

# The unfulfilled promise of the antidepressant medications

“An unfortunate nexus has developed between the diagnosis of depression of any severity and the reflexive prescription of medications as monotherapy”

We need more effective treatments for depression, because current treatments avert less than half of the considerable burden caused by the illness.<sup>1</sup> Antidepressants are the most commonly used medications, taken by 10% of adult Australians each day, and at a rate that has more than doubled since 2000 to be among the highest in the world.<sup>2</sup> Two broad forces have been argued to have driven this trend — in Australia, as in other economically developed countries. First was the broadening of the diagnostic concept of depression with publication of the *Diagnostic and statistical manual of mental disorders*, third edition (DSM-III) in 1980. Previously, depressive illness was considered to have two subtypes — a “neurotic” illness that responded to psychological therapies and a rarer melancholic depression that had a biological cause and responded to medications. But starting with the DSM-III, the distinction was dropped and the categories were collapsed into the broader “major depressive disorder”. This was followed shortly afterwards by the release of the first selective serotonin reuptake inhibitors (SSRIs) — the short-lived zimelidine in 1982, and then fluoxetine in 1986 — and the ensuing cultural phenomenon that encouraged us to think of depression as resulting from a chemical imbalance that could be corrected with medication. Evidence for depression being caused by a serotonin deficiency is inconclusive and contested.<sup>3</sup>

The use of antidepressants has continued to rise despite accumulating evidence that they are not as effective as was previously thought. Recent meta-analyses show a modest overall effect size of about 0.3 (although it is larger in severe depression compared with mild depression).<sup>4</sup> The overall effect size, while modest, is similar to that of other treatments in medicine: of similar magnitude, for example, to corticosteroids for chronic obstructive pulmonary disease.<sup>5</sup> Earlier studies had reported much larger effect sizes for the medications, in part driven by the influences of the pharmaceutical industry on selective publishing of positive results, and the substitution of outcome measures to report ambiguous findings as positive.<sup>6</sup> Revelations of these publication strategies have done significant damage to the reputation of the medications and to the pharmaceutical companies who make and market them.<sup>7</sup>

Antidepressant use in children and adolescents has increased over the past two decades in the same way as it has for the population in general,<sup>8</sup> and similarly, meta-analyses of their use in this group have shown smaller effect sizes than had previously been reported.<sup>9</sup> Reanalysis of previously published trial data has shown how it was manipulated to inflate the effectiveness of the medications — by substituting pre-specified outcome measures with those more favourable to the trial medications.<sup>10</sup> However, just as significantly, meta-analytic

## Summary

- Australia has one of the highest rates of antidepressant use in the world; it has more than doubled since 2000, despite evidence showing that the effectiveness of these medications is lower than previously thought.
- An increasing placebo response rate is a key reason for falling effectiveness, with the gap between response to medications and placebo narrowing.
- Psychotherapies are effective treatments, but recent evidence from high-quality studies suggests that their effectiveness is also modest.
- Combined treatment with medication and psychotherapy provides greater effectiveness than either alone.
- The number of patients receiving psychotherapy had been declining, although this trend is probably reversing with the Medicare Better Access to Mental Health Care initiative.
- Antidepressant medications still have an important role in the treatment of moderate to severe depression; they should be provided as part of an overall treatment plan that includes psychotherapy and lifestyle strategies to improve diet and increase exercise.
- When medications are prescribed, they should be used in a way that maximises their chance of effectiveness.

approaches have confirmed what had previously been suspected clinically: that antidepressants can induce an increase in suicidal thoughts and behaviours (although not completed suicides) in some young patients.<sup>9</sup> A recent study reported that antidepressants can also cause an increase in aggressive behaviour in children and adolescents.<sup>11</sup> Both problems are likely to be mediated by the capacity of antidepressants to cause increased agitation in some young people. Although these problems are not common (the number needed to treat for antidepressants in youth depression is 10, while the number needed to harm, in terms of increased suicidal thoughts and behaviours, is 112<sup>9</sup>), they should be considered when assessing the potential benefits and risks of using these medications in young patients.

