Weighing up the benefits of antidepressant drugs

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The systematic review and network meta-analysis of the efficacy of 21 antidepressants by Andrea Cipriani and colleagues has been hailed as a major contribution to the body of evidence that supports the use of these drugs in managing major depressive disorder. This article summarises the review’s findings and their implications for practice.

Almost half of ill health is attributable to mental illness among people under 65 years of age in the UK. Depression is a leading cause of disability and ill health. According to the World Health Organization (WHO), it affects more than 300 million people of all ages worldwide. Indeed, the number of people living with depression increased by 18% in the 10 years from 2005 to 2015. According to the Organisation for Economic Co-operation and Development (OECD), the UK ranks seventh out of 25 countries in Europe for the number of adults reporting they have depression (10% of those aged 25–64 years).

Perhaps not surprising then that the number of prescriptions for antidepressant drugs dispensed on FP10 in England has risen by more than 100% to 64,703,568 in the years from 2006 to 2016. The five most frequently dispensed antidepressants in the community in England in 2016 were: citalopram, amitriptyline, sertraline, mirtazapine and fluoxetine. Even so, the authors of the Centre for Economic Performance’s report (albeit published in 2012) commented: “It is a real scandal that we have 6,000,000 people with depression or crippling anxiety conditions and 700,000 children with problem behaviours, anxiety or depression. Yet three-quarters of each group get no treatment.”

The King’s Fund noted that the Health and Social Care Act 2012 created a new legal responsibility for the NHS to deliver “parity of esteem” between mental and physical health, and the government pledged to achieve that by 2020, following on from the launch of a new mental health strategy ‘No health without mental health’ in 2011. And yet mental health problems account for 23% of the burden of disease in the UK but spending on mental health services accounts for only 11% of the NHS budget.

So, there can be little doubt that depression poses a significant health and social burden. It also engenders significant risk to individuals; as well as their ongoing symptoms, people with depression are at an increased risk of suicide.
Indeed, affective disorders are among the most common diagnoses (32–47%) in patients who die by suicide who were in contact with mental health services within 12 months of their death.7

New data confirming the efficacy of antidepressants is therefore welcome, as these drugs form a key part of clinicians’ armamentarium to help people with depression, whose lives are impacted by sadness, a lack of interest in enjoyable activities and general inability to carry on with daily life as they try to deal with disturbed sleep, feelings of low self-worth, poor concentration and even medically unexplained symptoms.2

A comprehensive evidence base

The recent systematic review and network meta-analysis by Cipriani et al. of 522 double-blind, randomised controlled trials carried out between 1979 and 2016 confirms the efficacy of 21 antidepressants evaluated as oral monotherapy compared with placebo in adults with major depressive disorder.8 In all, 421 trials from the database search, 86 unpublished studies from trial registries and pharmaceutical company websites, and 15 studies from personal communication or hand-searching other review articles were included in the analysis. The authors say the analysis included the “largest amount of unpublished data to date, which are associated with less favourable effect sizes for antidepressants”. While acknowledging there are limitations to the work (often outside the authors’ control because of, for example, lack of information provided in the trial reports themselves), the researchers claim the work represents “the most comprehensive currently available evidence base to guide the initial choice about pharmacological treatment for acute major depressive disorder in adults”.

The mean age of the men and women in the studies analysed was 44 years, and 62.3% of the sample population were women. Studies in the analysis included 116,477 participants (87,052 received active drug and 29,425 were given placebo). Most of the patients had moderate to severe depression (mean reported baseline severity score on the Hamilton Depression Rating Scale 17-item was 25.7 [SD 3.97] among 464 [89%] of 522 studies). Patients received acute treatment for a median of eight weeks.

The analysis revealed that all antidepressants were more effective than placebo, with odds ratios (ORs) ranging between 2.13 (95% credible interval [Crl] 1.89–2.41) for amitriptyline and 1.37 (1.16–1.63) for reboxetine. Agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were found to be more effective than other antidepressants (ORs ranging from 1.19 to 1.96) in head-to-head studies (see Table 1). Least efficacious were: fluoxetine, fluvoxamine, reboxetine and trazodone (ORs 0.51–0.84). The authors note, however, that the efficacy in children and adolescents is different, with fluoxetine “probably the only antidepressant that might reduce depressive symptoms”.

The proportion of patients discontinuing treatment for any reason (a measure of acceptability that encompasses efficacy and tolerability) was lowest with agomelatine, citalopram, escitalopram, fluoxetine, sertraline and vortioxetine, and highest for amitriptyline, cimipramine, duloxetine, fluvoxamine, reboxetine, trazodone and venlafaxine (see Table 2).

