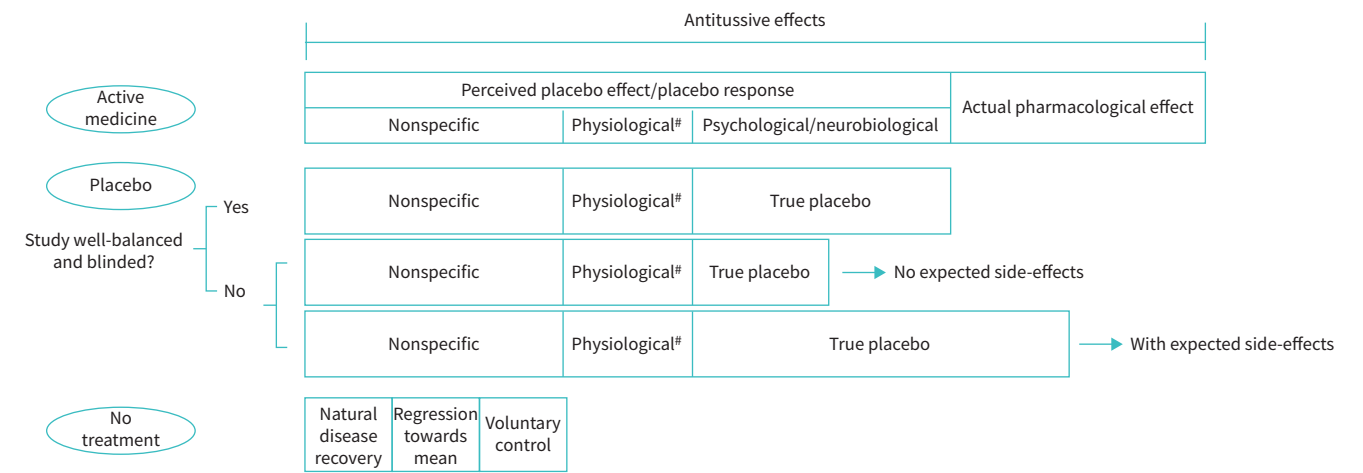


FIGURE 1 Common components of antitussive effects. [#]: Only applies to interventions with perceived physical and chemical properties (colour, taste, smell, viscosity, acidity, temperature, texture, etc.) that may initiate the physiological effect. Reproduced and modified from [63–66] with permission.

The pharmacological effect

The pharmacological effect relates to the active ingredient of the cough medicine that directly acts on the central or peripheral cough pathway to reverse the heightened cough sensitivity. For example, the pharmacological antitussive roles of morphine and codeine occur through their interactions with mu opioid receptors [67]. Another opiate, nalbuphine, a selective kappa opioid agonist and mu opioid antagonist, also reported a >50% placebo-adjusted efficacy in 24-h cough counts in idiopathic pulmonary fibrosis, demonstrating an alternative receptor-specific antitussive activity [68, 69]. Similarly, gefapixant (brand name LYFNUA) passed the regulatory requirements in Europe and Japan, proving its ability against the ATP-gated ion channels, P2X3 receptors, as peripheral extracellular ATP is now well recognised as the key damage signal (alarmin) to activate C fibres and initiate cough hypersensitivity [70–74].

Studies that focus on inhibiting coughs aim to investigate the pharmacological effect (pharmacokinetic and pharmacodynamic properties) of the developing antitussive medication. The therapeutic effect is usually determined by subtracting the measured benefits from the placebo according to the current guidance [75]. However, the antitussive mechanisms of several neuromodulators currently used in some clinical sites, like amitriptyline and gabapentin, have not been specifically identified, with the exception of their well-known sedative effects [76, 77].