## The increasing power of placebos

Much effort has gone into delineating the reasons for the apparent falling effectiveness of antidepressants. There are likely to be multiple reasons, including the unearthing of unpublished negative trial results for inclusion in meta-analyses, thereby diluting the positive outcomes from published studies,<sup>6</sup> and the inclusion of more “real

**Christopher G Davey**  
MB BS(Hons), PhD,  
FRANZCP<sup>1,2</sup>

**Andrew M Chanen**  
MB BS(Hons), PhD,  
FRANZCP<sup>1,2</sup>

<sup>1</sup>Orygen, The National Centre of Excellence in Youth Mental Health, Melbourne, VIC.

<sup>2</sup>University of Melbourne, Melbourne, VIC.

c.davey@  
unimelb.edu.au

doi: 10.5694/mja16.00194

**Podcast** with Dr Chris Davey available at [www.mja.com.au/multimedia/podcasts](http://www.mja.com.au/multimedia/podcasts). More coverage of this issue at [www.mja.com.au/insight](http://www.mja.com.au/insight).

world" patients (those with comorbid conditions and clinical complexity) in effectiveness trials. Perhaps the culprit given most attention, however, is the increasing rate of response to placebo, which is particularly high in young people. The proportion of patients responding to placebo has increased steadily over the past two decades, leading to a narrowing of the gap between response to medication and placebo.<sup>12</sup> The placebo response is a complicated phenomenon. In part, it is driven by a positive expectation bias, but it also illustrates the statistical concept of regression to the mean, whereby patients with depressive symptoms at baseline tend to recover over time irrespective of treatment.

Why should these properties of the placebo be becoming more powerful? It is not clear. One hypothesis is that since the broadening of the diagnostic criteria for depression in the DSM-III, patients with less severe symptoms have been enrolled in treatment trials, and such patients are more susceptible to the placebo response. While there is some evidence for this,<sup>4</sup> an analysis of severity cut-offs for study entry showed that where these were higher (ie, when depression had to be more severe for patients to be included), the placebo response rate was even greater.<sup>13</sup> An alternative explanation is that patients in more recent trials have had a greater expectation that they will get better with medication: the placebo response rate is greatest in trials when the chance of receiving placebo is low (ie, in multi-arm trials), and lowest in two-arm trials when the chance is high, lending weight to this theory.<sup>14</sup> The factors behind the increasing rate of response to placebo, and consequent decreasing effectiveness of medications, are evidently complicated.

### Modest effect sizes are not confined to antidepressants

Despite these concerns, antidepressant medications are effective, even if only modestly so. Other treatments for depression are also effective, although the most studied of these — the psychotherapies — also have evidence of declining effectiveness in more recently published trials.<sup>15</sup> Two particular psychotherapies have the most favourable evidence: cognitive behavioural therapy (CBT) and interpersonal psychotherapy (IPT). Both are structured, time-limited therapies that directly address the core features of depression. While both psychotherapies are effective, meta-analyses have shown that early studies reported inflated effect sizes.<sup>16,17</sup> The reasons for this are clearer for psychotherapies than for medications. Many psychotherapy trials, especially those conducted earlier, adopted low-quality methods that were biased towards overestimating the interventions' effects. Many therapy trials enrolled non-clinical participants (previously undiagnosed patients who scored above a threshold on a rating instrument), used non-active control conditions (eg, patients on a waiting list), analysed only participants who had completed treatment (rather than using the more rigorous intention-to-treat principle), or did not use blinded assessors.<sup>16,17</sup> The effect size of high-quality psychotherapy trials ( $d = 0.2$ )

is, consequently, less than a third of the effect size for low-quality trials ( $d = 0.7$ ), and similar in magnitude to the effect size for antidepressants.<sup>17</sup>

