The effect of mindfulness meditation on cough reflex sensitivity

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► Instructions for the participants and an additional figure are published online only at http://thorax.bmj.com/content/vol64/issue11

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ABSTRACT

Background: Chronic cough is common, and medical treatment can be ineffective. Mindfulness is a psychological intervention that aims to teach moment-to-moment non-judgemental awareness of thoughts, feelings and sensations.

Method: 30 healthy subjects and 30 patients with chronic cough were studied in two sequential trials. For both studies, cough reflex sensitivity to citric acid (C5) was measured on two occasions, with urge to cough rated following each inhalation; between challenges subjects were randomised to (1) no intervention, (2) mindfulness or (3) no intervention but modified cough challenge (subjects suppress coughing). For the healthy volunteers, measures were 1 h apart and mindfulness was practised for 15 min. For the patients with chronic cough measures were 1 week apart and mindfulness was practised daily for 30 min.

Results: In healthy volunteers, median change (interquartile range (IQR)) in cough reflex sensitivity (logC5) for no intervention, mindfulness and suppression was +1.0 (0.0 to +1.3), +2.0 (+1.0 to +3.0) and +3.0 (+2.8 to +3.0) doubling concentrations ($p = 0.003$); there were significant reductions for both mindfulness ($p = 0.043$) and suppression ($p = 0.002$) over no intervention. In patients with cough, median change (IQR) in logC5 for no intervention, mindfulness training and voluntary suppression was 0.0 (−1.0 to +1.0), +1.0 (−0.3 to +1.0) and +1.0 (+1.0 to +2.0) doubling concentrations ($p = 0.046$); there was a significant reduction for suppression ($p = 0.02$) but not mindfulness ($p = 0.35$). Urge to cough did not change after mindfulness compared with control in either healthy subjects ($p = 0.33$) or those with chronic cough ($p = 0.47$).

Conclusion: Compared with control, mindfulness decreased cough reflex sensitivity in healthy volunteers, but did not alter cough threshold in patients with chronic cough. Both groups were able to suppress cough responses to citric acid inhalation.

Chronic cough, defined as cough lasting >8 weeks, has a prevalence of around 12% in the general population[1] and is associated with significant co-morbidity including anxiety and depression.[2] Despite comprehensive investigation, it is increasingly recognised that a proportion of patients fail to respond to treatment targeted at identified potential causes.[3 4] For these patients both effective antitussive treatments and supportive interventions are lacking despite the acknowledgement that chronic cough is associated with significant physical, psychological and social burdens. The effect of psychological interventions on cough reflex sensitivity and whether such interventions are useful in the management of patients with chronic cough have not been investigated.

An outpatient Mindfulness Based-Stress Reduction (MB-SR) programme, developed by Kabat-Zinn,[5] teaches moment-to-moment non-judgemental awareness of thoughts, feelings and sensations,[6] and has proven effective in the management of several chronic disease states including chronic pain,[7] depression,[8] fibromyalgia[9] and psoriasis.[6] Mindfulness training is classically led by experts and practised in group sessions over an 8- to 10-week period with regular homework activities to encourage integration of the coping strategies into everyday life. A 10-week MB-SR group-based programme directed at patients with fibromyalgia reduced subjective ratings of physical and psychosocial symptoms.[9] Prolonged psychological benefits were demonstrated in a 4-year study of 225 patients with chronic pain who had participated in an intensive 8-week MB-SR programme although the initial reductions in the Pain Rating Index (PRI) returned to pre-intervention levels at 6 months.[7] However, there is some evidence to suggest that mindfulness training can be effective at reducing disease severity. In moderate to severe psoriasis, customised mindfulness tape recordings, played during individual phototherapy treatment, accelerated rates of skin clearing compared with a "no-tape" control group.[6]

