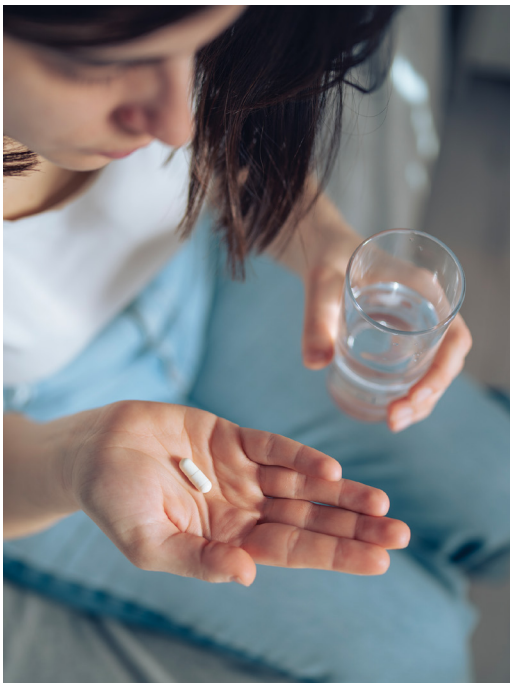
Continuing antidepressants or not: Evaluating the potential benefits and harms



Mark A Horowitz, Katharine A Wallis, Joanna Moncrieff

Refer to the associated Letter by Looi et al, which is also published in this issue of AJGP.

Background
Many Australians use antidepressants for longer periods, and for less severe conditions, than current guidelines recommend. Recent commentary has explored the rationale for stopping antidepressants, but overlooked flaws in the evidence for continuing antidepressants long-term.

Objective
To critically appraise the evidence for continuing antidepressants long-term (>12 months).

Discussion
The evidence for long-term use of antidepressants stems primarily from discontinuation studies in which people taking antidepressants are randomised to either stop or continue. These studies do not distinguish withdrawal symptoms from relapse. Worsening mood/anxiety in the discontinued group is interpreted as relapse and findings interpreted as evidence that long-term therapy prevents relapse, ignoring the possibility that the apparent benefits of continuing antidepressants might lie in suppressing withdrawal symptoms. Due to the lack of robust evidence for benefit, and established evidence showing harm with long-term use, antidepressant treatment should be regularly reviewed with shared decision making about whether to continue or stop.

NEARLY 4 MILLION AUSTRALIANS (one in seven) now take antidepressants, with use increasing each year. One-third of use is longer than 1 year, and one-quarter for more than 2 years (representing a million patients).[1] General practitioners prescribe 92% of antidepressants in Australia,[2] sometimes when clinical guideline criteria are not met.[3] Increasingly, long-term antidepressant use is recognised as not benign, including substantial evidence that withdrawal symptoms are common and can be severe, particularly after longer term use.[4,5]

There is now general recognition that antidepressants do not work by rectifying any underlying serotonin deficiency or 'chemical imbalance',[6] with The Royal Australian and New Zealand College of Psychiatrists (RANZCP) updating its website in 2022 to reflect this.[7] No alternative biological mechanisms for depression have been established, despite numerous competing theories.[8] Amplified placebo effects or emotional numbing (as reported by most antidepressant users in self-selected surveys, and also seen in healthy volunteers given antidepressants)[9] might explain the small drug-placebo differences observed in short-term trials.[10] Emotional numbing might be useful short term, providing relief from anxiety, panic or low mood, but can become problematic in the long-term, leading to reduced capacity to cry, diminished enjoyment, and a narrowed emotional range with consequences for relationships and identity.[11] Yet, most of the public still believes that depression is caused by a 'chemical imbalance'[12] and belief in a 'serotonin deficiency' has been identified as a barrier to stopping antidepressants even when no longer indicated.[13]

A recent article by Looi et al in *Australian Journal of General Practice* (AJGP) exemplifies the weakness of the evidence base for long-term use of antidepressants by presenting antidepressants as preventing relapse[14] while relying on studies in which antidepressants are stopped quickly and do not distinguish relapse from withdrawal.[15] Because emotional symptoms such as anxiety and low mood are common to both withdrawal and relapse, these studies misclassify withdrawal as relapse.[15,16] Further, Looi et al do not adequately address risks associated with long-term treatment, including the escalating risk of withdrawal symptoms. Their article contributes to the

widespread minimisation of withdrawal symptoms and the lack of focus on safe deprescribing pathways in primary care.[17]

Aim

To critically appraise the evidence for continuing antidepressants long-term (>12 months).

Evidence for benefits of long-term antidepressants

Short-term efficacy trials

Most of the evidence for antidepressants comes from randomised controlled trials (RCTs) lasting only 6–12 weeks.[18] Meta-analyses of these studies consistently find a 2-point drug-placebo difference on a 52-point depression scale,[10] which is below clinicians' threshold for minimum clinical importance (7 points).[19] Even in severe depression, the difference is only about 3 points.[20] These small effects are likely over-estimated due to unblinding, publication bias, and short follow-up (meaning tolerance effects are missed),[10] but in any case, they cannot be extrapolated to long-term antidepressant use.

