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Early View

Research letter

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An open-label study of the tolerability and potential efficacy of memantine for treating refractory chronic cough

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Take home message

Blocking NMDA Receptors with memantine in refractory chronic cough patients is poorly tolerated and demonstrates no improvement in cough.

To the Editor

Refractory chronic cough (RCC) is defined as cough lasting longer than eight weeks either in the absence of an identifiable underlying cause or that remains resistant to treating any potential underlying causes (1). Affected patients have a poor quality of life and suffer from fatigue, disturbed sleep, incontinence, frustration, anxiety, and depression (2). Despite being a debilitating condition, there is no licensed treatment available.

RCC patients exhibit features suggesting hyperexcitability of the neuronal pathways mediating cough with coughing induced by minor stimuli (3). Sensitisation of both airway nerves (peripheral sensitisation) and/or central processes mediating cough (central sensitisation) are thought to play key roles in the pathogenesis of RCC, analogous to the processes described in neuropathic pain (4). N-Methyl-D-Aspartate receptors (NMDARs) are present throughout the central nervous system (CNS), are the target for the excitatory neurotransmitter glutamate and thought to be pivotal for the initiation and maintenance of CNS plasticity in neuropathic pain (5,6). Blocking NMDARs could therefore be a potential therapeutic target in RCC. Dextromethorphan, a weak antagonist of NDMARs, is used in many over-the-counter antitussive preparations but compared with placebo, it reduces acute cough by no more than 17%; evidence of efficacy in chronic cough is lacking (7,8). Memantine, an approved medication for Alzheimer's disease, is a low-affinity uncompetitive NMDAR antagonist, preferentially targeting activated receptors (6). Memantine has previously been shown to block cough experimentally evoked by inhalation of citric acid and bradykinin in conscious guinea pigs (9). The aims of this study were: a) to explore the tolerability and efficacy of escalating doses of memantine in RCC patients; b) to generate data for sample size estimation for future randomised controlled trials.

We conducted an open-label feasibility study of escalating doses (10-40mg/day) of memantine in RCC patients. Although up to 80mg daily was used in trials of chronic pain, doses >40mg were associated with significant side effects (10). Adult patients were recruited from Wythenshawe Hospital (Manchester, UK) tertiary cough clinic between February and August 2013. Patients had undergone extensive investigations for their cough according to a diagnostic algorithm (11). Exclusion criteria included recent upper respiratory tract infection (<4 weeks), current smoking, former smoking within 6 months or >20 pack-years smoking history, and current treatment with medications that may affect cough e.g., angiotensin-converting enzyme inhibitors, opioids, anticonvulsants, and tricyclic antidepressants. The study received approval from Haydock North West Research Ethics Committee (11/NW/0840) and the Medicines and Healthcare Products Regulatory Agency (35030/0003/001). All participants provided written informed consent, and the study was conducted according to ICH-GCP and the Declaration of Helsinki.

Patients completed the Cough-Specific Quality-of-Life Questionnaire (CQLQ) and were attached to a validated 24-hour ambulatory cough monitoring device (VitaloJAK^{TM}; Vitalograph Ltd, UK) at baseline and end of treatment (12). Memantine was initiated at 10mg daily and increased by 10mg every week until either the maximum tolerated dose or 40mg was reached, whichever was the greater. Patients were asked to stay on this maximum dose for four weeks. The primary endpoint was the change in awake cough frequency (coughs/ hour) from baseline to end of four weeks treatment with the maximum tolerated memantine dose. Secondary endpoints were the tolerability of memantine and the change from baseline in CQLQ scores. Sample size was not calculated as this was a pilot study. A paired t-test (SPSS, version 20.0) compared the difference in the ratio of geometric

mean cough frequency and CQLQ scores before and after treatment. A conventional two-sided 5% significance level was used.

Of 17 patients screened, 14 received memantine (13 females; mean age, 57.9±11.8 years; 11 never-smokers; mean cough duration, 13.7±6.8 years). Twelve completed the study (withdrawals were due to intolerance of medication (n=1) and worsening of cough (n=1)). Eleven participants completed cough recordings at both baseline and end of treatment; omitted in one patient with a URTI at the end of treatment. The CQLQ analysis included 11 subjects. One participant who did not respond fully to the CQLQ at end of treatment visit was excluded from the analysis.