Cough can be experimentally induced by chemical stimulation of pulmonary afferent nerve fibres. The concentration of inhaled citric acid or capsaicin eliciting five or more coughs in the first minute after inhalation, known as the C5, is a reproducible measure of cough reflex sensitivity[10] and is known to be moderately correlated with objective cough frequency in respiratory conditions.[11] Cough reflex sensitivity cannot be used to differentiate reliably between health and disease since there is considerable overlap of C5 in healthy subjects and patients with chronic cough, but on average subjects with chronic cough have a lower C5 (more sensitive reflex),[10] which increases following successful treatment of the cough.[12]

Anecdotally, patients with chronic cough often describe a sensation of irritation located in the throat which provokes spontaneous coughing. An 'urge to cough' also occurs during the inhalation of capsaicin and citric acid, increasing in magnitude dose dependently and preceding the motor cough response.[13] However, the cough reflex is under considerable voluntary control. Healthy volunteers are able to resist the urge to cough and voluntarily suppress coughing during capsaicin challenge.[14]

Table 1 Age, gender and baseline C5 compared by randomisation group

	No intervention	Mindfulness training	Voluntary suppression	p Value
Healthy volunteers				
Number	10	10	10	
Mean (SD) age, years	34.4 (11.1)	33.1 (11.1)	34.4 (10.2)	0.921
Gender M:F*	3:7	1:9	2:8	0.001
Median (IQR) baseline logC5	−0.2M (−0.4 to 0.0)	−0.9M (−0.9 to 0.0)	−0.2M (−0.3 to 0.0)	0.062
Subjects with chronic cough				
Number	11	10	9	
Mean (SD) age, years	54.2 (10.8)	60.2 (8.1)	61.11 (8.4)	0.350
Gender M:F*	3:8	3:7	4:5	0.068
Median (IQR) baseline logC5	−0.9M (−1.5 to 0.0)	−0.8M (−1.3 to −0.5)	−0.9M (−0.9 to −0.3)	0.798

Comparisons were made by Kruskall–Wallis test except where marked with an asterisk which were by χ^2 test.
F, female; IQR, interquartile range; M, male.

The urge to cough is an unpleasant sensation that may be associated with negative cognitions, especially in circumstances where coughing would be maladaptive. Psychological interventions aimed at reducing the negative cognitions associated with experiencing the urge to cough may reduce the magnitude of the urge to cough sensation and therefore reduce cough reflex sensitivity. We hypothesised that a mindfulness intervention would reduce perceived urge to cough on inhaling tussive agents and therefore reduce motor cough response and cough reflex sensitivity. Two randomised controlled trials were performed assessing the effect of mindfulness on cough reflex sensitivity; first testing the immediate effect of mindfulness in healthy volunteers and secondly a short duration outpatient intervention programme in patients with chronic cough.

METHODS

Subjects

Thirty healthy volunteers and 30 patients presenting with chronic cough (>8 weeks duration) to a tertiary referral cough clinic (University Hospital of South Manchester) were studied. Subjects performed a baseline citric acid cough challenge and were excluded from further participation if they did not have a measurable C5—that is, did not cough five times after inhaling the maximum concentration of citric acid. Other exclusion criteria were a history of recent upper respiratory tract infection (<4 weeks) or current treatment with opiates, angiotensin-converting enzyme inhibitors or any over-the-counter cough medicines. Current smokers were also excluded. The chronic cough patients had received targeted 8-week treatment trials for underlying gastro-oesophageal reflux disease, asthma and/or upper airway cough syndrome (UACS). None of the patients had undergone any behavioural therapy for their cough. Ethics approval was granted by the local research ethics committee and written informed consent was obtained from all subjects.