Discontinuation trials

Despite the claims by Looi et al,[14] there is no robust evidence demonstrating that antidepressants prevent relapse, because discontinuation, or 'relapse prevention', trials fail to distinguish between withdrawal and relapse.[16] Guidelines that recommend 6–12 months antidepressant therapy for a first episode of depression and 2 years or more for recurrent episodes are based on discontinuation trials in which patients are randomised to maintain or rapidly stop antidepressants,[16,21] (on average over 4 days)[21] likely provoking withdrawal effects.[21]

Antidepressant withdrawal symptoms are now recognised as common, especially after long-term use, and can be severe and long-lasting.[5,22,23] Withdrawal symptoms include anxiety, low mood and insomnia, all of which register strongly on the depression scales used to define relapse in discontinuation studies.[15] Yet, despite Looi et al's claim that withdrawal effects can be easily distinguished from relapse, no discontinuation trial has attempted to do so.[16,24] Some analyses have estimated that most or all of the relapse-prevention effects reported in these studies can be attributed to withdrawal mis-classified as relapse.[16,25] Additionally, evidence for antidepressants preventing relapse beyond 24 months is notably sparse as few studies have long follow-up.[14,26] Therefore, long-term antidepressant use could merely be preventing withdrawal effects.

The Antidepressants to Prevent Relapse in Depression (ANTLER) study is highlighted by Looi et al as evidence for continuation therapy to prevent relapse. Conducted in UK primary care, it recruited people with recurrent depression (at least two episodes) who felt well enough to consider stopping antidepressants.[27] A total of 70% had taken antidepressants for more than 3 years.[27] Tapering occurred over 4–8 weeks, and relapse rates mirrored earlier discontinuation trials.[27] Almost half (44%) of the discontinuation group were able to stop antidepressants without recording a relapse (vs 61% who did not record a relapse in the maintenance group).[27]

Nonetheless, the ANTLER outcomes remain confounded by withdrawal symptoms, which the study reported occurred frequently and persisted for months, yet did not attempt to distinguish from relapse.[27] Therefore, like other discontinuation trials, ANTLER does not provide robust evidence that continuing antidepressants prevents relapse;[28] it is consistent with the explanation that maintenance merely prevents withdrawal symptoms.

Analogically, if smokers were randomised to continue or cease smoking and anxiety/irritability was measured, while withdrawal effects were ignored, results would spuriously suggest that smoking prevents anxiety. Supporting this notion, a recent meta-analysis found that when antidepressants were withdrawn gradually with psychological support relapse rates did not differ from those continuing antidepressants.[29]

Discontinuation trials also have limited generalisability to primary care. A Cochrane review found that most were conducted in secondary care with patients with recurrent and chronic depression, who are at much higher risk of relapse than typical primary care patients.[30,31] Even the ANTLER trial specifically recruited patients with at least two episodes of depression.

Guidelines recommending continuing antidepressant treatment to prevent relapse should be revised and updated to reflect the possibility that continuing antidepressants long-term merely prevents antidepressant withdrawal symptoms.[16,28]

Evidence from other study designs

Anxiety and depression are very common experiences, with longitudinal studies finding that most people (70%) fulfil formal criteria for these conditions by the age of 45 years,[32] which is mostly explained by stressful life events and personality.[33] Cohort studies of untreated depression show high remission rates at 12 months (53[34]–85%).[35] In comparison, the largest and longest antidepressant trial, the Sequenced treatment alternatives to relieve depression (STAR-D) trial, found only 3.7% of those who remained in the study showing remission at the 12-month final follow-up.[36] Meta-analyses of long-term RCTs show cognitive-behavioural therapy is more effective than antidepressant treatment.[37] People treated with cognitive therapy have much lower rates of relapse than those treated with antidepressants alone.[38]

Evidence for harms of long-term antidepressant use

Adverse effects and physical health consequences

Harms associated with long-term antidepressant treatment include sexual dysfunction (50–80% of users), emotional numbing, cognitive impairment (shown in healthy volunteers), insomnia, and weight gain.[39–43] Sexual dysfunction persists after antidepressants are stopped in a proportion of users, known as Post-SSRI (selective serotonin reuptake inhibitor) Sexual Dysfunction (PSSD), with the Therapeutic Goods Administration (TGA) issuing warnings about this in 2024.[44] Observational studies demonstrate an increased risk of strokes, falls, cataracts, heart disease, sudden cardiac death, cognitive decline and early mortality (up to an absolute increased risk of death of 3–4% per year) in people over the age of 65 years, with uncertainties about the degree of confounding.[45–47]

