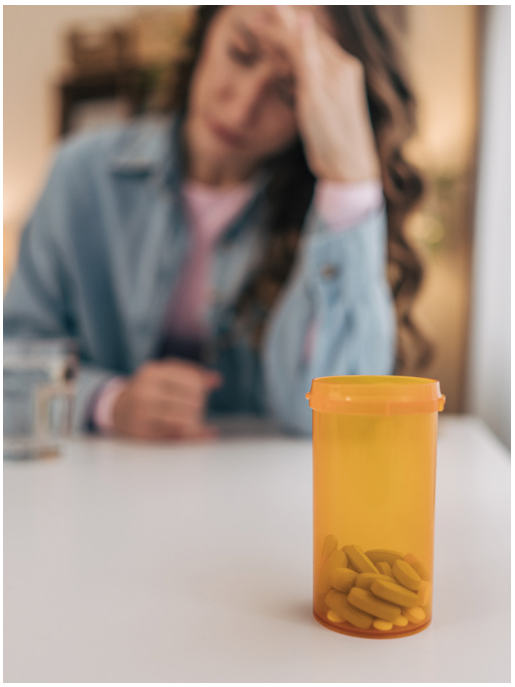
Stopping antidepressants or not?



Jeffrey CL Looi, Stephen Allison, Tarun Bastiampillai, Steve Kisely, Paul A Maguire, Luke Woon, Katrina Anderson

Background
Recently, there has been media and public interest regarding discontinuation of antidepressant treatment, especially in primary care. In this context, we provide a primary care update on the maintenance or discontinuation of antidepressant medication for the treatment of moderate-to-severe depression in adults.

Objective
This article aims to provide a primary care update on the maintenance or discontinuation of antidepressant medication for the treatment of moderate-to-severe depression in adults. To this end, we performed a qualitative narrative review and provide commentary on recent research and systematic reviews.

Discussion
In primary care, recent research has shown that there are substantial risks of depressive relapse resulting from antidepressant discontinuation. For a first episode of moderate-to-severe depression, antidepressants should be continued for 9–12 months after remission. Systematic reviews indicate that, overall, there is limited evidence of benefits from ceasing antidepressant treatment for recurrent depression. The existing evidence base on antidepressant withdrawal is limited in quality and extent, providing some evidence of harms, such as relapse, and not necessarily any gains, although reducing the burden of adverse effects is a consideration. There is a benefit-to-risk ratio in any decision to continue or withdraw antidepressant treatment.

ANTIDEPRESSANTS have a modest, but clinically significant, effect in moderate-to-severe depression in adults, consistent with many other medical interventions.[1,2] Whole-person-centred treatment approaches, such as psychological therapy, wellbeing strategies and exercise, can assist all patients who suffer from depression, and are recommended first-line treatments for mild-to-moderate depression.[3]

For an initial episode, current evidence-based clinical practice guidelines for moderate-to-severe depression recommend antidepressant treatment for 9–12 months after remission.[3] After this, discontinuation might be attempted.[3] For people who have experienced two or more episodes of depression, continuation of antidepressant treatment ranging from two years to indefinitely has been recommended.[3,4]

In Australia, antidepressants are primarily prescribed by general practitioners (GPs).[5] The prevalence of depression has increased in Australia, and the total number of antidepressant prescriptions per 1000 Australians has risen since these Australian Institute of Health and Welfare data were reported in 2006 (coinciding with the inception of the Australian Government-subsidised primary care Better Access to Mental Health program[6]) until 2022. A retrospective study of 10% of the Pharmaceutical Benefits Scheme (PBS)-dispensed antidepressant data from 2013 to 2019 found that of the 239,944 patients who commenced antidepressant treatment, 52% were prescribed selective serotonin reuptake inhibitors (SSRIs), 25% were prescribed tricyclic antidepressants (TCAs) and 13% were prescribed serotonin–norepinephrine reuptake inhibitors (SNRIs) or other agents.[7] TCAs are most likely used in general practice for chronic pain and not in doses that would have an antidepressant effect, despite a recent umbrella review showing limited efficacy.[8] In this paper, we are mainly referring to SSRIs and SNRIs. The median time on treatment was 4.5 months, with SSRIs being used for a median of 5.8 months.[7] Of those treated, 22% and 6% received a second and third medication, respectively, likely related to comorbidity as well as lack of efficacy.[7]

