



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

Copyright ©The authors 2021

This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact [permissions@ersnet.org](mailto:permissions@ersnet.org)

Received: 5 July 2021  
Accepted: 6 July 2021

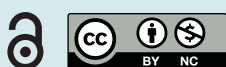
*To the Editor:*

Refractory chronic cough (RCC) is defined as cough lasting longer than 8 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, no licensed treatment is 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 NMDARs, 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: 1) to explore the tolerability and efficacy of escalating doses of memantine in RCC patients; and 2) to generate data for sample size estimation for future randomised controlled trials.

We conducted an open-label feasibility study of escalating doses (10–40 mg per day) of memantine in RCC patients. Although up to 80 mg daily was used in trials of chronic pain, doses >40 mg 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 past 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-h ambulatory cough monitoring device (VitaloJAK; Vitalograph Ltd, UK) at baseline and end of treatment [12]. Memantine was initiated at 10 mg daily and increased by 10 mg every week until either the maximum tolerated dose or 40 mg was reached, whichever was the greater. Patients were asked to stay on this maximum dose for 4 weeks. The primary end-point was the change in awake cough frequency (coughs per hour) from baseline to end of 4 weeks treatment with the maximum tolerated memantine dose. Secondary end-points were the tolerability of memantine and the change from baseline in CQLQ scores.



Shareable abstract (@ERSpublications)

**Blocking NMDA receptors with memantine in refractory chronic cough patients is poorly tolerated and demonstrates no improvement in cough** <https://bit.ly/3kgx2g1>

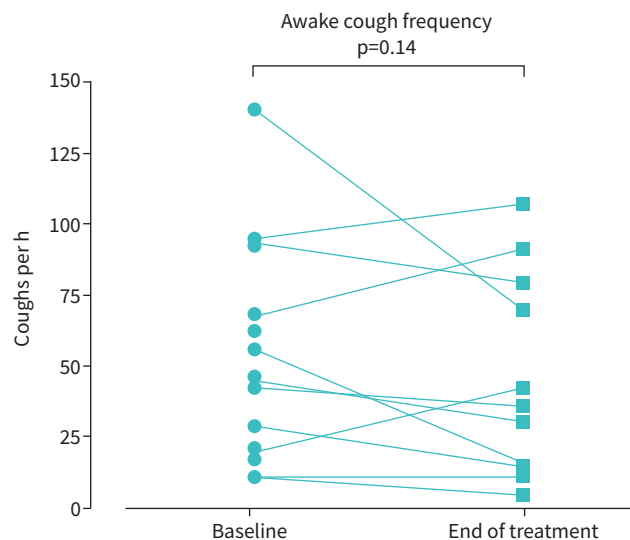
**Cite this article as:** Abdulqawi R, Satia I, Holt KJ, *et al.* An open-label study of the tolerability and potential efficacy of memantine for treating refractory chronic cough. *ERJ Open Res* 2021; 7: 00447-2021 [DOI: 10.1183/23120541.00447-2021].



Sample size was not calculated as this was a pilot study. A paired t-test (SPSS, version 20.0; IBM Corp., Armonk, NY, USA) 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 $\pm$ SD age 57.9 $\pm$ 11.8 years; 11 never-smokers; mean $\pm$ SD cough duration 13.7 $\pm$ 6.8 years). 12 completed the study (withdrawals were due to intolerance of medication (n=1) and worsening of cough (n=1)). 11 participants completed cough recordings at both baseline and end of treatment; omitted in one patient with an upper respiratory tract infection 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 10 mg, 20 mg, 30 mg and 40 mg 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 10 mg; 2 (14.3%) were on 20 mg, 2 (14.3%) were on 30mg, and none remained on 40 mg. The median (minimum–maximum) 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 (10 mg (n=6), 20mg (n=2), 30mg (n=1)). Median (minimum–maximum) treatment duration in the remaining five 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 per h (95% CI 22.9–73.8) versus end of treatment 30.8 coughs per 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 10 mg, eight 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 20 mg daily dose of memantine (n=12) was associated with adverse events in nine (75%) participants, which tended to be more bothersome than those associated with taking 10 mg. Of the six participants whose dose was escalated to 30 mg, one had severe dizziness, slurred speech, perception of “funny sensation” on their right side, feeling “spaced out” and moderate nausea; one felt “spaced out”, which affected their ability to work and drive; two had moderate light-headedness; and the remaining two reported no adverse events. The one participant who had their dose increased to 40 mg did not tolerate it well enough to remain on it due to light-headedness. There were no reported serious adverse events.



**FIGURE 1** Changes in objective awake cough frequency from baseline to end of the treatment period.

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 10 mg. There was some evidence suggesting an antitussive 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].

Rayid Abdulqawi<sup>1,2,3,6</sup>, Imran Satia<sup>1,4,5,6</sup>, Kimberley J. Holt<sup>1,3</sup>, Rachel Dockry<sup>1,3</sup>, Shilpi Sen<sup>3</sup> and Jaclyn A. Smith<sup>1,3</sup>

<sup>1</sup>University of Manchester, Division of Infection, Immunity and Respiratory Medicine, and Manchester Academic Health Science Centre, Manchester, UK. <sup>2</sup>King Fahad Specialist Hospital-Dammam, and Dept of Medicine, Alfaisal University, Riyadh, Saudi Arabia. <sup>3</sup>Manchester University NHS Foundation Trust, Manchester, UK. <sup>4</sup>McMaster University, Dept of Medicine, Division of Respiriology, Hamilton, Canada. <sup>5</sup>Firestone Institute for Respiratory Health, St Joseph's Healthcare, Hamilton, Canada. <sup>6</sup>These authors contributed equally.