Withdrawal effects

There is qualitative, survey and RCT evidence showing withdrawal symptoms on stopping antidepressants,[23,48,49] which include increased suicidality (occurring even in patients who had not been suicidal before taking antidepressants)[22] and akathisia (a state of profound agitation and terror).[50] Protracted withdrawal syndromes are increasingly recognised, which can include debilitating somatic, psychological and neurological symptoms persisting for months and years, occurring in up to 15% of long term users.[51,52] In a recent analysis of National Health Service (NHS) patients in the UK who had tried to stop an antidepressant, 10% reported withdrawal symptoms lasting for more than 12 months and 15% reported severe symptoms.[4] Notably, the longer people used antidepressants, the greater their risk of severe and long-lasting withdrawal symptoms.[4,53]

Discussion

There is a lack of robust evidence demonstrating benefit with long-term antidepressant therapy and some evidence for harm. The following considerations apply at different stages of prescribing.

When considering starting an antidepressant

Most patients will recover naturally from a depressive episode without specific treatment.[35] Antidepressants offer marginal benefit in the short term.[10] Non-drug options are effective and have fewer harms.[37] These approaches include examining current stressors with problem solving approaches, lifestyle changes (mindfulness, exercise, diet[54]) and evidence-based psychotherapies.[55] Watchful, supportive waiting is highly effective.[56]

Misconceptions about a 'chemical imbalance' and biological causes of depression can reduce self-efficacy and promote unnecessary long-term use.[13,26] If antidepressants are commenced, it is important to have a clear timeline and plan to stop,[57] especially given the lack of robust evidence for long term treatment.

Regular review

The National Institute for Health and Care Excellence (NICE) in the UK recommends regular review of antidepressant use,[57] typically every 6 months, including assessment of antidepressant effectiveness, side effects, signs of physical dependence (eg withdrawal effects on missed doses), ongoing need for antidepressants, and patient preference.[57] Some patients might prefer to remain on antidepressants despite not meeting criteria to do so because life stressors make discontinuation too daunting or preferring the emotionally restricting effects, but this decision could be revisited periodically.

There is an increased risk of withdrawal symptoms with increasing duration of antidepressant use.[4] Patients who feel worse on missing doses or attempting to stop often interpret this as evidence of relapse but these are often withdrawal effects.[15] The occurrence of these symptoms does not indicate that antidepressants cannot be stopped, but that a more gradual, hyperbolic taper might be required.

Safely stopping an antidepressant

A supported, individualised, patient-centred approach will help patients who want to stop their antidepressant. Slow, hyperbolic tapering might be required for people who have been taking antidepressants long-term or have particular difficulties with withdrawal. Schedules are available, for example, in resources that have been officially recognised by The Royal Australian College of General Practitioners (RACGP) as Accepted Clinical Resources – the Maudsley Deprescribing Guidelines,[50] and the RELEASE (Redressing Long-term Antidepressant Use) toolkit.[58] The Royal College of Psychiatrists' guidance on 'Stopping antidepressants'[59] is also helpful.

Conclusion

The evidence justifying long-term use of antidepressants is likely to exaggerate the relapse prevention properties of antidepressants by mis-classifying withdrawal effects as relapse. Given a lack of reliable evidence for benefit and established evidence of harm, antidepressants should be regularly reviewed with shared decision-making about whether to continue or stop.

Key points

- The evidence justifying long-term antidepressant use is flawed, because discontinuation trials confound withdrawal with relapse.
- There is no compelling evidence that depression is caused by a 'chemical imbalance'.
- Antidepressant withdrawal symptoms are common, can be severe and long-lasting, and yet are often misinterpreted as symptoms of relapse.
- Longer duration of antidepressant use increases the risk of adverse effects including withdrawal effects.
- Regular review of antidepressant use is important to weigh up the risk of harm and benefit.

Authors

Mark A Horowitz BA, BSc, GDPsych, MSc, MBBS, PhD, Associate Professor of Psychiatry, Critical and Ethical Mental Health Research Group, Adelaide University, Adelaide, SA; Clinical Research Fellow, Research and Development Department, North East London NHS Foundation Trust, Ilford, UK; Visiting Lecturer in Psychopharmacology, Institute of Pharmaceutical Sciences, King's College London, London, UK

Katharine A Wallis, MBChB, PhD, MBHL, FACRRM, Mayne Professor and Head of the Mayne Academy of General Practice, and Head of the General Practice Clinical Unit, The University of Queensland, Brisbane, Qld

Joanna Moncrieff MBBS, MD, MRCPsych, Professor of Critical and Social Psychiatry, Division of Psychiatry, University College London, London, UK; Consultant Psychiatrist, Research and Development Department, North East London NHS Foundation Trust, Ilford, UK

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Correspondence to:
mark.horowitz@nelft.nhs.uk

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