However, antidepressants might also have side effects that affect the quality of life of those taking them.[3,4] These side effects include sexual dysfunction, weight gain, gastrointestinal disturbances and sleep disturbance.[3] More serious potential but rare harms include falls, stroke, upper gastrointestinal tract bleeding, hyponatraemia and seizures; however, these data are from older populations, and there are risks of confounding from comorbidities and related phenomena.[9] Some side effects, such as post-SSRI sexual dysfunction, might also persist after cessation, although the exact prevalence is unclear.[10]

Despite these concerns, the number of antidepressant prescriptions and duration of treatment have continued to increase, indicating that patients are continuing to take antidepressants.[11] What are the reasons for which patients might continue to take antidepressants longer term?

Aim

The aim of this paper is to provide a primary care update on the maintenance or discontinuation of antidepressant medication for the treatment of moderate-to-severe depression in adults.

What are the risks and benefits of antidepressant discontinuation?

Some authors have highlighted that the evidence base from randomised control trials (RCTs) for maintenance of antidepressant treatment does not extend beyond two years.[11] This reflects the challenges of conducting RCTs over several years, but does not mean there is no real-world evidence on the long-term utility of antidepressants, although, equally, findings have also been mixed. For example, a large UK RCT of antidepressant discontinuation in 150 general practices (ANTidepressants to prevent reLapse in dEpRession [ANTLER] RCT), reported a relapse rate of 56% in 240 patients who were well enough to be randomised to discontinue antidepressants (citalopram, fluoxetine, sertraline or mirtazapine).[12] This compared to a relapse rate of 39% in the 238 patients randomised to maintenance treatment, resulting in a hazard ratio of 2.06 (95% confidence interval [CI]: 1.56–2.70; $P<0.001$).[12] An accompanying health economic evaluation reported that participants who discontinued had worse utility scores at three months, and fewer quality-adjusted life-years over 12 months, with increased associated costs.[13] In contrast to these results, a more detailed non-peer-reviewed health technology assessment by the same ANTLER RCT authors observed that of those who discontinued, 53% (95% CI: 44–62%) chose to recommence antidepressants.[13] There is a further primary care antidepressant discontinuation trial underway in the UK, 'Reviewing long-term antidepressant use by careful monitoring in everyday practice'(REDUCE) RCT, the findings of which are yet to be reported.[14]

A further complicating factor in the discontinuation of antidepressants is the presence of withdrawal phenomena and the possibility that these might be misdiagnosed as symptoms of relapse.[15] Although similar, withdrawal symptoms can be differentiated by their speed of onset, quick response when the medication is restarted (usually within hours to days) and unique symptoms, such as dizziness, nausea and 'brain zaps'.[15,16] On average, approximately 53.6% of people experience withdrawal when stopping SSRIs based on 14 different studies, although this varies by SSRI.[16] Nevertheless, distinguishing between relapse and withdrawal remains a complexity in evaluating studies on antidepressant discontinuation, especially of those of shorter duration, such as four weeks. For example, a recent Cochrane Collaboration systematic review on antidepressant discontinuation highlighted this as a potential confounder in evaluating available research findings.[16] What evidence the review's authors did find was of low certainty and limited to short-term approaches in people with recurrent or long-term depression in specialist mental health settings.[16] These patients might neither be representative of primary care nor be prime candidates for discontinuation. The review therefore recommended further studies of longer-term approaches to discontinuation in people in primary care with no more than one prior depressive episode, as well as of what was termed 'successful discontinuation' (ie discontinuation with no adverse outcomes).[16] For many patients suffering from depression, comorbidities such as chronic pain and comorbid somatic symptoms will have an impact on the decision to stop treatment, as will stigma regarding antidepressant treatment.

What should GPs recommend to their patients regarding antidepressant discontinuation?