There has been a recent focus on exercise and diet as potential interventions. While it is clear that exercise and healthy eating are associated with good mental health, it is less clear that they are effective interventions for depression.<sup>18,19</sup> One reason for this is that adherence to exercise and diet plans is often insufficient to produce improvement,<sup>19</sup> and even when they are adhered to, the effect sizes for such non-specific interventions are unlikely to be large. While there is yet insufficient evidence to suggest that exercise and dietary interventions can be effective as stand-alone treatments, they are still worth pursuing as adjunctive treatments — and the evidence suggests that clinicians do not recommend them often enough.<sup>20</sup>

### Combined treatments

The modest effect sizes for depression treatments — and there are no well-studied treatments for depression that have large effect sizes — suggest that combining treatments might provide the best outcomes for patients. The combination of psychotherapy and medication is more effective than either alone. In adults, the effect of combined treatment compared with placebo is about twice that of medication only compared with placebo.<sup>21</sup> Combined treatment also seems to be more effective in children and adolescents,<sup>22</sup> although there have been fewer studies in these groups. The effects of psychotherapy and medication appear to operate independently of each other,<sup>21</sup> providing a good rationale for their combination.

Despite the evidence of superior effectiveness for combined treatments, recent reports suggest that psychotherapy is being offered less rather than more often, at least in the United States. In the decade from 1998 to 2007, the percentage of adult patients with depression who were treated with psychotherapy declined from 54% to 43%.<sup>23</sup> A similar decline was noted in children and adolescents, although more recent evidence suggests that this has been reversed with the increasing concerns about the safety of medications.<sup>8</sup> In Australia, while we have clear evidence that the rate of antidepressant use is increasing, we lack comparable data for the use of psychotherapy. There are some promising signs that it is becoming easier to access psychotherapy. The federal government's Better Access to Mental Health Care scheme was introduced in 2006, and allows general practitioners to refer depressed patients to qualified therapists for up to ten sessions of Medicare-funded treatment. It has led to significant uptake and is helping to reverse the trend,<sup>24</sup> albeit with demographic distortions in the groups who access the scheme. The uptake of psychotherapy is disproportionately higher in wealthier suburbs, and lowest in outer suburban and regional communities where rates of depression are highest.<sup>24</sup> And although the gender gap is narrowing, use of

psychotherapy is still disproportionately higher among women.<sup>25</sup> While there is evidence that access to therapy is improving, we are yet to see whether this is translating into a reduction in the prevalence of depression.

An unfortunate nexus has developed between the diagnosis of depression of any severity and the reflexive prescription of medications as monotherapy, for which the medical profession must accept some responsibility. There is a long tradition of medical psychotherapy — important psychotherapies were developed by medical practitioners such as Sigmund Freud, Aaron Beck (CBT), and Gerald Klerman (IPT) — that seems to be in decline. Fewer doctors now have the expertise to deliver psychotherapy, the teaching of which has been de-emphasised in psychiatry training,<sup>26</sup> and psychotherapy is now largely the domain of psychologists, social workers, and other health professionals. This appears to have had the effect of encouraging psychiatrists and other doctors to consider medication, which is their area of expertise, rather than psychotherapy as the first-line treatment for depression.

### Future directions

The pharmaceutical industry has scaled back investment in developing new drugs for mental illnesses, mainly because of so many development failures,<sup>27</sup> and it is unlikely that we will see new medications with substantially greater effectiveness in the coming years. The psychotherapies too have their limitations, and while they can be made more available, it is unlikely that new forms of psychotherapy will be developed that will have substantially greater effectiveness than existing therapies.