Psychological/neurobiological effects (true placebo effect)

The placebo effects measured in clinical trials usually include the true placebo effect and any other physiological effects. The true placebo effect comes from the belief that the result can be influenced by multiple factors, such as treatment properties (taste, smell, colour, etc.), the Hawthorne effect (i.e. individuals modifying behaviour when aware of being observed), expectations [78], social learning and human connections (i.e. doctor–patient interactions) [79–81]. The psychosocial context around the therapy, such as the patient’s belief in the expertise of the doctor and whether the patient is treatment-naïve or experienced, also provides valuable environmental information that may impact the strength of the placebo effect. This largely explains the huge placebo response in phase III trials, where patients who were considered refractory felt that their coughs were being taken seriously by being offered more opportunities to discuss their conditions and believed that the investigational drug would work wonders [82].

These psychosocial factors can cause the generation of endogenous opioids (endorphin), endocannabinoids, and serotonins, as well as the activation of dopamine receptors in the affective and cognitive brain regions [83–85]. Increased activities were found to be located at the prefrontal cortex (PFC), particularly the right dorsolateral PFC [86]. The belief may also activate the right inferior frontal gyrus and anterior insula, both of which have descending inhibitory pathways to the cough-control area in the brainstem [65, 86, 87]. This is why many over the counter drugs are manufactured with sapid and sensory excipients. In addition to the potential physiological benefits, such as encouraging saliva production, swallowing and direct pharmacological activity through menthol (TRPM8) and capsaicin (TRPV1), the sensory information can also enhance the placebo effect via reward mechanism [66, 88].

Certain genetic variations have the potential to influence the placebo effects. For example, catechol-O-methyltransferase (COMT) is a key regulator of dopamine turnover in the PFC. It metabolises endogenous catechol-containing neurotransmitters and hormones and has been reported to affect the magnitude of the placebo effect [89, 90]. The genetic variation at *COMT* rs4860 locus has been shown to result in a substantial reduction (three-to-four fold) in enzymatic activity. The polymorphism of *COMT* val158met (G to A transition leading to amino-acid substitution at codon 158 in the transmembrane form of the enzyme) has emerged as a potential biomarker of the placebo effect in patients with IBS), one of the conditions most commonly associated with CC [91, 92].

Thus, the placebo effect is a family of overlapping psychological phenomena and ultimately triggers the activity of neurotransmitters in the brain, in a similar way to the real pharmacological intervention [93, 94].

Nonspecific effects

Nonspecific effects often refer to regression towards the mean and natural disease recovery. In addition, cough has a special nature that it is under voluntary control. Whether the voluntary control of cough belongs to the placebo effect is still debatable.

Regression towards the mean and natural disease recovery

To have more chance of succeeding, clinical trials usually are designed to include patients with extreme conditions and those with mild cough are excluded. The signal-to-noise ratio makes it apparently easier to prove efficacy in highly symptomatic patients. However, since “sick people always get better” [30], it also increases regression towards the mean so cough severity is very likely to decrease during the trials. This statistical effect was first discovered by Francis Galton and is a powerful potential source of bias when interpreting clinical trial results [95].

For clinical trials without a placebo control, it is hard to extract the bias due to regression towards the mean or natural disease recovery. In a study directly comparing placebo (vitamin E) with no treatment, the placebo caused a 50% reduction in cough frequency while the no-treatment group saw a 7% cough reduction [96]. This 43% difference can only be explained by the true placebo effect since the cough numbers were recorded over a short time (15 min) in this study, which was not long enough for the tasteless vitamin E to be absorbed and exert any physiological effect. Due to the claimed ethical considerations, the no-treatment design is very rare in CC studies, so a placebo control is very important for removing nonspecific effects.

Voluntary control

In clinical trials where any sort of cough frequency is used as an end-point, the voluntary control of coughing can compound the results. The belief in the efficacy of the investigational medical products or placebo can potentially enhance the placebo response and make patients cough less. However, voluntary cough control can also be achieved without intervention. It is not possible to differentiate between conscious voluntary cough control and unconscious suppression on a placebo.