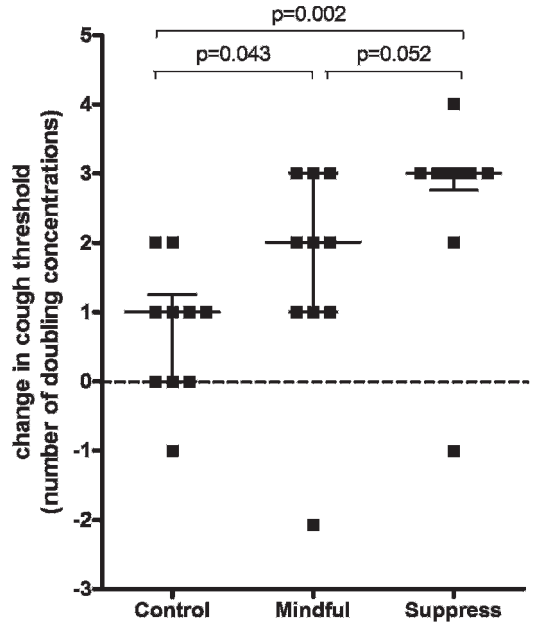

Figure 1 Changes in cough reflex sensitivity to citric acid in healthy volunteers for the control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values and error bars represent the interquartile range.

Study design

Two sequential studies were performed. First, the immediate effects of a mindfulness intervention on cough reflex sensitivity were tested in healthy volunteers to assess the ability of a relaxation technique to modulate the cough reflex. Secondly, we examined the effect of mindfulness on cough reflex sensitivity in subjects with chronic cough. This study was of similar design, but mindfulness was taught and practised over a period of 1 week to investigate the longer term effects of mindfulness in a patient group and therefore its potential as a treatment.

Study 1: immediate effect of mindfulness in healthy volunteers

Cough reflex sensitivity was measured at baseline using a citric acid challenge, following which subjects were randomised to one of three possible groups: (1) no intervention (control), (2) mindfulness training or (3) voluntary suppression. Randomisation by minimisation was performed and subjects were stratified according to cough reflex sensitivity and gender.[15]

Control

Repeat citric acid challenge was according to the standard protocol described below after 1 h.

Mindfulness intervention

A 15 min mindfulness training exercise was performed just prior to their second cough challenge at 1 h.

Voluntary suppression

No intervention was performed between baseline and repeat citric acid challenges at 1 h, but at the beginning of the repeat challenge

subjects were instructed to try not to cough and reminded of this following each subsequent inhalation of citric acid. Patients were not provided with any particular strategies to achieve this.

Study 2: effect of mindfulness course in subjects with chronic cough

As for study 1, patients with chronic cough had cough reflex sensitivity testing at baseline, but also the Spielberger State–Trait Anxiety Inventory (STAI), and then were randomised/stratified in the same manner to (1) no intervention, (2) mindfulness training or (3) voluntary suppression. However, repeat cough challenges for this study were performed after a longer interval, 7–10 days later, to allow a more prolonged mindfulness intervention. For this mindfulness intervention patients with cough took part in an educational interview delivered by the researcher during which meditative techniques were explained. The interview was recorded on an audio-cassette for home practice, at least 30 min per day until their return visit. Patients did not keep a record of their compliance with home practice.

Procedures

Citric acid challenge

Citric acid cough challenge was performed using the single-breath, doubling dose method, delivered by a dosimeter (Koko dosimeter, Ferraris Ltd, Hertford, UK) with inspiratory flow rate limitation.[16] In brief, serial doubling concentrations of citric acid ranging from 0.03 to 4 M were administered 1 min apart with three interspersed placebo inhalations (normal saline) to which both researcher and subject were blinded. Subjects were instructed to cough freely and not try to suppress coughing (except in voluntary suppression challenges). The number of coughs, defined as explosive sounds, that occurred in the minute after each inhalation, was recorded and the test stopped when the subject coughed at least five times (C5). To ensure consistency the same nebuliser pot was used throughout the experiment for each individual, and re-calibrated at regular intervals. Spirometry was performed before and after each challenge and if forced expiratory volume in 1 s (FEV_1) fell by ⩾20% following citric acid inhalation subjects were excluded from further study.

