
Article:
Tesfaye, S., Sloan, G., White, D. orcid.org/0000-0003-2871-7946 et al. (3 more authors) (2023) Who really benefits from drug combinations and long titrations for pain? – Authors' reply. The Lancet, 401 (10372). pp. 192-193. ISSN 0140-6736

https://doi.org/10.1016/s0140-6736(23)00057-0

RESPONSE

Solomon Tesfaye, Gordon Sloan, David White, Mike Bradburn, Didier Bouhassira, Dinesh Selvarajah, on behalf of the OPTION-DM trial group

We thank Prof Perry for taking the time to read our study and respond to our published manuscript.[1] In the option DM trial we included pregabalin rather than gabapentin as pregabalin is a twice-daily drug which made blinded dosing easier for the trial, has 3-4 times faster absorption after oral administration, has dose-dependent predictable plasma concentration, and requires a shorter titration period.[2,3] Moreover, there was little rationale in having two drugs with a similar mechanism of action. We disagree with the statement "evidence for dose response from analgesics is tenuous" as some analgesics such as pregabalin have dose-dependent efficacy.[4]

We agree that analgesic "effects are maximal within a few weeks", and indeed in the OPTION-DM trial the drugs were titrated over two weeks both at the start of the mono- and combination- therapy phases. The drugs were not continuously titrated over the 16 weeks. Although the greatest drop in pain scores occur over the first two weeks, trials have shown full treatment effects often require a longer period, and IMMPACT recommends a trial period of at least 12 weeks in most circumstances.[5] We disagree with the assertion "addition of a second drug after 6 weeks of the first, accomplish little more" as there is a further drop of 1 NRS point (37%) at week sixteen, with 14% more participants achieving $\geq$50% pain relief (40%→54%) and 18% greater achievement of NRS $\leq$3 (36%→54%) in those that had sub-optimal response (NRS>3) to a monotherapy.

Patients' global impression was recorded only at the end of each 16-week pathway as the primary endpoint was pain relief at the end of treatment pathways.

Finally, we disagree that "Excluding patients with ischemic heart disease and heart failure, dysrhythmias, or prostatic hyperplasia limits generalizability of this study in older people" as we had a reasonable representation of older people, with mean age of 61 years and it would have been negligent not to have had these exclusions (known contraindications) which has been the case in previous similar trials.[6]

References

1. Tesfaye S, Sloan G, Petrie J, et al. Comparison of amitriptyline supplemented with pregabalin, pregabalin supplemented with amitriptyline, and duloxetine supplemented with pregabalin for the treatment of diabetic peripheral neuropathic pain (OPTIONDM): a multicentre, double-blind, randomised crossover trial. *Lancet* 2022; published online Aug 22. https://doi.org/10.1016/S0140-6736(22)01472-6.

2. Bockbrader, H.N., Wesche, D., Miller, R. *et al.* A Comparison of the Pharmacokinetics and Pharmacodynamics of Pregabalin and Gabapentin. *Clin Pharmacokinet* 2010*;* **49**: 661–669. https://doi.org/10.2165/11536200-000000000-00000
3. Neuropathic pain treatment: Gabapentin, updated in August 2022. https://cks.nice.org.uk/topics/neuropathic-pain-drug-treatment/prescribing-information/gabapentin/ accessed on 25th November 2022.
4. Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. *Diabetes Care*. 2008 Jul;**31(7)**:1448-54. doi: 10.2337/dc07-2105. Epub 2008 Mar 20. PMID: 18356405; PMCID: PMC2453685.
5. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Considerations for improving assay sensitivity in chronic pain clinical trials: IMMPACT recommendations. *Pain* 2012; **153:** 1148–58.
6. Gilron I, Bailey JM, Tu D, Holden RR, Jackson AC, Houlden RL. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: a double-blind, randomised controlled crossover trial. *Lancet* 2009; **374:** 1252–61.