Interpreting the findings

Writing in the same issue of The Lancet in which the Cipriani analysis was published, Parikh and Kennedy comment that taking efficacy and acceptability together, agomelatine, escitalopram and vortioxetine might be seen as first-line choices, while clinicians might consider avoiding fluvoxamine, reboxetine and trazodone initially, in favour of other more “efficacious” drugs. They add that there might also be a case for amitriptyline and venlafaxine to be used first-line based on their efficacy in response to more severe depression or other patient characteristics.9

It is encouraging to see that the research team comments that pharmaceutical company funding of trials was not associated with substantial differences in terms of response or dropout rates, although they note that there were few non-industry funded trials and in many cases, funding was not reported. Interestingly, drug efficacy seemed to be better for novel drugs used experimentally than when they had been available for some time. The researchers thought this may be a result of new drugs being perceived as more effective and better tolerated. Another explanation could be that “selective analyses and outcome reporting bias might be more prominent when a treatment is first launched”, they comment.

While this latest analysis is welcome, it cannot, of course, answer all the clinical questions a GP will face when an individual patient presents with depression. As Parikh and Kennedy point out, even the most basic question, namely which is the most effective antidepressant to prescribe for a specific patient, is not fully answered because current research techniques cannot determine how effective a drug will be in any one individual. Parikh and Kennedy note that combining clinical diagnosis with neuroimaging to identify “neurophysiological biotypes” may be helpful in predicting response. They also comment that the analysis’ focus on outcomes at eight weeks still leaves the question of what the antidepressants’ long-term effects will be, in particular in terms of functional outcomes. However, they acknowledge the major contribution to our knowledge of antidepressants made by the analysis, “which is relevant to healthcare economists and policy makers, clinicians, and patients”.

<table>
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<tr>
<th>Most effective antidepressants</th>
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<th>Table 1. Summary of antidepressant efficacies in adults, according to the meta-analysis by Cipriani et al.8</th>
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<tr>
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<td>Amitriptyline</td>
<td>Escitalopram</td>
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<td>Vortioxetine</td>
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<td>Least effective antidepressants*</td>
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is not clear, evidence is emerging that points to some of the risks drugs such as amitriptyline may pose in later life. For example, a recent analysis of UK general practice data for 40,770 patients aged 66–99 years with a recorded diagnosis of dementia looked at the use of drugs with significant anticholinergic activity (including tricyclic antidepressants such as amitriptyline) and the risk of dementia, up to 20 years before a diagnosis was made. The study authors concede that the association they found between anticholinergic drug use and increased risk of dementia is moderate (an OR of 1.19 for antidepressant use, for example) but the overall incidence of dementia means the risk for patients is appreciable.

It should also be remembered that managing depressive symptoms is not all about drugs. As NICE reminds us, people with mild symptoms should be offered non-pharmacological interventions such as low-intensity psychological interventions or group cognitive behavioural therapy (CBT) first. Indeed, in response to the publication of the Cipriani paper, mental health charity MIND said: “Giving people a choice of treatments is key, whether that’s drugs, talking therapies, alternatives such as arts therapy or exercise, or a combination of some or all of these. Someone managing their mental health problems should be treated as a whole person and they should be able to access whatever treatment, or combination of treatments, works best for them.” And that underlines the importance of involving patients in decision-making where treatment is concerned – it is only the individual themselves who can know what is more important to them in terms of the balance between efficacy and tolerability.

**Conclusion**

The Cipriani analysis adds to the body of evidence clinicians can rely on to help them navigate the wide range of therapy choices available to people who have depression. Questions still remain, of course, but some aspects of mental illness and its management are becoming clearer.

For example, depression is common: according to the Adult Psychiatric Morbidity Survey (APMS) conducted by NatCen Social Research, in collaboration with the University of Leicester, for NHS Digital, around one in six adults (17%) surveyed in England met the criteria for a common mental disorder in 2014. A similar percentage (18%) had some evidence indicating depression or anxiety based on the General Health Questionnaire (GHQ). In 2014, over a third (39%) of adults aged 16–74 years with conditions such as anxiety or depression, surveyed in England, were accessing mental health treatment – up from the one in four (24%) identified when the previous survey was carried out in 2007.

Depression is associated with significant morbidity, but with the right help and support it is often manageable. Cipriani et al.’s review provides further guidance on the use of antidepressants as an effective strategy for managing depressive symptoms.

In the final analysis, though, it is still about the patients and endeavouring to find what will bring them the greatest benefit when trying to tame the ‘black dog’. As Guardian editor Mark Rice-Oxley eloquently pointed out when commenting on the Cipriani paper: “…the millions of people (including me) who take them – reluctantly, sceptically, hopefully – can continue to do so without feeling guilt, shame or doubt about the course of treatment.”

**References**


Declaration of interests
None to declare.

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