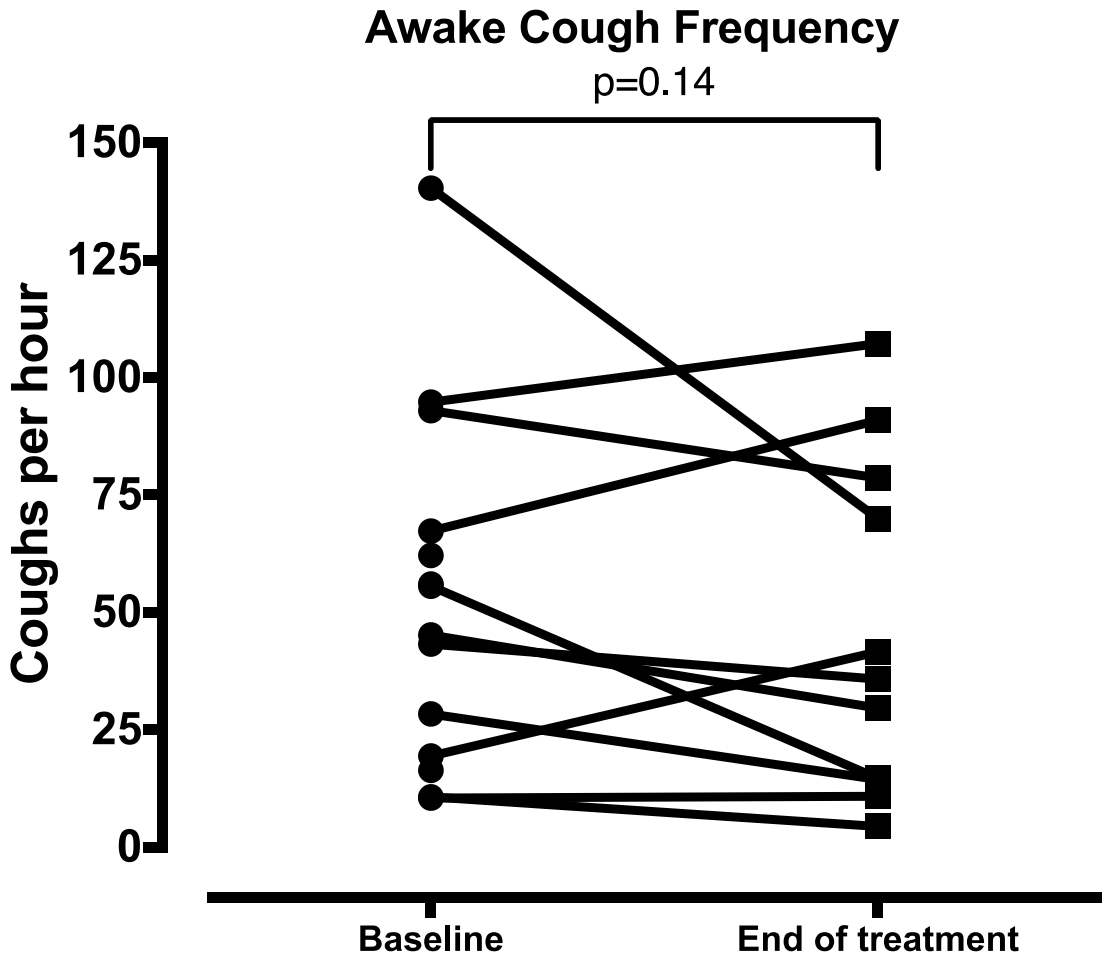
Of the 14 participants enrolled in the study, the number (%) of patients who took memantine doses of 10mg, 20mg, 30mg and 40mg were 14 (100%), 12 (85.7%), 6 (42.9%), and 1 (7.1%), respectively. However, as memantine was poorly tolerated most patients subsequently reduced the dose due to adverse effects. At the end of the study, most participants (n=10; 71.4%) only tolerated a maximum dose of 10mg; 2 (14.3%) were on 20mg, 2 (14.3%) were on 30mg, and none remained on 40mg. The median (min, max) duration of memantine treatment, including dose escalation, was 38.5 days (7–49). Nine of the 14 participants (64.3%) remained on the maximum tolerated dose for 4 weeks (10mg (n=6), 20mg (n=2), 30mg (n=1)). Median (min, max) treatment duration in the remaining 5 participants who did not complete 4 weeks of maximum dose treatment was 18 days (4-23) due to intolerance (n=3), worsening of cough (n=1) and going on holiday (n=1). Although awake cough frequency decreased with memantine treatment by 25% (95% CI -50 to +12%), the reduction was not statistically significant (baseline geometric mean 41.1 coughs/h (95% CI, 22.9–73.8) versus end of treatment 30.8 coughs/h (95% CI, 15.6–61.2); p=0.14); individual change in cough frequencies is depicted in Figure 1. Total CQLQ scores did not

change significantly (mean 61.9 (95% CI, 53.4-70.4) versus 66.1 (95% CI, 60.3-71.9); p=0.12). The mean difference in total CQLQ scores was minimal at -4.2 (95% CI, -9.6 to +1.2). The most common adverse events reported were dizziness, tiredness, and drowsiness. Even at a daily dose of 10mg, 8 of the 14 participants (57%) experienced adverse events related to memantine (mainly drowsiness n=4, tiredness n=3, dizziness n=3, headache n=3). The 20mg daily dose of memantine (n=12) was associated with adverse events in 9 (75%) participants, which tended to be more bothersome than those associated with taking 10mg. Of the 6 participants whose dose was escalated to 30mg, 1 had severe dizziness, slurred speech, perception of 'funny sensation' on their right side, feeling 'spaced out' and moderate nausea; 1 felt 'spaced out', which affected their ability to work and drive; 2 had moderate lightheadedness; the remaining 2 reported no adverse events. The 1 participant who had their dose increased to 40mg did not tolerate it well enough to remain on it due to lightheadedness. There were no reported serious adverse events.

This study indicates that the NMDAR antagonist memantine is poorly tolerated by patients with RCC and therefore dosing is limited by adverse effects; most patients were unable to tolerate doses above 10mg. There was some evidence suggesting an anti-tussive effect although statistical significance was not reached and a placebo response cannot be excluded due to the open label nature of this study. In addition, there was no improvement in patient reported quality of life (CQLQ). Interestingly, however, the reduction in cough frequency was greater than that reported in controlled trials of dextromethorphan, a frequently used over-the-counter cough suppressant, for acute cough (8). We have previously studied other NMDAR antagonists (ketamine, V3381) in patients with RCC and found similar issues with CNS side effects (13,14). Likewise, two commercial studies of a modified formulation of memantine were performed and although results were never

published, no follow up studies occurred (15,16). In summary, this study's findings did not favour progression to a randomised controlled trial of memantine in RCC as adverse effects seemed to outweigh the small estimated treatment effect. Antagonists selective for NMDAR subunits thought to be specific to cough pathways may still provide novel future treatment options (9). Importantly, these would need to demonstrate better tolerability to allow optimisation of dosing and efficacy (17).

Figure 1: Changes in objective awake cough frequency from baseline to end of the treatment period



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