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Antidepressants may work for people with major depression: where do we go from here?

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The publication of our updated network meta-analysis about antidepressants for the acute treatment of major depression[1] has generated a wide discussion in newspapers,[2,3] social media[4] and also scientific journals.[5] Based on 522 trials and more than 116,000 patients, this network meta-analysis of 21 drugs and placebo represents the most comprehensive analysis of the evidence base ever undertaken. We take the opportunity of this commentary not to repeat our findings, but to reflect on the implications of this research and, most importantly, on what needs to be done next to improve the outcome of patients with major depression.

Clinical implications

Antidepressants can be on average an efficacious and acceptable treatment for adults with moderate to severe major depression in the acute phase of illness.[1] However, our analysis is based on aggregate data from the included studies, so it cannot provide information to clinicians and patients about who will respond to which treatment and how well. It is likely that some patients may experience greater benefit, while others may have no benefit. Differences between antidepressants are small on average, but exceptions exist. The average response to placebo – defined as 50% reduction of depressive symptoms over an 8-week period in our analysis – is 35%; by contrast, in the same trials the average response to antidepressants range between 42% (reboxetine) and 53% (amitriptyline).

To be methodologically sound, any systematic review should answer a well-defined, specific question. In our network meta-analysis we specifically addressed the issues of efficacy and acceptability of antidepressants for acutely ill patients because a priority for most people who are acutely unwell is to get better. We are also conducting parallel projects to investigate the profile of specific adverse events for each drug, the dose-response association, the long-term outcomes, treatment-resistant depression and the efficacy/acceptability of non-pharmacological interventions for depression: medicines are not the only effective treatment for major depression. All this

information is needed to guide the shared decision-making process between patients, carers and clinicians. Our network meta-analysis may be only part of the full picture, but it provides the best available evidence to inform clinical practice. Would anybody feel that these data were valueless if we were talking about cancer,[6] hypertension or stroke?

Overall we were impressed by the interest and meticulousness of the media coverage (once one read beyond the headlines), but inevitably some coverage in the media and social platforms was inaccurate (especially an undue focus on the binary and polarising question of clinical significance). People can always manipulate information to fuel controversy and this appears to frequently occur in the stigmatised area of mental health. We firmly believe that the best approach to dealing with stigma and entrenched beliefs is by improving knowledge and understanding about mental disorders. There are some grounds to believe that the large-scale evidence we reported may have helped people overcome resistance to talk in public about major depression and their personal treatment experience. One of the most remarkable phenomena was the powerful upsurge of the patient's voice via the Twitter hashtags #MedsWorkedForMe and #MedsDidntWorkForMe. "*I think seeing people you look up to publicly admitting to their depression and anxiety helps you realise you're not alone and sharing real advice on what works for them — drugs, mental exercises or whatever — is probably one of the most powerful things someone can do*," one Twitter user said.

Where should we move from now?

It took us more than six years to collect all the published and unpublished data included in the analyses. In the spirit of open science and transparency we have made the data freely available.[7] We committed to do this when drafting the review protocol, not only because we would like others to check the robustness and accuracy of our findings, but also because we think that open science provides an opportunity to build the interdisciplinary and collaborative networks that make

optimum use of resources, including secondary analysis of existing datasets. Open science is a hugely promising way to facilitate reproduction and hence the reliability of science, and speed of progress.[8]

The World Health Organization, the Nordic Trial Alliance and the US Institute of Medicine recently called for a transformation of the existing scientific culture to one where "data sharing is the expected norm".[9] Open access to data from clinical trials at the individual patient level is not yet a reality. Such data are indispensable to answer the next, most crucial questions: how much do patients differ in their response and are there predictors of better response in specific patients and with specific drugs? We are confident that once patients' privacy and confidential commercial information are protected, we should be able to do with randomised data what we can already do with observational data from national registries.[10]

While new methods of synthesizing evidence are developed to support timely decision making,[11] new barriers, including national data protection laws or controlled access to trial data, need to be tackled soon and internationally. Some pharmaceutical companies and study authors are already able to share individual patient data: this means that it must be possible to do more generally. If the substantial incentives of open science are not strong enough to motivate action, then it will need to be made mandatory. Funders, regulatory agencies and scientific journals should support this and could play an active role in facilitating the process. Access to individual patient data makes it possible to carry out individual patient data network meta-analyses.[12] We believe this should be the next step. This approach would be a powerful step towards enabling personalised treatment in psychiatry. Of course, we also need better treatments for depression. Access to all the current data will get us so far, but we also need treatments which, whether pharmacological or non-pharmacological, are more precisely targeted at mechanism and better tolerated.

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