Ideally, predictors of individual relapse risk after antidepressant discontinuation should be used to guide treatment decisions, including understanding previous and ongoing psychosocial precipitants as well as comorbid conditions. However, current evidence is still limited, and validated clinical and neurobiological markers are still lacking.[17]

In the case of the first episode of moderate-to-severe depression, which most likely would present to GPs, the guidelines recommend continuation for 9–12 months.[3] At the end of that period, there should be a collaborative decision on whether to continue treatment, based on the balance of benefits and harms, and patient preference. It is important to carefully explore patient fears, expectations and ideas about antidepressant discontinuation.[18] Good therapeutic alliance is a significant predictor of a higher subjective sense of success for antidepressant discontinuation.[19] Although evaluating patients on longer-term therapy, the recent primary care ANTLER RCT highlights the drawbacks of antidepressant discontinuation, such as a significantly higher risk of relapse, compared with antidepressant continuation.[12]

For patients with recurrent depression of two or more episodes, more likely to be seen in secondary specialist psychiatric care, the recommendation is treatment for two years to indefinitely.[3] This is especially the case after previously unsuccessful antidepressant trials. There should be differentially higher weighting of benefits (due to risk of relapse) versus harms, as well as the issue of withdrawal symptoms, while still incorporating patient preferences.

In light of the issues regarding problematic antidepressant discontinuation, the UK Royal College of Psychiatrists has provided detailed examples of longer hyperbolic (smaller decrements in dosage near termination of treatment) withdrawal regimens based on best practice guidelines.[20] However, as outlined in the most recent Cochrane

review,[16] the effectiveness of such protocols is yet to be fully evaluated. Based on expert opinion,[20] these withdrawal regimens are worthy of consideration for improving the chances of deprescribing antidepressants, if indicated.

GPs will recommend lifestyle changes and preventative activities as part of their whole-person approach to the patient, and these activities are important but difficult to capture in large studies. This approach should encompass psychotherapy and/or counselling to identify and manage predisposing and precipitating factors. Based on recent studies, a sequential depression treatment model, with antidepressant treatment in the acute phase followed by psychotherapy in the continuation phase, has been suggested, but remains to be more fully evaluated.[21–23] Unfortunately, the results of the Cochrane review cited above also indicate that there is limited benefit from psychological therapy for the prevention of relapse of depressive symptoms in those on longer-term antidepressants who discontinue these medications.[16]

Conclusion

The ongoing role of antidepressant treatment for patients successfully treated for moderate-to-severe depression needs to be reconsidered. A key issue is whether a patient is likely to relapse following antidepressant discontinuation. While acknowledging there is concern whether some withdrawal symptoms might be mistaken for relapse, the ANTLER RCT long-term follow-up study demonstrates that there is a very substantial risk of relapse after discontinuation of long-standing antidepressant treatment.[12] For patients in primary care, this indicates there should be a clear and careful discussion with them about whether discontinuation is feasible for them. It is important to highlight to the patient that withdrawal symptoms are common and so a staged process of slow medication withdrawal, particularly for high doses, is important. Follow-up is needed to review symptoms and consider relapse. In shared secondary, psychiatric care settings, for patients who are more likely to have recurrent depressive episodes, discontinuation might not be advisable if patients are in successful remission, given current recommendations to treat for two years to indefinitely.

Future research might include a deidentified clinical registry of patients receiving treatment for depression to understand what is prescribed, to whom and for what reason, including whether withdrawals have been attempted, according to evidence-based guidelines.[3]

Despite the high rate of antidepressant use internationally, public and professional perceptions of effectiveness might lag behind the current evidence base. In this context, the above evidence on benefits and harms of antidepressant treatment can be discussed with patients in collaborative primary care planning.

Key points

- Antidepressant treatment for moderate–severe depression in adults is effective.
- Discontinuation of antidepressant medications might lead to relapse of depression.
- For first episodes of depression, treatment is recommended for 9–12 months.
- For recurrent episodes of depression, treatment is for two years to indefinitely.
- Recent research shows there is a high risk of depressive relapse on discontinuation of longstanding treatment.