Some psychiatrists and researchers argue that reinstating melancholia as an illness, separate from neurotic depression, provides a solution to refining treatments.<sup>28</sup> They argue that melancholic depression shows a distinct and selective response to antidepressant medications. Differentiating the illness subtypes, however, was never as clear in practice as some now argue. Australian psychiatrist, Sir Aubrey Lewis, pointed out in 1934 that the separation between the two was arbitrary — “a setting up of types or ideal forms, a concession to the requirements of convenient thinking in categories”<sup>29</sup> — with most patients showing aspects of both. The belief that melancholia responds much better to medications has also not been reliably confirmed. A recent large study could find no difference in medication response between those with and without melancholic symptoms.<sup>30</sup>

Major depressive disorder is undoubtedly a heterogeneous disorder, and clearer distinctions between subtypes would make it easier to target treatments, but there is little at present to guide us as to how best to make such

divisions. There is, however, a significant research effort aimed at characterising treatment biomarkers — genetic, brain imaging and neuropsychological parameters that might predict a patient's response to particular treatments. With no likelihood that significantly better treatments for depression will emerge in the near future, better targeting of existing treatments towards patients who are most likely to respond to them is probably our best hope for improving treatment outcomes.

### Treatment recommendations

While recent evidence might have tempered the initial enthusiasm for antidepressants, these agents still have a role in treating depression. Some patients show particularly strong responses to the medications<sup>31</sup> (although we are not reliably able to predict who they will be), and there is good evidence that antidepressants are effective in preventing relapse of depression.<sup>32</sup> The task for medical practitioners now is to place antidepressant medications in an overall treatment framework.

All patients should be offered psychotherapy where it is available, and medication should be considered if

- the depression is of at least moderate severity;
- psychotherapy is refused; or
- psychotherapy has not been effective.

When medications are prescribed, they should be used in a way that maximises their chance of effectiveness. The dose should be increased if there has been no improvement after 4 to 6 weeks. The medication should be changed if there has been no improvement after a subsequent 6 weeks. Usually, the medication should be changed to another within the same class in the first instance (eg, from an SSRI to an alternative SSRI), and to an antidepressant of an alternative class (eg, from an SSRI to a serotonin-noradrenaline reuptake inhibitor, such as venlafaxine) if a second change is required. If this strategy is ineffective, more expert guidance is indicated: this might include considering augmentation strategies, such as lithium, or the use of neurostimulation (electroconvulsive therapy and transcranial magnetic stimulation).<sup>33</sup> At all stages, therapy with ineffective medications should be ceased and unnecessary polypharmacy avoided. Alongside these treatment strategies, we should continue to recommend and encourage good eating and exercise, both of which are likely to help engender a healthy mind and a healthy body.

**Competing interests:** No relevant disclosures.

**Provenance:** Commissioned; externally peer reviewed. ■

© 2016 AMPCo Pty Ltd. Produced with Elsevier B.V. All rights reserved.

References are available online at [www.mja.com.au](http://www.mja.com.au).

