Antidepressants in unipolar major depression: what we need to know

Depression is a common condition, with estimates of lifetime risk varying from 10 to 30% depending on the study. The mainstay of treatment is antidepressants. It is vital that hospital doctors understand the evidence base for pharmacological interventions in depression, as they increasingly encounter patients who have taken or are taking antidepressants. Moreover, depression is associated with longer lengths of stay in hospital and poorer outcomes (Prina et al, 2012). This editorial presents the best available evidence to answer four questions of clinical relevance with respect to unipolar, non-treatment resistant, acute major depression:

1. Do antidepressants work?
2. Who should be treated?
3. Which, if any, is the best antidepressant to prescribe?
4. For how long should antidepressants be continued?

Do antidepressants work?

In the past 30 years many drugs have been approved for the treatment of major depression. Notwithstanding this and the rise in use of antidepressants, there is still a long-lasting debate in psychiatry as to whether antidepressants have any real clinical benefit over placebo (Cipriani and Geddes, 2014). On average, 50–60% of adults in trials respond to antidepressants and about 30–40% respond to placebo, but the difference between drug and placebo decreases when unpublished data are included (Barbui et al, 2008).

Some argue that unblinding as a result of adverse effects leads to an increased effect in the drug group, overestimating the efficacy of antidepressants. If this were the case, one would expect that trials showing larger differences in adverse events between drug and placebo would show larger differences in efficacy, but a meta-analysis by Barth et al (2016) failed to demonstrate this. These findings were consistent across different efficacy outcomes and statistical methods. However, because of the fundamental methodological challenges inherent to placebo-controlled study design, these results should be interpreted with caution and considered only as preliminary evidence.

Who should be treated?

Antidepressants work 'on average' for people with unipolar major depression, which means that they may be effective for some patients but not others. There are clinical moderators of response to treatment, for instance, the baseline severity of illness.

The routine use of antidepressants is not recommended to treat subthreshold depressive symptoms or major depression of mild severity (see *Table 1* for definitions), on the basis of the results from a meta-analysis which included only patients with so-called minor depression and found no significant difference in efficacy or acceptability between placebo and antidepressants (Barbui et al, 2011). Despite some limitations, such as the short follow-up duration and incomplete outcome assessment in the included studies, these results make it difficult to justify the prescription of antidepressants, with all their side effects, to patients with milder illness.

Which antidepressant should be used?

It is easy to think of antidepressants as classes of drugs, which have similar efficacy and acceptability. This is the position adopted by current international guidelines, which conclude there is little difference in efficacy between individual drugs. This view is supported by one meta-analysis (Gartlehner et al, 2011), but is contradicted by a network meta-analysis (Cipriani et al, 2009), which used a multiple-treatments meta-analysis technique, allowing for direct and indirect comparisons between antidepressants included in the systematic review (Mavridis et al, 2015). Both found statistically significant differences between treatments, but the conclusions widely differed.

The clinical interpretation of study findings may vary and it is worth remembering that the practice of evidence-based medicine implies the integration of the best available research data with individual clinical expertise and patients' preferences

Table 1. Definitions of depression as reported in the National Institute for Health and Care Excellence (2009) guidelines*

Category	Definition
Subthreshold depressive symptoms or 'minor' depression	Fewer than five symptoms of depression
Mild depression	Few, if any, symptoms in excess of the five required to make the diagnosis, and symptoms result in only minor functional impairment
Moderate depression	Symptoms or functional impairment are between 'mild' and 'severe'
Severe depression	Most symptoms, and the symptoms markedly interfere with functioning. Can occur with or without psychotic symptoms

**These guidelines are based on DSM-IV criteria, where the distinction between mild, moderate and severe depression depends on the degree functional impairment, as shown above. In the ICD-10, however, the criteria depend on the number of symptoms, with a lower threshold for mild depression (four symptoms), and five or six, and seven or more symptoms required for moderate and severe depression respectively.*

Miss Sarah Barber is Medical Student, University of Oxford, Oxford

Professor Andrea Cipriani is Associate Professor in the Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX

Correspondence to: Professor A Cipriani (andrea.cipriani@psych.ox.ac.uk)

and values. Evidence-based practice is not 'cookbook' medicine and, similarly, ranking antidepressants is not intended to provide clinicians and patients with a list of drugs to mechanically scroll down from top to bottom. Cipriani et al (2009) challenged the standard thinking that most antidepressants are of similar average efficacy and tolerability, and even when significant differences were observed between drugs these tended to be minimized and considered clinically insignificant (Gartlehner et al, 2011). This may be a comfortable position for industry as it sets a low threshold for the introduction of new agents which can then be marketed on the basis of small differences in specific adverse effects rather than on clear advantages in terms of overall average efficacy and acceptability (Geddes and Cipriani, 2015).

Nonetheless, accumulating evidence suggests that antidepressants may vary not only in their efficacy and acceptability, but also in terms of hard outcome measures, e.g. the risk of suicide (Stone et al, 2009). Efficacy is not the sole consideration when choosing a drug – tolerability must always be taken into account. The National Institute for Health and Care Excellence recommends selective serotonin-reuptake inhibitors as first line on the basis of their superior side-effect profile to other antidepressants. In particular, selective serotonin-reuptake inhibitors are safer in overdose and along with the other second-generation antidepressants are associated with less drowsiness and anticholinergic side effects than tricyclics and monoamine oxidase inhibitors.