Urge to cough

Following each inhalation of citric acid, healthy subjects were asked to rate their urge to cough intensity on a visual analogue scale (VAS) from 0 to 100 mm anchored by "no urge" to "severe urge". Patients with chronic cough rated their urge to cough on a modified Borg scale ranging from 0 (no need to cough) to 10 (maximum urge to cough) as described by Davenport.[13]

Mindfulness intervention

The mindfulness intervention aimed to train subjects to experience sensations without evaluation or judgement. We predicted that mindfulness would enable subjects to experience the urge to cough without focusing either on the possibility of coughing or on any associated distress. The intervention was adapted for this study by psychologists and intended to be delivered by non-experts after brief training. For this study a breathing exercise was used to aid mindfulness.[5] Subjects were given written instructions consisting of an explanation of the principles of mindfulness and then specific directions as to how to perform the breathing and mindfulness exercises (see online supplement). Subjects are asked to notice their breathing and the sensations associated with it but not consciously try to change their breath or relax. They were seated in a quiet room, and told to close their eyes and focus on their breathing "being with each inhalation" for its full duration and "with each exhalation" for its full duration. Subjects were instructed to return their attention to their breathing each time they noticed their mind had wandered. This exercise was conducted with support from the researcher. Healthy volunteers spent 15 min

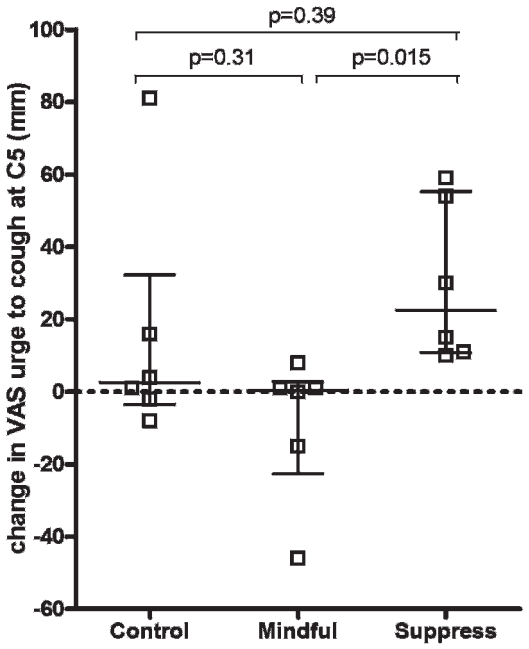

Figure 2 Changes in urge to cough at the citric acid cough threshold (C5) in healthy volunteers for the control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values, and error bars represent the interquartile range. VAS, visual analogue scale.

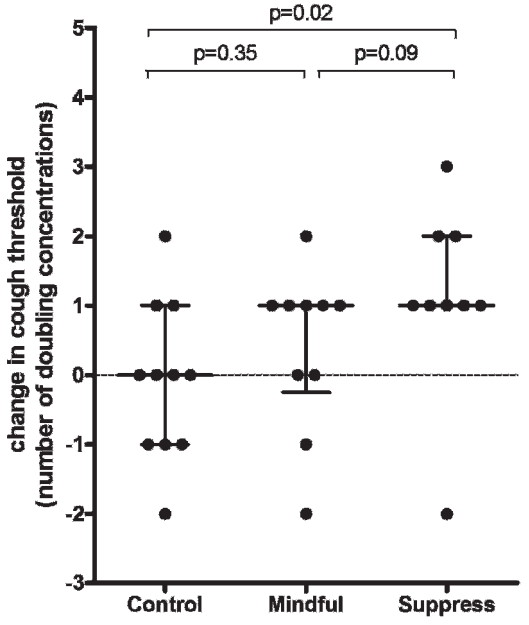

Figure 3 Changes in cough reflex sensitivity to citric acid in patients with chronic cough for the control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values, and error bars represent the interquartile range.