Solutions for addressing the placebo response in future cough medication development

Study design

Placebo run-in/lead-in

One strategy to minimise the placebo response is to use a placebo run-in or lead-in design and exclude placebo responders. This is debatable. Several meta-analyses that focused on psychoactive clinical trials found that the withdrawal of placebo responders did not make a statistically significant difference in trial sensitivity compared with trials without a placebo run-in phase; however, they did show that placebo withdrawal produced larger absolute effect sizes [97, 98]. It must be noted that early exclusion of the placebo responders may increase ethical concerns and decrease the external validity.

Crossover design

The lower placebo response observed in several trials may be attributed to the crossover design. As shown in table 1, the majority of studies in which patients were significantly in favour of the investigational medical product over placebo, such as the filipixant (a P2X3 antagonist) phase I/IIa study, two investigator-initiated morphine studies and AX-8 (a TRPM8 antagonist) phase II studies, had a crossover design, although the shorter durations of these studies may also be a contributor. Crossover design mitigates the between-subject variability and is particularly valuable for evaluating active treatments that only offer marginal improvements over placebo response [99]. However, when evaluating active treatments with carryover effects such as discernible efficacy or side-effects (e.g. gefapixant), crossover increases the risk of unblinding and may lead to an overestimation of the efficacy of the active treatment [100].

Adaptive design

Sequential parallel comparison design (SPCD) and two-way enriched design (TED), an extension of SPCD, can be considered where placebo effect may confound evaluation [101–103]. The basic idea of these designs is to include two stages of identical duration and consider the outcome as binary data.

The SPCD was initially proposed by FAVA *et al.* [101] in 2003. Participants are usually unequally randomised into the following three groups, with more patients receiving the placebo: 1) receiving active treatment in stage 1 then switching to placebo in stage 2 (AP); 2) receiving placebo in stage 1 followed by active treatment in stage 2 (PA); and 3) receiving placebo in both stages (PP). In stage 2, all placebo/active treatment responders from stage 1 either discontinue the study or enter an open label active treatment, while non-responders remain in their initially assigned groups in a double-blind manner. Since patients in stage 2 have previously failed to respond to the placebo, their placebo responses will be reduced. The primary efficacy analysis involves pooling data from both stages, including all stage 1 data and stage 2 data based on the non-responders from stage 1. The original SPCD pre-determines randomisation at stage 1. However, if the numbers of placebo responders and/or dropouts differ between PP and PA groups in stage 1, the participants taking placebo in stage 1 may be unbalanced when they enter stage 2. This imbalance may lead to insufficient power to detect a treatment difference in stage 2, particularly when only a few patients enter stage 2 [104]. To address this issue, re-randomisation of placebo non-responders before starting stage 2 was suggested by CHEN *et al.* [104]. Several other modifications have also been recommended, such as blinding responders throughout the trial and allowing active treatment non-responders to continue taking active treatment rather than switching to placebo in stage 2 to collect more safety and efficacy data (figure 2) [105].

Unlike SPCD, TED involves two subsets entering the second stage. Non-responders to placebo and responders to the active treatment are randomly allocated to receive either the active treatment or placebo. Primary efficacy analysis also involves weighted pooling data from the two stages but includes three subgroups: 1) all stage 1 data; 2) stage 2 data collected based on the active treatment responders in stage 1; and 3) stage 2 data collected based on the placebo non-responders in stage 1. Similar to SPCD, the placebo responders from stage 1 and the active treatment non-responders from stage 1 still receive treatment, regardless of whether they are unblinded, in stage 2, although these data are not included in the final analysis (figure 3a) [103, 106].