Corresponding author: Jaclyn A. Smith ([jacky.smith@manchester.ac.uk](mailto:jacky.smith@manchester.ac.uk))

Author contributions: Study design and concept: R. Abdulqawi and J.A. Smith. Data collection: R. Abdulqawi, K.J. Holt, R. Dockry and S. Sen. Data analysis and interpretation: R. Abdulqawi, I. Satia and J.A. Smith. Manuscript preparation: R. Abdulqawi, I. Satia and J.A. Smith. All authors reviewed and agreed on the final manuscript.

Provenance: Submitted article, peer reviewed.

Conflict of interest: R. Abdulqawi reports personal fees from AstraZeneca, Boehringer Ingelheim and Mundipharma outside the submitted work. I. Satia reports personal fees from educational talks for GPs from GSK and AstraZeneca, grants and personal fees from Merck Canada, and an ERS Respire 3 Marie Curie Fellowship, outside the submitted work. K.J. Holt has nothing to disclose. R. Dockry has nothing to disclose. S. Sen has nothing to disclose. J.A. Smith reports grants and personal fees from GSK, NeRRe Pharmaceuticals, Menlo, Bayer, Boehringer Ingelheim, Axalbion, Afferent and Merck; personal fees from Genentech, Neomed, Bellus, Chiesi, AstraZeneca and Algenon; and nonfinancial support from Vitalograph, all outside the submitted work. In addition, J.A. Smith has a patent (A method for generating output data) licensed.

Support statement: The Medical Research Council as part of a fellowship award made to J.A. Smith. J.A. Smith is funded by the NIHR Manchester Biomedical Research Centre and a Wellcome Investigator Award (207504/B/17/Z), and is an NIHR Senior Investigator. I. Satia is currently supported by the E.J. Moran Campbell Early Career Award, Dept of Medicine, McMaster University. Funding information for this article has been deposited with the Crossref Funder Registry.

## References

- 1 Morice AH, Millqvist E, Bieksien K, *et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55: 1901136.
- 2 French CL, Irwin RS, Curley FJ, *et al.* Impact of chronic cough on quality of life. *Arch Intern Med* 1998; 158: 1657–1661.
- 3 Choudry NB, Fuller RW. Sensitivity of the cough reflex in patients with chronic cough. *Eur Respir J* 1992; 5: 296–300.
- 4 O'Neill J, McMahon SB, Udem BJ. Chronic cough and pain: Janus faces in sensory neurobiology? *Pulm Pharmacol Ther* 2013; 26: 476–485.

- 5 Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. *Pain* 1991; 44: 293–299.
- 6 Chaffey H, Chazot PL. NMDA receptor subtypes: structure, function and therapeutics. *Curr Anaesth Crit Care* 2008; 19: 183–201.
- 7 Jaffe DB, Marks SS, Greenberg DA. Antagonist drug selectivity for radioligand binding sites on voltage-gated and N-methyl-D-aspartate receptor-gated Ca<sup>2+</sup> channels. *Neurosci Lett* 1989; 105: 227–232.
- 8 Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a metaanalysis. *Chest* 2001; 120: 1121–1128.
- 9 Smith JA, Hilton ECY, Saulsberry L, et al. Antitussive effects of memantine in guinea pigs. *Chest* 2012; 141: 996–1002.
- 10 Kavirajan H. Memantine: a comprehensive review of safety and efficacy. *Expert Opin Drug Saf* 2009; 8: 89–109.
- 11 Morice AH. Recommendations for the management of cough in adults. *Thorax* 2006; 61: Suppl. 1, i1–24.
- 12 Smith J, Holt K, Dockry R, et al. Performance of a digital signal processing algorithm for the accurate quantification of cough frequency. *Eur Respir J* 2021; 58: 2004271.
- 13 Young E, Pawsey S, Woodcock A, et al. An open-label pilot study of V3381, a novel N-Methyl-D-Aspartate Receptor (NMDA-R) antagonist in chronic cough. *Lung* 2012; 190: 63–68.
- 14 Hilton ECY. Towards an understanding of the neurophysiology of cough in humans. Manchester, University of Manchester, 2012.
- 15 [clinicaltrials.gov](http://clinicaltrials.gov). An Exploratory Study of FP01 Lozenges in Subjects With Chronic Refractory Cough. [www.clinicaltrials.gov/ct2/show/NCT01703923](http://www.clinicaltrials.gov/ct2/show/NCT01703923)
- 16 [clinicaltrials.gov](http://clinicaltrials.gov). Antitussive Effects of FP01 Lozenges in Subjects With Cough Due to Upper Respiratory Tract Infection. [www.clinicaltrials.gov/ct2/show/NCT01597349](http://www.clinicaltrials.gov/ct2/show/NCT01597349)
- 17 [clinicaltrials.gov](http://clinicaltrials.gov). Efficacy, Safety and Tolerability of NP-120 on Idiopathic Pulmonary Fibrosis and Its Associated Cough. [www.clinicaltrials.gov/ct2/show/NCT04318704](http://www.clinicaltrials.gov/ct2/show/NCT04318704)