Is there any evidence of differences in tolerability between second-generation antidepressants? Future studies should specifically address this using a comparative statistical technique (like a network meta-analysis); however, this is difficult to do because adverse events are not collected systematically in randomized controlled trials, with a high risk of selective reporting bias.

For how long should antidepressants be continued?

Over half of people with major depression will have more than one episode, with each further episode increasing the risk of relapse. However, continuing antidepressant treatment over 6 months to 3 years can reduce the risk of relapse up to more than 50%. Some researchers argued that switching to placebo increases the risk of withdrawal symptoms that mimic a relapse, thereby over-estimating the benefit of medication. However, a meta-analysis of six trials of selective serotonin-reuptake inhibitors *vs* placebo, with no discontinuation design but longer follow up, demonstrated an advantage of active medication over placebo at 6 months (Deshauer et al, 2008). Current National Institute for Health and Care Excellence guidelines recommend continuing treatment for a minimum of 6 months, but 2 years if there is a high risk of relapse. Of course, it is the patient who, with the psychiatrist or GP, will ultimately decide if the benefit outweighs the potential harms of side effects.

Conclusions

This editorial has considered four key 'pragmatic' questions, which are at the centre of the debate in the scientific literature about antidepressants in the treatment of unipolar, non-resistant major depression. It is clear that these questions cannot be considered in isolation. For example, we cannot answer the question 'do antidepressants work?' without knowing for who, for how long, and – potentially most importantly – which drug? While relevant meta-analyses consistently found statistically significant differences between drugs in terms of efficacy and acceptability, there is remains no agreement as to what constitutes a clinically significant effect for the patient. Methodological development of evidence synthesis can probably help overcome this uncertainty (Cipriani et al, 2013). Future network meta-analyses should incorporate as many drugs as possible (old and new antidepressants, together with placebo), in order to better inform clinical practice, and not only in developed countries (Furukawa et al, 2016). **BJHM**

KEY POINTS

- Antidepressants are widely used, but there is still debate in the literature over their clinical benefit.
- Antidepressants are not recommended routinely for patients with mild depression.
- There appear to be material differences in terms of efficacy and tolerability between different antidepressants, which can be clinically significant.
- To reduce the risk of relapse, antidepressants should be continued for at least 6 months after an acute episode.

Barbui C, Furukawa TA, Cipriani A (2008) Effectiveness of paroxetine in the treatment of acute major depression in adults: a systematic re-examination of published and unpublished data from randomized trials. *CMAJ* **178**(3): 296–305 (doi: 10.1503/cmaj.070693)

Barbui C, Cipriani A, Patel V, Ayuso-Mateos JL, van Ommeren M (2011) Efficacy of antidepressants and benzodiazepines in minor depression: systematic review and meta-analysis. *Br J Psychiatry* **198**(1): 11–16 (doi: 10.1192/bjp.bp.109.076448)

Barth M, Kriston L, Klostermann S, Barbui C, Cipriani A, Linde K (2016) Efficacy of selective serotonin reuptake inhibitors and adverse events: meta-regression and mediation analysis of placebo-controlled trials. *Br J Psychiatry* **208**(2): 114–19 (doi: 10.1192/bjp.bp.114.150136)

Cipriani A, Furukawa TA, Salanti G et al (2009) Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. *Lancet* **373**(9665): 746–58 (doi: 10.1016/S0140-6736(09)60046-5)

Cipriani A, Geddes JR (2014) Placebo for depression: we need to improve the quality of scientific information but also reject too simplistic approaches or ideological nihilism. *BMC Medicine* **12**: 105 (doi: 10.1186/1741-7015-12-105)

Cipriani A, Higgins JPT, Geddes JR, Salanti G (2013) Conceptual and technical challenges in network meta-analysis. *Ann Intern Med* **159**(2): 130–7 (doi: 10.7326/0003-4819-159-2-201307160-00008)

Deshauer D, Moher D, Fergusson D, Moher E, Sampson M, Grimshaw J (2008) Selective serotonin reuptake inhibitors for unipolar depression: a systematic review of classic long-term randomized controlled trials. *CMAJ* **178**(10): 1293–301 (doi: 10.1503/cmaj.071068)

Furukawa TA, Salanti G, Atkinson LZ et al (2016) Comparative efficacy and acceptability of first- and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. *BMJ Open* (in press)

Gartlehner G, Hansen RA, Morgan LC et al (2011) Comparative benefits and harms of second-generation antidepressants for treating major depressive disorder: an updated meta-analysis. *Ann Intern Med* **155**(11): 772–85 (doi: 10.7326/0003-4819-155-11-201112060-00009)

Geddes JR, Cipriani A (2015) Time to abandon placebo control in pivotal phase III trials? *World Psychiatry* **14**(3): 306–7 (doi: 10.1002/wps.20246)

Mavridis D, Giannatsi M, Cipriani A, Salanti G (2015) A primer on network meta-analysis with emphasis on mental health. *Evid Based Ment Health* **18**(2): 40–6 (doi: 10.1136/eb-2015-102088)

National Institute for Health and Clinical Excellence (2009) Depression in adults: recognition and management. Clinical guideline 90. http://guidance.nice.org.uk/CG90 (accessed 29 June 2016)

Prina AM, Deeg D, Brayne C, Beekman A, Huisman M (2012) The association between depressive symptoms and non-psychiatric hospitalisation in older adults. *PloS One* **7**(4): e34821 (doi: 10.1371/journal.pone.0034821)

Stone M, Laughren T, Jones ML et al (2009) Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. *BMJ* **339**: b2880 (doi: 10.1136/bmj.b2880)