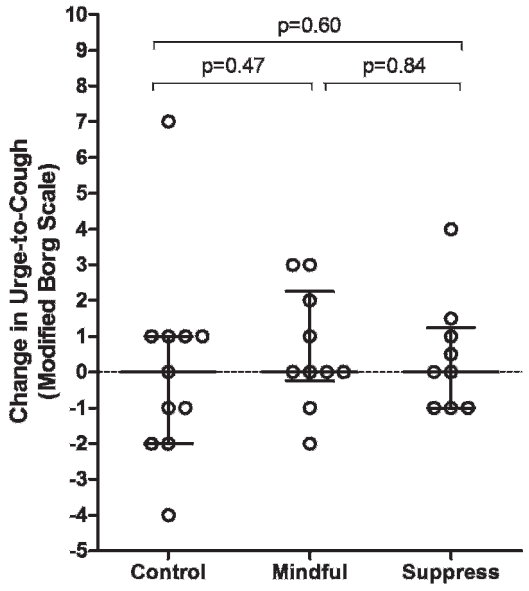

Figure 4 Changes in urge to cough at the citric acid cough threshold (C5) in patients with chronic cough for the control, mindfulness intervention and voluntary cough suppression groups. Horizontal lines represent median values, and error bars represent the interquartile range.

practising the mindfulness exercise prior to the cough challenge. Subjects with chronic cough were given the same instructions and asked to practise the exercise at home for at least 30 min per day until the next visit.

State/trait anxiety

The Spielberger STAI is a self-report scale for measuring state (present) and trait (general) anxiety levels that has been used extensively in research.[17] State anxiety is sensitive to change following intervention. Patients with cough completed the scale at baseline and at repeat cough challenge.

Statistical analyses

Cough reflex sensitivity was log transformed (logC5) prior to analysis. The Kruskall–Wallis test was used to compare change in cough reflex sensitivity, urge to cough rating at C5 and anxiety scores across the three groups. Where the Kruskall–Wallis test suggested a significant difference, post hoc pairwise comparisons were made with the Mann–Whitney test.

RESULTS

Thirty healthy volunteers (24 female, 6 male) and 30 patients with cough (20 female, 10 male) meeting eligibility criteria took part in the studies. Mean age was 34 years (SD 10.5) in healthy subjects compared with 58 years (SD 9.46) in the patients with cough. None of the participants was a current smoker, but 11 (37%) of the patients with cough were ex-smokers >6 months, with a median smoking history of 0.0 (0–45) pack-years. Pre-challenge mean percentage predicted FEV_1 was 104.98% (SD 13.45%) in healthy subjects compared with 97.04% (SD 20.45%) in the patients with cough. Age, gender and baseline C5 are compared between randomisation groups in table 1. Significantly more females were randomised to mindful intervention in the healthy volunteer study, but groups were otherwise well matched.

Study 1: healthy subjects

Baseline median (IQR) logC5 for all healthy volunteers was −0.3M (−0.6 to 0.0). Ten subjects were randomised to each group and median change (IQR) in logC5 for the no intervention, mindfulness intervention and voluntary suppression groups was +1.0 (0.0 to +1.3), +2.0 (+1.0 to +3.0) and +3.0 (+2.8 to +3.0) doubling concentrations, respectively, p = 0.003. The mindfulness intervention significantly reduced cough reflex sensitivity compared with the no intervention group (p = 0.043). Voluntary suppression of coughing also significantly improved cough reflex sensitivity (p = 0.002) but was not significantly better than the mindfulness intervention (p = 0.052) (see fig 1).

Urge to cough data were available in 18 (60%) healthy subjects and showed a log-linear relationship with concentration of citric acid (online supplement fig E1). Median (IQR) baseline urge to cough at C5 (rated on a VAS from 0 to 100 mm) was 92 (69 to 99) mm. Median change (IQR) in urge to cough at C5 for the no intervention, mindfulness and voluntary suppression groups was +3 (−4 to +32) mm, +1 (−23 to +3) mm and +13 (+3 to +55.3) mm, respectively, with a trend towards a difference between the groups (p = 0.069). There was no statistically significant difference in change in urge to cough at C5 between the no intervention and mindfulness groups (p = 0.31) or between the no intervention and voluntary suppression groups (p = 0.39), but there was the suggestion of a lower urge to cough for the mindfulness group compared with voluntary suppression (p = 0.015) (see fig 2).