- 1 Andrews G, Sanderson K, Corry J, Lapsley HM. Using epidemiological data to model efficiency in reducing the burden of depression. *J Ment Health Policy Econ* 2000; 3: 175-186.
- 2 Organisation of Economic Co-operation and Development. Pharmaceutical market, 2016. <http://dx.doi.org/10.1787/data-00545-en> (accessed Feb 2016).
- 3 Lacasse JR, Leo J. Serotonin and depression: a disconnect between the advertisements and the scientific literature. *PLoS Med* 2005; 2: e392.
- 4 Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. *PLoS Med* 2008; 5: e45.
- 5 Leucht S, Hierl S, Kissling W, et al. Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. *Br J Psychiatry* 2012; 200: 97-106.
- 6 Turner EH, Matthews AM, Linardatos E, et al. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008; 358: 252-260.
- 7 Kessel M. Restoring the pharmaceutical industry's reputation. *Nat Biotechnol* 2014; 32: 983-990.
- 8 Olfson M, Blanco C, Wang S, et al. National trends in the mental health care of children, adolescents, and adults by office-based physicians. *JAMA Psychiatry* 2014; 71: 81-90.
- 9 Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA* 2007; 297: 1683-1696.
- 10 Le Noury J, Nardo JM, Healy D, et al. Restoring Study 329: efficacy and harms of paroxetine and imipramine in treatment of major depression in adolescence. *BMJ* 2015; 351: h4320.
- 11 Sharma T, Guski LS, Freund N, Göttsche PC. Suicidality and aggression during antidepressant treatment: systematic review and meta-analyses based on clinical study reports. *BMJ* 2016; 352: i65.
- 12 Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA* 2002; 287: 1840-1847.
- 13 Khan A, Schwartz K, Kolts RL, et al. Relationship between depression severity entry criteria and antidepressant clinical trial outcomes. *Biol Psychiatry* 2007; 62: 65-71.
- 14 Sinyor M, Levitt AJ, Cheung AH, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. *J Clin Psychiatry* 2010; 71: 270-279.
- 15 Johnsen TJ, Friborg O. The effects of cognitive behavioral therapy as an anti-depressive treatment is falling: a meta-analysis. *Psychol Bull* 2015; 141: 747-768.
- 16 Klein JB, Jacobs RH, Reinecke MA. Cognitive-behavioral therapy for adolescent depression: a meta-analytic investigation of changes in effect-size estimates. *J Am Acad Child Adolesc Psychiatry* 2007; 46: 1403-1413.
- 17 Cuijpers P, van Straten A, Bohlmeijer E, et al. The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol Med* 2010; 40: 211-223.
- 18 Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public Health Nutr* 2015; 18: 2074-2093.
- 19 Krogh J, Nordentoft M, Sterne JA, Lawlor DA. The effect of exercise in clinically depressed adults: systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2011; 72: 529-538.
- 20 Jacka FN, Berk M. Depression, diet and exercise. *Med J Aust* 2012; 1: 21-23. <https://www.mja.com.au/journal/2013/199/6/depression-diet-and-exercise>
- 21 Cuijpers P, Sijbrandij M, Koole SL, et al. Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. *World Psychiatry* 2014; 13: 56-67.
- 22 March J, Silva S, Petrycki S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; 292: 807-820.
- 23 Marcus SC, Olfson M. National trends in the treatment for depression from 1998 to 2007. *Arch Gen Psychiatry* 2010; 67: 1265-1273.
- 24 Meadows GN, Enticott JC, Inder B, et al. Better access to mental health care and the failure of the Medicare principle of universality. *Med J Aust* 2015; 202: 190-194. <https://www.mja.com.au/journal/2015/202/4/better-access-mental-health-care-and-failure-medicare-principle-universality>
- 25 Harris MG, Diminic S, Reavley N, et al. Males' mental health disadvantage: an estimation of gender-specific changes in service utilisation for mental and substance use disorders in Australia. *Aust N Z J Psychiatry* 2015; 49: 821-832.
- 26 Parker S, Bylett M, Leggett A. Challenges faced by trainee psychiatrists working towards competency in psychotherapies. *Australas Psychiatry* 2013; 21: 56-59.
- 27 Hyman SE. Revolution stalled. *Sci Transl Med* 2012; 4: 155cm11.
- 28 Carroll BJ. Bringing back melancholia. *Bipolar Disord* 2012; 14: 1-5.
- 29 Lewis AJ. Melancholia: a clinical survey of depressive states. *J Ment Sci* 1934; 80: 277-378.
- 30 Arnow BA, Blasey C, Williams LM, et al. Depression subtypes in predicting antidepressant response: a report from the iSPOT-D trial. *Am J Psychiatry* 2015; 172: 743-750.
- 31 Vittengl JR, Jarrett RB, Weitz E, et al. Divergent outcomes in cognitive-behavioral therapy and pharmacotherapy for adult depression. *Am J Psychiatry* 2016. In-press.
- 32 Hansen R, Gaynes B, Thieda P, et al. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. *Psychiatr Serv* 2008; 59: 1121-1130.
- 33 Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Aust N Z J Psychiatry* 2015; 49: 1087-1206. ■