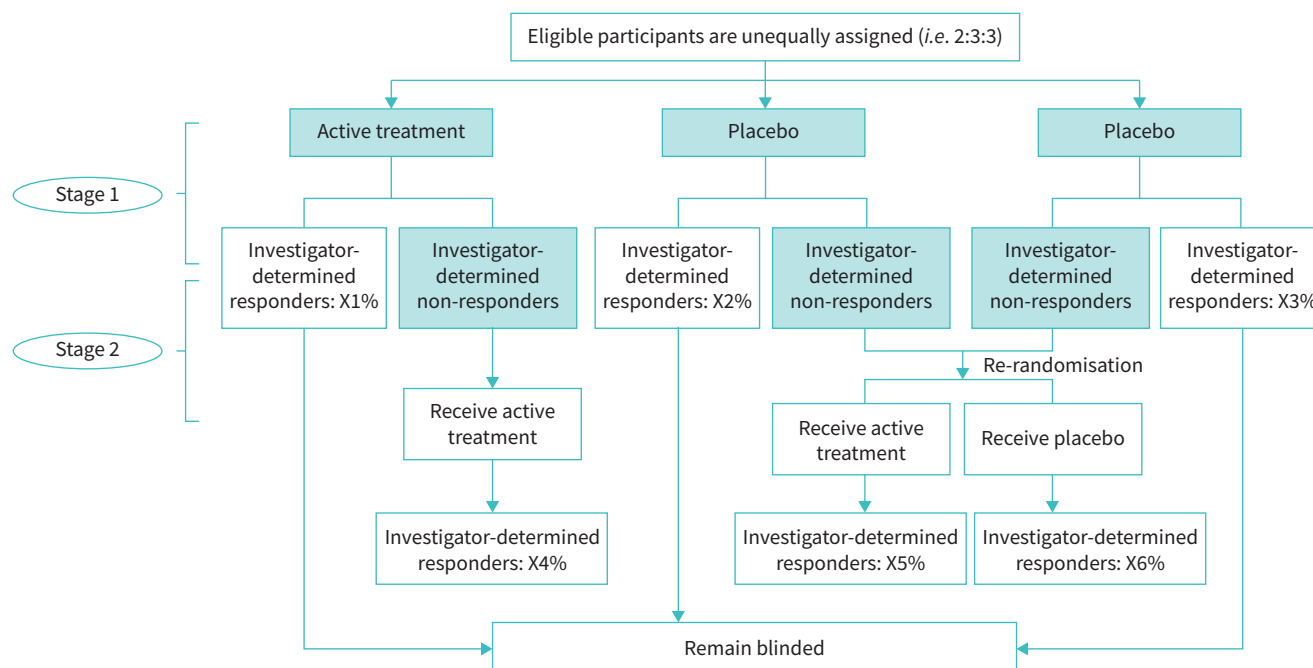


FIGURE 2 The sequential parallel comparison design. Primary efficacy analysis will be conducted in the green-highlighted population. The response rate of active treatment is pooled weighted data from X1%, X4% and X5%. The response rate of placebo is pooled data from X2%, X3% and X6%.