Study 2: patients with cough

Baseline median (IQR) log C5 for all patients was −0.9M (−1.2 to −0.3), significantly lower than in the healthy volunteer study (p = 0.001). Eleven patients were randomised to no intervention, 10 to the mindfulness programme and 9 to voluntary cough suppression. Median change (IQR) in log C5 for no intervention, mindfulness and voluntary suppression groups was 0.0 (−1 to +1), +1.0 (−0.3 to +1) and +1.0 (+1.0 to +2.0) doubling concentrations, respectively (p = 0.046). There was no statistically significant difference in change in logC5 between the no intervention and mindfulness groups (p = 0.35). Comparison of the control and voluntary suppression groups revealed a significant difference (p = 0.02) with an increase in cough threshold (see fig 3).

Urge to cough data were collected for all patients. Median (IQR) baseline urge to cough at C5 as rated by a modified Borg scale was 4 (3–6.3). Median change (IQR) in urge to cough at C5 was not significantly different between the no intervention, mindfulness and voluntary suppression groups (0 (−2 to +1), 0 (0 to +2) and 0 (−1 to +1), respectively (p = 0.70); fig 4).

Compared with a working population sample mean,[17] both male and female patients with cough had high trait anxiety levels (mean (SD) in males, 36.60 (16.21) vs 34.89 (9.19); in females, 40.50 (11.00) vs 34.79 (9.22)) but below average state anxiety scores (mean (SD) in males, 30.50 (10.30) vs 35.72 (10.40); in females, 34.15 (8.83) vs 35.20 (10.61)). There were no significant changes in either state (p = 0.23) or trait (p = 0.78) anxiety for any of the patient groups.

DISCUSSION

In this study we have shown that healthy volunteers undergoing a mindfulness intervention had a prompt reduction in cough reflex sensitivity compared with a no intervention control group. Patients with chronic cough performing a brief

outpatient mindfulness programme, however, had no change in cough reflex sensitivity compared with controls. Mindfulness did not significantly alter the perceived urge to cough at the C5 cough threshold in either subject group and did not appear to reduce state/trait anxiety levels in the patients with chronic cough compared with the controls. Voluntary suppression of coughing after citric acid inhalation was able to decrease cough reflex sensitivity significantly in both trials, but appeared to be more effective in the healthy volunteers than in the patients with chronic cough.

There are a number of possible explanations for the failure of mindfulness to alter cough reflex sensitivity in the chronic cough study compared with the healthy volunteer study. First, the healthy volunteer study was designed to assess any immediate effect of mindfulness training. In contrast, the chronic cough study assessed whether more prolonged mindfulness training might have a clinical role in this distressing condition. It is possible that any improvements in cough reflex sensitivity following a mindfulness exercise are only very short-lived; however, the optimal duration of mindfulness training is not known. A longer more intensive supervised course may be required to have a prolonged effect in patients compared with healthy volunteers, although this has never been investigated. Secondly, cough reflex sensitivity in patients with chronic cough may be more resistant to change. Voluntary suppression reduced cough reflex sensitivity in patients with chronic cough but appeared to be less effective than in healthy controls. This is in keeping with the experience of patients with chronic cough who complain of an inability to control coughing, leading to social embarrassment.[18] During cough challenges, as the intensity of the urge to cough increases, the ability to suppress coughing decreases until coughing becomes an irresistible response. We speculate that in patients with chronic cough, coughing may result not only from an increased sensitivity to irritants but also from poorer conscious control over coughing which may be mediated by impairment of descending cortical pathways. This could also explain why psychological interventions such as mindfulness may be less effective than in healthy volunteer studies.

It may be important that this mindfulness training encouraged subjects to focus on their breathing. Attending to the sensations associated with inhalation and exhalation rather than the urge to cough may have motivated the individual to prioritise continued breathing over coughing. This could explain the effect of mindfulness in the healthy volunteer group. It would be interesting to explore whether mindfulness of another non-respiratory bodily sensation or external influence (eg, music) would have a similar inhibitory effect on behavioural cough response.

