Reply to Ratan K. Banik

Sophie W. Kjær, Andrew S. C. Rice, Karolina Wartolowska, Lene Vase

Letter to Editor:

We would like to thank Dr. Banik for his interest in our review. The concerns raised have been discussed at length in the context of seminal placebo-controlled surgical trials [8,10,11], and we believe solutions also exist to counteract the issues in neuromodulation research.

Dr. Banik correctly points out that placebo effects have been associated with activation of descending pain modulatory networks [13] and accordingly, therapeutic effects following placebo treatment [3]. This evidence illustrates exactly why it is essential to include a placebo control, as this allows for a separation of effects attributable to the therapeutic ritual from the potential specific effects of the intervention [11]. Patients are enrolled into a placebo-controlled randomised trial not "for the sake of science" as Dr. Banik suggests, but to demonstrate that a procedure is truly effective, that the risks associated with the procedure outweigh the harm, and to resolve the state of equipoise, i.e. when the clinical community does not know what the best available treatment is [5,11]. Without appropriate placebo controls, invasive treatments may incorrectly be assumed to be effective due to therapeutic effects solely arising from the therapeutic ritual [5].

Dr. Banik outlines ethical, funding and technical challenges in neuromodulation research and we welcome a discussion of these important issues. We agree that inclusion of placebo controls warrants ethical considerations, however this is also the case for invasive procedures with unresolved benefits. Improvements in placebo arms of surgical trials are present in a substantial amount of trials, and often do not show additional benefits beyond placebo [16]. This demonstrates not only the importance of including placebo controls, but moreover that patients are potentially exposed to unnecessary risks of ineffective procedures, which may be more harmful and unethical than justified placebo controls [5,11]. A recent review in the Lancet, addresses the ethical and practical issues of including placebo controls and presents guidelines for their application in surgical trials [2] and we believe a similar thorough discussion and general guidelines are called for within neuromodulation research.

It is correct that funding for placebo-controlled trials of spinal cord stimulation represents a challenge. Nevertheless, this has largely been surpassed in surgical trials, for example, existing placebo-controlled trials of interventional procedures are equally often funded commercially and non-commercially [15]. This can similarly be overcome in neuromodulation. Presently a publicly funded, randomized, double-blind, placebo-controlled trial of high-frequency spinal cord stimulation is planned and, in preliminary meetings, participants expressed willingness to participate [1].

The technical and practical concerns of placebo controls in spinal cord stimulation, including recruiting and undertaking of such trials highlighted by Dr. Banik, can also be solved. The feasibility of these trials is shown by a recent systematic review and meta-analysis of placebo-controlled randomized trials of spinal cord stimulation for neuropathic pain, including eight studies, of which two included a placebo control mimicking the context of the active treatment condition [4]. Blinding may be difficult to successfully achieve, but remains possible [14]. Furthermore, the inclusion of placebo controls does not necessarily require placebo surgery. Placebo controls can be included using alternative designs, as has previously been done in neuromodulation research [6,7,9] and as has been outlined in our earlier publication [12].

To ensure the best possible care for patients it is essential to establish the effects of neuromodulation against placebo controls. We believe that the benefits of placebo effects should not be avoided in clinical practice, but neuromodulation procedures should nevertheless demonstrate efficacy beyond placebo effects. As outlined above, this research is both ethical and feasible and we look forward to seeing the empirical studies and evidence emerging in the field.

Conflict of interest statement

Andrew SC Rice conflicts of interest occurring in last 24 months:

- ASCR undertakes consultancy and advisory board work for Imperial College Consultants. In the last 24 months this has included remunerated work for: Pharmanovo, Galapagos, Toray, Quartet, Lateral, Novartis, Pharmaleads, Mundipharma, Orion, Asahi Kasei & Theranexis

- ASCR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which future milestone payments may occur.

ASCR is named as an inventor on patents:

- Rice A.S.C., Vandevoorde S. and Lambert D.M Methods using N-(2-propenyl)hexadecanamide and related amides to relieve pain. WO 2005/079771
- Okuse K. et al Methods of treating pain by inhibition of vgf activity EP13702262.0/ WO2013 110945

The remaining authors have no conflicts of interest to declare.

References

[1] Al-Kaisy A, Royds J, Palmisani S, Pang D, Wesley S, Taylor RS, Cook A, Eldabe S, McCracken L, Duarte R, Fairbank J. Multicentre, double-blind, randomised, sham-controlled trial of 10 khz high-frequency spinal cord stimulation for chronic neuropathic low back pain (MODULATE-LBP): A trial protocol. Trials 2020;21:1–13.