Authors

Jeffrey CL Looi MBBS, MD, DMedSc, FRANZCP, AFRACMA, Associate Professor of Neuropsychiatry, Old Age Psychiatry and Psychiatry and Head, Academic Unit of Psychiatry and Addiction Medicine, The Australian National University School of Medicine and Psychology, Canberra Hospital, Canberra, ACT; Coordinator, Consortium of Australian-Academic Psychiatrists for Independent Policy and Research Analysis (CAPIPRA), Canberra, ACT

Stephen Allison MBBS, FRANZCP, Member, CAPIPRA, Canberra, ACT; Associate Professor of Psychiatry, College of Medicine and Public Health, Flinders University, Adelaide, SA

Tarun Bastiampillai BMedSc, MBBS, FRANZCP, Member, CAPIPRA, Canberra, ACT; Professor of Psychiatry, College of Medicine and Public Health, Flinders University, Adelaide, SA; Clinical Professor of Psychiatry, Department of Psychiatry, Monash University, Melbourne, Vic

Steve Kisely MD, PhD, DMedRes, FRANZCP, FRCPsych, FAFPHM, FFPH, FAChAM, Member, CAPIPRA, Canberra, ACT; Professor of Psychiatry, School of Medicine, The University of Queensland, Princess Alexandra Hospital, Brisbane, Qld; Professor of Psychiatry, Metro South Addiction and Mental Health Service, Brisbane, Qld; Professor, Departments of Psychiatry, Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia

Paul A Maguire MBBS, PhD, FRANZCP, Senior Lecturer in Psychiatry, Academic Unit of Psychiatry and Addiction Medicine, The Australian National University School of Medicine and Psychology, Canberra Hospital, Canberra, ACT

Luke Woon MD, DrPsych, Lecturer in Psychiatry, Department of Psychiatry, Faculty of Medicine, The National University of Malaysia, Kuala Lumpur, Malaysia; Postgraduate Student, Academic Unit of Psychiatry and Addiction Medicine, The Australian National University School of Medicine and Psychology, Canberra, ACT; Clinical Observer, Canberra Hospital; Canberra, ACT

Katrina Anderson BMed, FRACGP, MTh, SFHEA, Associate Professor of General Practice and Director of GP Education, Academic Unit of General Practice, The Australian National University School of Medicine and Psychology, Canberra Hospital, Canberra, ACT

Competing interests: LW declares payments from Lundbeck Malaysia and Eisai Malaysia for lectures, presentations and meeting support. The remaining authors have no conflicts of interest to disclose.

Funding: None.

Provenance and peer review: Not commissioned, externally peer reviewed.

Correspondence to:
jeffrey.looi@anu.edu.au

References

1. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. Lancet 2018;391(10128):1357–66. doi: 10.1016/S0140-6736(17)32802-7.
2. Leucht S, Hierl S, Kissling W, Dold M, Davis JM. Putting the efficacy of psychiatric and general medicine medication into perspective: Review of meta-analyses. Br J Psychiatry 2012;200(2):97–106. doi: 10.1192/bjp.bp.111.096594.
3. Malhi GS, Bell E, Bassett D, et al. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry 2021;55(1):7–117. doi: 10.1177/0004867420979353.
4. Royal College of Psychiatrists (RCPsych). Antidepressants and depression. RCPsych, 2019. Available at www.rcpsych.ac.uk/docs/default-source/improving-care/better-mh-policy/position-statements/ps04_19---antidepressants-and-depression.pdf?sfvrsn=ddea9473_5 [Accessed 28 August 2023].
5. Australian Institute of Health and Welfare (AIHW). Mental health-related prescriptions. AIHW, 2023. Available at www.aihw.gov.au/mental-health/topic-areas/mental-health-prescriptions [Accessed 30 August 2023].
6. Services Australia. Better Access initiative – supporting mental health care. Australian Government, 2022. Available at www.servicesaustralia.gov.au/better-access-initiative-supporting-mental-health-care [Accessed 28 February 2022].
7. Malhi GS, Acar M, Kouhkamari MH, et al. Antidepressant prescribing patterns in Australia. BJPsych Open 2022;8:e120. 2022/07/01. doi: 10.1192/bjo.2022.522.
8. Ferreira GE, Abdel-Shaheed C, Underwood M, et al. Efficacy, safety, and tolerability of antidepressants for pain in adults: Overview of systematic reviews. BMJ 2023;380:e072415. doi: 10.1136/bmj-2022-072415.
9. Coupland C, Dhiman P, Morriss R, et al. Antidepressant use and risk of adverse outcomes

