# Randomized controlled comparison of agomelatine and escitalopram: Concerns about study design and methods

Sir,

Urade *et al*. described a 24-week, randomized, open-label comparison of agomelatine (25–50 mg/day) versus escitalopram (10–20 mg/day) in patients ($n$ = 70) with major depressive disorder. They found that escitalopram had superior antidepressant effects from 6 to 24 weeks and that, during the same period, agomelatine had superior effects on sleep outcomes.[1] We have important concerns about the design and methods of this study:

- When two established antidepressants are compared, it is unrealistic to expect that, if one is superior to the other, the difference in efficacy will be the same as that between active treatment and placebo (e.g., two points on the Hamilton Depression Rating Scale, as proposed by the authors in their statistical methods); hence, basing sample size estimates on such a criterion is flawed and could result in a failure to identify a difference should a difference truly exist. Therefore, the authors should realistically have set a far narrower margin. Furthermore, to conduct such a study without a placebo control could result in a failure to identify true differences between groups because of ceiling or floor effects (e.g. the sample is so responsive that all patients respond equally, regardless of treatment, or the sample is so unresponsive that all patients do not respond), resulting in what is technically known as a failed study. However, it would be unethical to include a placebo arm when comparing two drugs that are already known to be effective. Therefore, the standard approach would be to employ a noninferiority design, which, regrettably, the authors did not do
- What if one drug is truly superior to the other, and by a sizeable margin, as hoped for by the authors in their sample size estimation? In such an event, given the importance of the expectation, a double-blind study ought to have been performed. As the results stand, the conclusion of the authors that escitalopram is superior to agomelatine should be rejected because the findings may merely reflect the *a priori* biases of the investigators.

Both of these considerations could have been anticipated; in other words, this study should not have been designed as it was, nor should it have been approved by the appropriate supervising bodies because the fatal flaws should have been apparent at the outset. Studies that are fundamentally unsound waste time and money, and subject patients to unnecessary inconveniences and risks.

As a final note: If the authors intended to evaluate drug effects on sleep, they should have selected only patients with insomnia because depressed patients may have hypersomnia, rather than insomnia.

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### Conflicts of interest

There are no conflicts of interest.

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