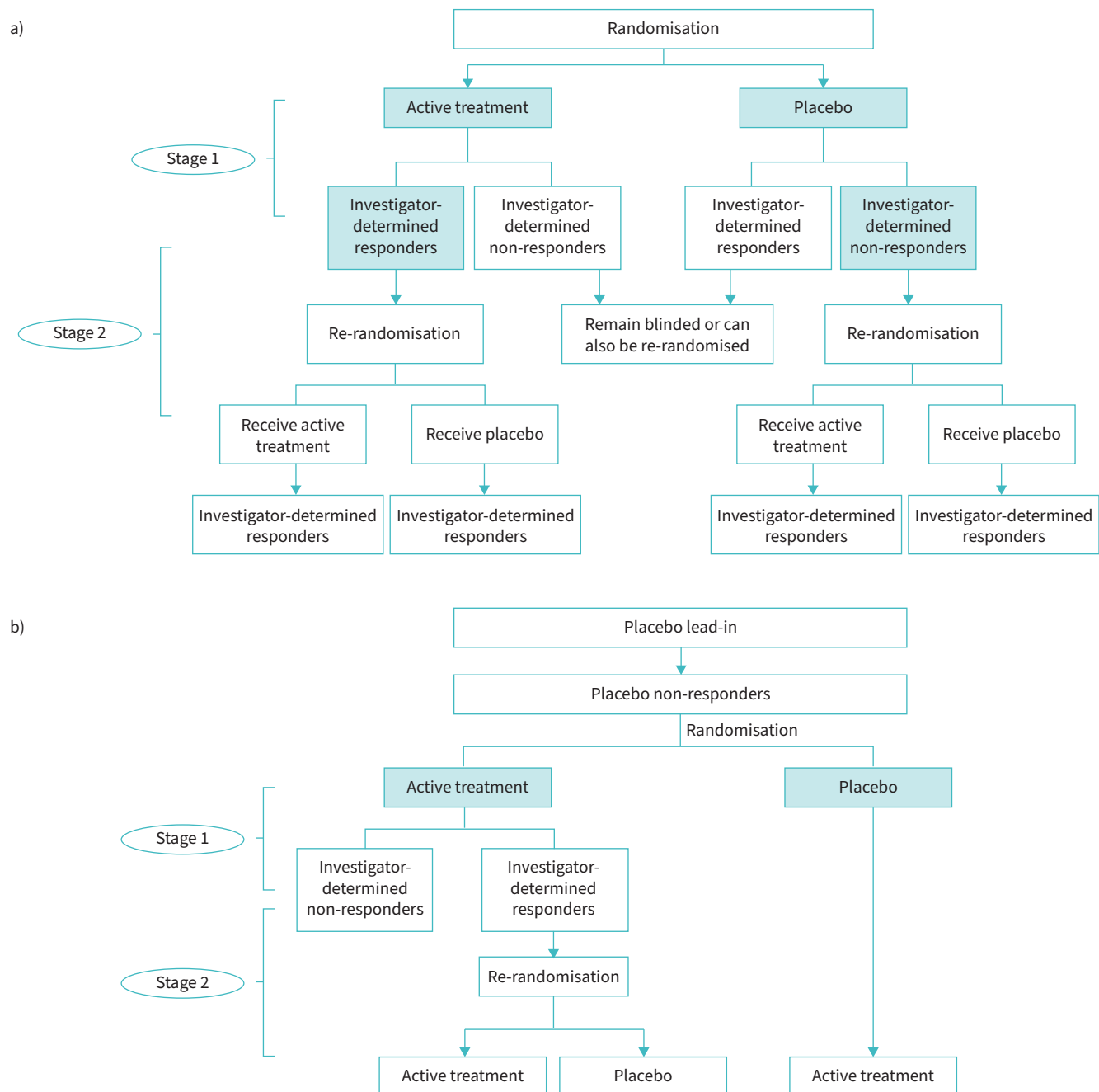


FIGURE 3 a) The two-way enriched design. b) The sequential enriched design. Primary efficacy analysis will be conducted in the green-highlighted population.

Another modified design called sequential enriched design (SED) was introduced to address the issue of high placebo response in clinical trials [107]. This design aims to sequentially identify the placebo non-responders and active treatment responders. It starts with a double-blinded placebo lead-in phase, after which placebo responders are excluded. Placebo non-responders are then randomised to take either placebo or active treatment (stage 1). Active treatment responders are then re-randomised to receive placebo or active treatment (stage 2) (figure 3b). This enrichment design is effective in excluding individuals who respond to placebo or do not respond to any treatment, thus potentially providing a less biased estimate of target treatment effect with only a slight reduction in statistical power over TED.

These designs have been widely used in major depressive disorders since they combine the strengths of placebo run-in and crossover, and are likely to reduce the placebo response and sample size [108, 109].