We found that compared with a no intervention control, there was no statistically significant change in the urge to cough experienced following mindfulness intervention or voluntary suppression in either study. However, as a secondary endpoint, the studies may well have been inadequately powered to demonstrate such effects. We hypothesised that mindfulness would reduce cough reflex sensitivity by reducing the urge to cough and that voluntary suppression would also reduce cough reflex sensitivity but at the expense of a more intense urge to cough. In the healthy volunteer study, despite some missing data, there was a suggestion that the urge to cough at C5 was lower in the mindfulness group compared with voluntary suppression.

Some studies investigating the effect of a mindfulness intervention in chronic disease have lacked control groups,[6 7 9] thereby not excluding a significant placebo effect from such treatment. We compared this mindfulness intervention with a no intervention control group and additionally included a modified cough challenge to act as a positive control, during which volunteers were instructed to ''try not to cough''. In the healthy volunteer study, cough reflex sensitivity did improve by one doubling dose in the control group; however, it is interesting to note that in the chronic cough study there was no such improvement with no intervention (decreased C5 in 23 of 30 healthy volunteers vs 11 of 30 patients with chronic cough).

The main limitation of this study is that the duration and intensity of the mindfulness programme may have been inadequate and we cannot be certain that the patients with chronic cough complied with home practice. However, our aim was to assess whether a brief intervention delivered by non-experts could be effective. Other studies with positive outcomes with symptoms other than cough have used an intensive 8- to 10-week programme and taught formal mindful meditative techniques such as yoga, body scan and sitting meditation.[7 8] Introduction of these formal techniques and modification of the programme by psychologists to be more in line with the specific concerns of a group of patients with chronic cough could improve future results. Also despite stratification, a greater proportion of females were randomised to the mindfulness intervention in the healthy volunteer study. Subjects were, however, reasonably well matched for baseline cough reflex sensitivity, which is likely to be more important.

In summary, the findings of this study suggest that a short-duration mindfulness outpatient programme cannot be recommended as a psychological intervention for chronic cough, although a potentially beneficial effect following a more prolonged intervention led by experts is not excluded. Since voluntary suppression reduced cough reflex sensitivity in both subject groups, a future randomised controlled study of voluntary cough suppression as a therapeutic strategy for chronic cough would be interesting, particularly to investigate whether prolonged practice improves the ability to suppress coughing successfully. Indeed speech and language therapy is the only supportive intervention shown to be effective in patients with chronic cough,[19] a component of which is strategies to suppress or replace the cough.

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Lung alert

Pharmacological manipulation of antituberculous therapies to improve treatment efficacy and compliance with ethionamide

The global multidrug-resistant tuberculosis epidemic has prompted efforts to develop new antimycobacterial compounds and strategies to improve efficacy and compliance of drugs already in use. Several antituberculous compounds require in situ metabolic activation to become inhibitory to the mycobacterium. Ethionamide, a thiocarbamide-containing drug, is activated by the mycobacterial mono-oxygenase EthA. The production of EthA is inhibited by the transcriptional repressor EthR.

This study investigated the use of inhibitors of EthR to boost activity of EthA, thus increasing the efficacy of ethionamide. The ligands BDM31381 and BDM31343 were identified as compounds that inhibit EthR in vivo, resulting in increased activity of EthA. The minimum concentrations of ethionamide needed in the presence and absence of both ligands showed that BDM31343 and BDM31381 increased the antibacterial potency of ethionamide towards *Mycobacterium tuberculosis* by factors of 10 and 20 respectively. BDM31381 also improved the potency of thiacetazone, another antimycobacterial compound, by a factor of 4. In vivo studies in mice infected with *M tuberculosis* showed that BDM31381 with ethionamide only had a minor effect on bacterial load compared with ethionamide alone, while BDM31343 with ethionamide reduced bacterial load as efficiently as a three times higher dose of ethionamide alone.

This study supports the hypothesis that the sensitivity of *M tuberculosis* to a prodrug can be increased by interfering pharmacologically with the regulatory mechanism of drug activation. This could result in lower drug dose requirements, improving side effect profiles and increasing compliance—a potential step forward in the fight against multidrug-resistant tuberculosis.

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