in older people: Population based cohort study. BMJ 2011;343:d4551. doi: 10.1136/bmj.d4551.
10. Healy D. Post-SSRI sexual dysfunction & other enduring sexual dysfunctions. Epidemiol Psychiatr Sci 2020;29:e55. doi: 10.1017/S2045796019000519.
11. Kendrick T. Strategies to reduce use of antidepressants. Br J Clin Pharmacol 2021;87(1):23–33. doi: 10.1111/bcp.14475.
12. Lewis G, Marston L, Duffy L, et al. Maintenance or discontinuation of antidepressants in primary care. N Engl J Med 2021;385(14):1257–67. doi: 10.1056/NEJMoa2106356.
13. Duffy L, Clarke CS, Lewis G, et al. Antidepressant medication to prevent depression relapse in primary care: the ANTLER RCT. Health Technol Assess 2021; 25(69):1–62. doi: 10.3310/hta25690.
14. Kendrick T, Geraghty AWA, Bowers H, et al. REDUCE (Reviewing long-term antidepressant use by careful monitoring in everyday practice) internet and telephone support to people coming off long-term antidepressants: Protocol for a randomised controlled trial. Trials 2020;21:419. doi: 10.1186/s13063-020-04338-7.
15. Horowitz MA, Taylor D. Distinguishing relapse from antidepressant withdrawal: Clinical practice and antidepressant discontinuation studies. BJPsych Adv 2022;28(5):297–311. doi: 10.1192/bja.2021.62.
16. Van Leeuwen E, van Driel ML, Horowitz MA, et al. Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database Syst Rev 2021;4:CD013495. doi: 10.1002/14651858.CD013495.pub2.
17. Berwian IM, Walter H, Seifritz E, Huys QJ. Predicting relapse after antidepressant withdrawal – a systematic review. Psychol Med 2017;47(3):426–37. doi: 10.1017/S0033291716002580.
18. Scholten W, Batelaan N, Van Balkom A. Barriers to discontinuing antidepressants in patients with depressive and anxiety disorders: A review of the literature and clinical recommendations. Ther Adv Psychopharmacol 2020;10. doi: 10.1177/2045125320933404.
19. Lincoln TM, Sommer D, Quazzola M, Witzgall T, Schlier B. Predictors of successful discontinuation of antipsychotics and antidepressants. Psychol Med 2023;53(7):3085–95. doi: 10.1017/S0033291721005146.
20. Royal College of Psychiatrists (RCPsych). Stopping antidepressants. RCPsych, 2020. Available at www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants [Accessed 28 August 2023].
21. Cosci F, Mansueto G, Fava GA. Relapse prevention in recurrent major depressive disorder. A comparison of different treatment options based on clinical experience and a critical review of the literature. Int J Psychiatry Clin Pract 2020;24(4):341–48. doi: 10.1080/13651501.2020.1779308.
22. Breedvelt JJF, Warren FC, Segal Z, Kuyken W, Bockting CL. Continuation of antidepressants vs sequential psychological interventions to prevent relapse in depression: An individual participant data meta-analysis. JAMA Psychiatry 2021;78(8):868–75. doi: 10.1001/jamapsychiatry.2021.0823.
23. Krijnen-de Bruin E, Scholten W, Muntingh A, et al. Psychological interventions to prevent relapse in anxiety and depression: A systematic review and meta-analysis. PLoS One 2022;17:e0272200. doi: 10.1371/journal.pone.0272200.

correspondence **ajgp@racgp.org.au**