A common challenge of these designs is how to treat the placebo responders. In most trials, placebo responders are allowed to continue in the study. However, in the case of an SED trial, there remains an ethical concern about having patients take placebo over an extended period. Currently, there is no consensus on how to handle this issue, as it may be appropriate for placebo responders to either discontinue the trial or switch to rescue therapy. The decision should be made based on specific factors, such as the trial duration, disease severity and response definition.

Adaptive designs in clinical trials may also introduce an increased risk of type I errors due to the repeated hypothesis testing. To control the overall type I error rate below a predetermined level (*e.g.* $\alpha=0.05$), adjustments to the nominal significance level are necessary [110, 111]. It is also important to maintain blinding during interim analysis where necessary to avoid the introduction of new biases. Before the trial commences, a clear statistical analysis plan should be established, as well as the criteria for early termination. An independent third party should perform statistical analysis on the interim data and provide a review to inform recommendations for decision-making regarding progression to the next stage of the trial.

Stratified randomisation

Factors that may impact on the magnitude of placebo response can be evenly distributed across the treatment arms using stratified randomisation (*e.g.* baseline cough counts).

End-points

Correct cough counter and longitude cough monitoring

A particular problem in CC is that, unlike other symptomatic diseases, objective cough counters have been developed. First-generation monitors (*e.g.* VitaloJAK [112] and the Leicester Cough Monitor [113]) have been widely used in clinical trials and whilst they accurately record, they can only record cough counts for 24 h. These bulky, visible devices will inevitably be subject to the Hawthorne effect and in most studies using these monitors the objective end-points, such as 24-h/daytime/awake cough frequency (or per hour), were found to be poorly correlated with PROs [114].

The day-to-day variability of cough can only be captured by a longitudinal cough counter [115–117]. 24-h snapshots are inherently inaccurate and are not reliably representative of patient experience. Even in individuals with problematic cough at baseline, their cough rates are not consistent with a daily change of up to 39% (unpublished data). Also, coughing does not occur uniformly throughout the day (figure 4) but in bouts, so average cough counts over 24 h are insufficiently granular to reflect the pattern of coughing experienced by the patient [117]. There are several cough monitors that can realise a longitudinal recording, such as the Hyfe Cough Tracker [118].

A shortcoming of some monitors is that they are smartphone application-based, meaning any extraneous cough within the 1.5 m operational range of the phone is very likely to be mistakenly captured as well. Therefore, an unobtrusive wearable cough recorder that can continuously monitor longitude cough is warranted for new cough medicine development, especially during phase III studies with a longer study duration where a more powerful placebo response has been observed (table 1).

More research should be conducted to establish a threshold for meaningful within-patient change in this end-point. Granular analysis of longitudinal cough data will be valuable to provide a visual representation of cough evolution and helps improve understanding about cough patterns. Continuous real time cough monitoring as provided by the SIVA [119] and other devices may increase the accuracy of objective assessment in the future.

Cough severity PROs within the FDA's guidance

In the recent guidance on the development of non-opioid analgesics for acute pain, the FDA considered the numeric rating scale (NRS) (*i.e.* 0–10-point scale, anchored at both ends) as the optimal PRO to measure pain intensity, citing concerns over difficulty in the comprehension of a visual analogue scale (VAS) [120]. The superiority of the NRS over the VAS has been widely reviewed in other clinical situations, establishing it as the gold standard for measuring pain intensity [121]. In cough studies, the continuous scale of the cough-severity VAS could amplify the effect of regression to the mean, especially in patients experiencing large score changes before and after treatment. At the end of phase II of gefapixant, the FDA also recommended the use of a NRS or a simple verbal response rate (*e.g.* a Likert-type scale) as the preferred scale for cough severity measurement to support labelling claims [61]. However, the comparison of NRS and VAS in measuring CC is yet to be investigated. RHATIGAN *et al.* [122] recorded cough severity with a single-item, six-point patient global impression of severity (PGI-S) scale that offered predefined severity categories. They found a strong association between PGI-S and VAS