[2] Beard DJ, Campbell MK, Blazeby JM, Carr AJ, Weijer C, Cuthbertson BH, Buchbinder R, Pinkney T, Bishop FL, Pugh J, Cousins S, Harris IA, Lohmander LS, Blencowe N, Gillies K, Probst P, Brennan C, Cook A, Farrar-Hockley D, Savulescu J, Huxtable R, Rangan A, Tracey I, Brocklehurst P, Ferreira ML, Nicholl J, Reeves BC, Hamdy F, Rowley SC, Cook JA. Considerations and methods for placebo controls in surgical trials (ASPIRE guidelines). Lancet 2020;395:828–838. doi:10.1016/S0140-6736(19)33137-X.

[3] Benedetti F. Mechanisms of placebo and placebo related effects across diseases and treatments. Eur Neuropsychopharmacol 2008;48:33–60.

[4] Duarte R V., Nevitt S, McNicol E, Taylor RS, Buchser E, North RB, Eldabe S. Systematic review and meta-analysis of placebo/sham controlled randomised trials of spinal cord stimulation for neuropathic pain. Pain 2020;161:24–35. doi:10.1097/j.pain.0000000000001689.

[5] George A, Collett C, Carr A, Holm S, Bale C, Burton S, Campbell M, Coles A, Gottlieb G, Muir K, Parroy S, Price J, Rice A, Sinden J, Stephenson C, Wartolowska K, Whittall H. When should placebo surgery as a control in clinical trials be carried out? Bull R Coll Surg Engl 2016;98:75–79. doi:10.1308/rcsbull.2016.75.

[6] Keitel A, Ferrea S, Südmeyer M, Schnitzler A, Wojtecki L. Expectation modulates the effect of deep brain stimulation on motor and cognitive function in tremor-dominant Parkinson's disease. PLoS One 2013;8:e81878. doi:10.1371/journal.pone.0081878.

[7] Mercado R, Constantoyannis C, Mandat T, Kumar A, Schulzer M, Stoessl AJ, Honey CR. Expectation and the placebo effect in Parkinson's disease patients with subthalamic nucleus deep brain stimulation. Mov Disord 2006;21:1457–1461. doi:10.1002/mds.20935.

[8] Moseley JB, O'Malley K, Petersen NJ, Menke TJ, Brody BA, Kuykendall DH, Hollingsworth JC, Ashton CM, Wray NP. A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the Knee. N Engl J Med 2002;347:81–88. doi:10.1056/NEJMoa013259.

[9] Pollo A, Torre E, Lopiano L, Rizzone M, Lanotte M, Cavanna A, Bergamasco B, Benedetti F. Expectation modulates the response to subthalamic nucleus stimulation in Parkinsonian patients. Neuroreport 2002;13:1383–1386. doi:10.1097/00001756-200208070-00006.

[10] Rogers W, Hutchison K, Skea ZC, Campbell MK. Strengthening the ethical assessment of placebo-controlled surgical trials: three proposals. BMC Med Ethics 2014;15:78. doi:10.1186/1472-6939-15-78.

[11] Savulescu J, Wartolowska K, Carr A. Randomised placebo-controlled trials of surgery: ethical analysis and guidelines. J Med Ethics 2016;42:776–783. doi:10.1136/medethics-2015-103333.

[12] Vase L, Wartolowska K. Pain, placebo, and test of treatment efficacy: a narrative review. Br J Anaesth 2019;123:e254e – e262. doi:10.1016/j.bja.2019.01.040.

[13] Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci 2015;16:403–418. doi:10.1038/nrn3976.

[14] Wartolowska K, Beard D, Carr A. Blinding in trials of interventional procedures is possible and worthwhile. F1000Research 2018;6:1663. doi:10.12688/f1000research.12528.2.

[15] Wartolowska K, Collins GS, Hopewell S, Judge A, Dean BJF, Rombach I, Beard DJ, Carr AJ. Feasibility of surgical randomised controlled trials with a placebo arm: a systematic review. BMJ Open 2016;6:e010194. doi:10.1136/bmjopen-2015-010194.

[16] Wartolowska K, Judge A, Hopewell S, Collins GS, Dean BJF, Rombach I, Brindley D, Savulescu J, Beard DJ, Carr AJ. Use of placebo controls in the evaluation of surgery: systematic review. BMJ 2014;348:g3253–g3253. doi:10.1136/bmj.g3253.