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Contents

Unjustified conclusions

Köhler-Forsberg and coauthors conclude from their findings that 'switching to the other drug resulted in significant improvement in depression scores', and argue for switching as a 'viable approach to achieve response among patients with MDD [major depressive disorder]'.[1] We doubt, however, that the method of the trial allows any such conclusion: It is well established that (a) depression can improve over time due to its episodic course,[2] (b) depression has a large placebo response,[3] and (c) the efficacy of antidepressants grows over time, even after 8 or 12 weeks.[4]

To tease apart possible reasons for improvement, it is necessary to compare, in a randomised setting, patients who switch with a group of patients continuing the antidepressant that has been ineffective so far (continuation arm).[5] In the study by Köhler-Forsberg *et al*, however, the entire group of patients switched to another antidepressant. It is therefore logically impossible to pin down the mechanism leading to the improvement seen in the study: Is it, indeed, because of the switch, to the prolonged treatment with any sort of antidepressant, or simply to the passing of time?

In a recent systematic review and meta-analysis, we found only four studies comparing switch strategies with continuation.[5] Not one of the trials resulted in a statistically significant advantage of switching over continuation with the first antidepressant (summary estimate: statistically non-significant standardised mean difference of –0.17 in favour of continuation (95% CI: –0.59 to 0.26)). One of the four studies, however (reference 11 in the paper by Köhler-Forsberg *et al*), revealed a statistically significant disadvantage for patients in the switch arm. Interestingly, the authors had used similar antidepressants to the study by Köhler-Forsberg *et al*: the primarily noradrenergic tricyclic antidepressant desipramine and the serotonergic selective serotonin reuptake inhibitor citalopram. In conclusion, neither in earlier attempts nor, we believe, in the current investigation, has switch been shown to be a promising option for patients unresponsive to antidepressant treatment.

1 Köhler-Forsberg O, Larsen ER, Buttenschøn HN, Rietschel M, Hauser J, Souery D, et al. Effect of antidepressant switching between nortriptyline and escitalopram after a failed first antidepressant treatment among patients with major depressive disorder. *Br J Psychiatry* 2019; **215**: 494–501.

2 Lehmann HE. Clinical evaluation and natural course of depression. *J Clin Psychiatry* 1983; **44**: 5–10.

3 Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002; **287**: 1840–7.

4 Henssler J, Kurschus M, Franklin J, Bschor T, Baethge C. Trajectories of acute antidepressant efficacy: how long to wait for response? A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. *J Clin Psychiatry* 2018; **79**: 17r11470.

5 Bschor T, Kern H, Henssler J, Baethge C. Switching the antidepressant after nonresponse in adults with major depression: a systematic literature search and meta-analysis. *J Clin Psychiatry* 2018; **79**: 16r10749.

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Authors' reply

We thank Drs Bschor and Baethge for their letter[1] regarding our study on the effect of switching between escitalopram and nortriptyline.[2] Drs Bschor and Baethge have performed important work in the area of switching between antidepressants,[3,4] and we would like to comment on their letter to continue this important discussion.

We agree that depression improves over time and has a large placebo effect, but it has been clearly established that antidepressants have better antidepressant effects compared with placebo.[5] Patients in the GENDEP trial, forming the population for our switching study,[2] were moderately to severely depressed and assessed by a psychiatrist to be in need of antidepressant treatment. Patients were followed at weekly intervals for up to 12 weeks, and the decision of switching between the two antidepressants (i.e. from escitalopram to nortriptyline or vice versa) was based on an overall evaluation of the treatment effects and side-effects and was taken together with the patient.

As emphasised in our discussion[2] and in the letter by Drs Bschor and Baethge, the major limitation of our study was the inability to compare the effect of switching antidepressants with a randomised continuation or placebo arm. Nevertheless, we argue that the strength of GENDEP and hence of our paper was the real-world setting and thus the ability to investigate treatments assigned based on real-world and guideline-based clinical decisions. In GENDEP, patients did not switch because of clearly defined cut-offs or randomisation but based on a decision made by the clinician together with the patient as a result of non-response and/or side-effects. Mostly, it was the combination of missing response and side-effects that led to the switching decision, which also often is the challenge in everyday clinical work.

Hence, although not including a comparison group, our study yields interesting and important clinical knowledge suggesting that switching antidepressant may represent one approach to achieve or continue an antidepressant response. Therefore, we do not agree with Drs Bschor and Baethge that our conclusions are unjustified. The clinical relevance of our findings refers to the challenging but frequent clinical situation of a patient in need of antidepressant treatment, but with the patient experiencing side-effects and/or non-response to the antidepressant. For this situation, our findings suggest that switching to an antidepressant from a different class (in our study between an selective serotonin reuptake inhibitor and a tricyclic antidepressant) may result in (continued) antidepressant response. We agree with Drs Bschor and Baethge that more high-quality randomised clinical trials are needed comparing the effect of switching to continuation or placebo.[3–4] Nevertheless, since antidepressants improve response and remission[5] but rather often are not well tolerated, our findings represent clinical evidence that switching between antidepressants can help to achieve or continue an antidepressant response when treatment with a first antidepressant cannot be continued.

1 Bschor T, Baethge C: Unjustified conclusions. *Br J Psychiatry* 2020; **216**: 345.

2 Köhler-Forsberg O, Larsen ER, Buttenschon HN, Rietschel M, Hauser J, Souery D, et al. Effect of antidepressant switching between nortriptyline and escitalopram after a failed first antidepressant treatment among patients with major depressive disorder. *Br J Psychiatry* 2019; **215**: 494–501.

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3 Bschor T, Kern H, Henssler J, Baethge C. Switching the antidepressant after nonresponse in adults with major depression: a systematic literature search and meta-analysis. *J Clin Psychiatry* 2018; **79**: 16r10749.

4 Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy. *Acta Psychiatr Scand* 2010; **121**: 174–9.

5 Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018; **391**: 1357–66.

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