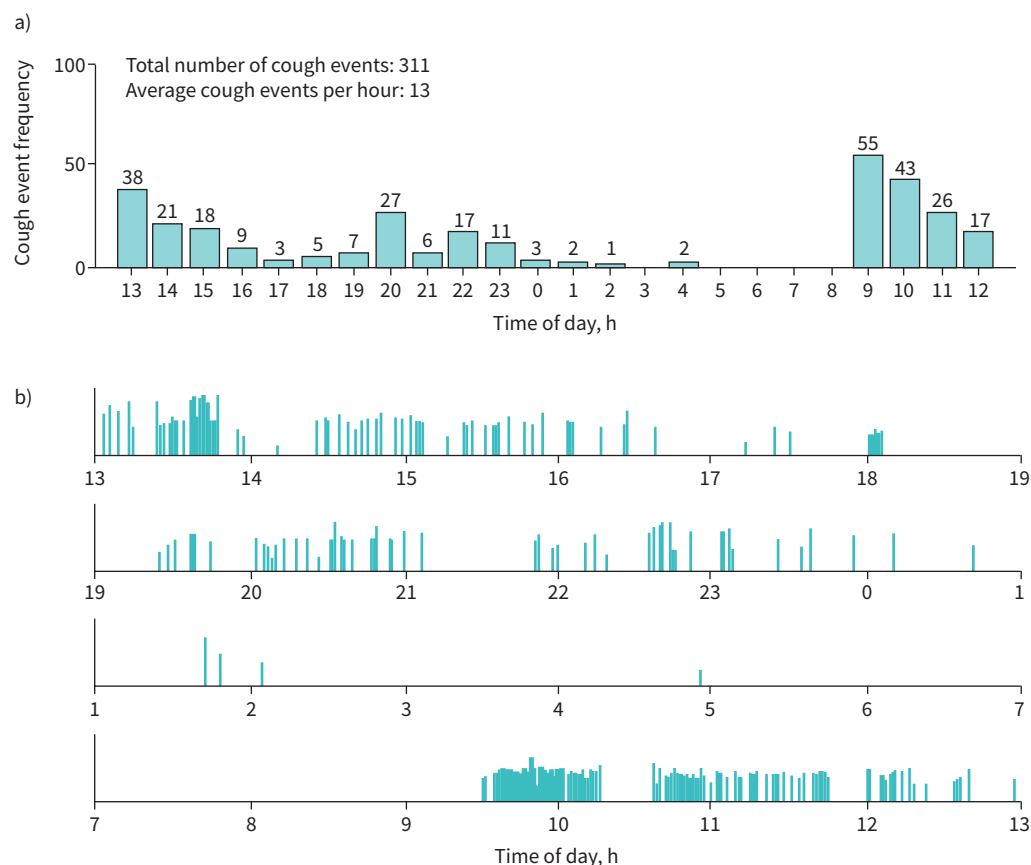


FIGURE 4 The episodic cough pattern over 24 hours [114]. Cough attacks often occur in the mornings, when rising from bed, and at mealtimes, but rarely occur during the night. **a)** Cough frequency per hour; **b)** Time distribution of cough events per minute.

and proposed a VAS threshold of ≥ 61 mm to define severe cough. This study was limited to patients attending a single specialist clinic with the change in VAS below the minimum clinically important change (20 mm). Further validation is needed across a broader patient population.

Co-primary end-points

For diseases with multiple clinically important different features, the FDA recommends the use of co-primary end-points to demonstrate the clinical benefit [123]. As a symptomatic condition, the improvements in both objective cough numbers alone and subjective feelings of patients alone are insufficient, in their opinion, to indicate a clinically meaningful benefit of CC. In IBS studies, placebo response was found to be reduced by using the more stringent FDA co-primary end-points [124, 125]. Although using the co-primary endpoints may cause the expense of lower estimates of response, it might also apply to the cough case and offer more compelling evidence to inform regulatory decision-making. This needs further validation by reanalysing the phase III data in CC trials.

Patient selection

The placebo response in cough medicine development is likely to be linked to the voluntary control over coughing behaviour. A study on acute cough found a negative correlation between baseline cough frequency and the magnitude of the placebo response, suggesting that patients with more severe coughs are less likely to experience placebo benefits [126]. In phase III studies of gefapixant, participants with a baseline of ≥ 20 coughs per h favoured gefapixant, further suggesting a diminished placebo response in those with severe cough [25]. However, it is important to note that such patients may exhibit regression to the mean and that the day-to-day variability in average cough counts may mean that any effect is lost in the noise of this variability in low 24-h cough counts. While certain biomarkers (*e.g.* COMT genotype) could potentially predict the placebo response, their implementation might also escalate costs and increase recruitment burden.

A self-administered questionnaire, the Hull Airway Reflux Questionnaire (HARQ), was used to assess CC at baseline in COUGH-1 and COUGH-2 [25], and 95% of participants were scored above the upper limit of normal range, which is 14 [127]. The HARQ has been recognised as an effective screening tool for identifying patients with a positive diagnosis of RCC, as opposed to diagnoses made by exclusion [128]. Thus, in addition to the proof of previous cough consultations in source documents, the HARQ score might streamline participant selection and reduce diagnostic heterogeneity and misclassification in clinical trials.

Analysis to find confounding factors

A stratified analysis and adjustment for covariates might help to improve the efficiency of the estimate of the treatment effect and find the potential source of the placebo response [129–131]. Another method is to conduct a *post hoc* subgroup analysis stratifying the participants based on responder analysis of placebo responsive outcomes, followed by re-analysis using the methods developed for the primary outcome [132].

Others

As mentioned above, placebo response is highly subject to human interaction and ecological relationships. The expectations and experiences of the participants within a clinical trial should be formally assessed and reported. The investigators should possess adequate knowledge and skills to mitigate the impact of environmental factors (for example, media attention [133]) and induced expectations regarding the new drug and decrease the potential unblinding risks. Moreover, thorough protocol training is crucial to ensure consistency and standardisation of the operational procedures, thus minimising any potential clinical site effects. This is particularly important in phase III multi-regional studies where trialists less experienced in the disease of CC are recruited.

Conclusion

In conclusion, placebo responses have been commonly observed in cough studies and have complicated the interpretation of outcome. This has created dilemmas for antitussive drugs in obtaining regulatory approval. Given the limited regulatory experience with drugs indicated for CC, it is crucial to cautiously reconsider the study design, appropriate end-points and patient selection to obviate the powerful placebo responses in cough trials based on understanding the interaction of antitussive effects and placebo responses. The following improvements are needed in future antitussive drug development: more appropriate adaptive study design, correct measurement of longitude cough frequency, more stringent co-primary end-points, exploration of effective markers for fit-in-purpose patient population with a standard CC diagnosis, *post hoc* analysis of phase III trial data, more consistent reporting of data, and formal assessment and reporting of patients' expectations across clinical trial sites.

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Conflict of interest: A.H. Morice declares that he has received consulting fees from Bayer (2019–2021), Shionogi (2019–2021), Bellus (2019–present), Merck (2019–present), NeRRi (2019–present) and Trevi (2019–present); and lecture fees from Chiesi (2019–2021), Boehringer Ingelheim (2019–2022) and Merck (2019–present); as well as grant support from Bayer (2019–2021), Shionogi (2019–2021), Bellus (2019–present), Merck (2019–present), Nacion (2019–present), Philips (2019–present), NeRRi (2019–present) and Trevi (2019–present). A.H. Morice is also the founder and CEO of Tussogenics Ltd (2019–present) and an associate editor of this journal. M. Zhang has nothing to disclose. B. Zhang declares that he receives grant support from Shanghai Pumonary Hospital (SHDC2023CRS050).

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