BJPsych Open (2020)
6, e24, 1–3. doi: 10.1192/bjo.2020.6

Editorial

Discontinuing psychotropic drug treatment

Leonardo Tondo and Ross J. Baldessarini

Summary

Interruption of ongoing treatment with benzodiazepines, antidepressants, antipsychotics and mood stabilisers including lithium can be followed by clinically significant withdrawal reactions within hours or days, as well as later increases in relapses or recurrences of the illness being treated. Such observations support the view that stopping treatment is not equivalent to being untreated. With lithium, antipsychotics and antidepressants, there is consistent evidence that abrupt or rapid discontinuation is followed by earlier clinical worsening than with more gradual removal of treatment. Moreover, treatment discontinuation can complicate interpretation of responses to changes in treatment, including in clinical practice and in experimental treatment trials. Notably, terminating preceding treatments can lead to both discontinuation and carry-over effects that can have an impact on the interpretation of observed outcomes.

Declaration of interest

None.

Keywords

Antianxiety drugs; antidepressants; antipsychotics; mood stabilisers; treatment discontinuation.

Leonardo Tondo (pictured) is currently Director of the Lucio Bini Mood Disorder Center in Cagliari, where he has systematically collected clinical research data from more than 6500 patients. He has published four books and more than 200 articles in international journals. **Ross J. Baldessarini** has helped to establish the Psychiatric Research Laboratories at Massachusetts General Hospital, later leading them at McLean Hospital's Mailman Research Center, where he founded the Psychotic Disorders Program, and later the International Consortium for Mood & Psychotic Disorders Research, which he continues to direct as Professor of Psychiatry (Neuroscience) at Harvard.

A recent report by Öhlund and her colleagues[1] adds valuable information concerning effects of discontinuing long-term lithium treatment. This 'mirror-image' study considered risk of psychiatric hospital admission before treatment versus within 2 years after ending long-term treatment with lithium in patients with bipolar disorder type I or II (BD-I, BD-II) or other types of bipolar disorder or schizoaffective disorder. Both the mean number of psychiatric hospital admissions and days in hospital per patient doubled within 2 years without lithium. As expected, this adverse clinical outcome was limited mainly to patients diagnosed with BD-I or schizoaffective disorder, and hospital admission was more likely with mania, absence of alternative treatments and was non-significantly associated with rapid discontinuation of lithium. These findings encourage a brief comment on the broader topic of important clinical and research implications of discontinuing treatment with various psychotropic drugs.

Withdrawal reactions

Interruption of ongoing treatment with various psychotropic medicines sometimes is followed by clinically significant withdrawal reactions within hours or days, as well as later increases in morbidity, relapses or recurrences of the illnesses being treated. Early withdrawal reactions commonly follow discontinuation of benzodiazepines[2] as well as some antidepressants, particularly selective serotonin reuptake inhibitors.[3] They include rapidly emerging physiological syndromes as well as new neuropsychiatric symptoms including sensory changes, anxiety and agitation, all of which can persist for weeks.[4,5] Adverse clinical effects of discontinuing psychotropic drugs also can arise in changing from active drug to placebo in clinical trials.[6,7]

Pharmacodynamic mechanisms underlying discontinuation syndromes

Mechanisms underlying early reactions to withdrawal of various psychotropic agents, and particularly later relapses or recurrences, remain uncertain. It is likely that complex pharmacodynamic adaptations to long-term drug treatment are involved.[6,8,9] Long-term exposure to antidepressant, antipsychotic, anxiolytic, mood stabilising and other psychotropic drugs leads to neuropharmacological adaptations that include changes in postsynaptic receptor and autoreceptor sensitivity, neurotransmitter synthesis and release, and various downstream molecular and genetic mechanisms in multiple brain systems.[8,9] Agents with long elimination half-lives appear to carry lower risk of withdrawal effects, including fluoxetine among antidepressants and long-acting antipsychotics.[6] Effects of adaptative changes during prolonged drug exposure evidently become manifest as clinically apparent neurobehavioural responses when treatment is removed. Restoring the withdrawn medicine, even temporarily and at lower doses, sometimes may reduce the clinical manifestations of withdrawal reactions.[6]

Later adverse clinical effects of drug discontinuation

Of great clinical importance is the phenomenon of increased risk of earlier relapses (re-emergence of recent, and possibly not fully remitted, episodes) or recurrences (new episodes) of illnesses following discontinuation of their treatment, possibly related to a 'rebound' effect associated with removal of effects of a drug.[10] Such outcomes appear to represent more than a return of illness without treatment, and include an iatrogenic component arising from treatment discontinuation itself as a significant physiological

https://doi.org/10.1192/bjo.2020.6 Published online by Cambridge University Press

and psychological stressor. That is, stopping treatment evidently is not equivalent to being untreated. That earlier relapses or recurrences are a consequence of treatment discontinuation itself is supported by differences in morbidity in patients after discontinuing a treatment versus their spontaneous illness course before starting treatment.[11] Such adverse clinical responses have been reported in association with discontinuing lithium or other treatments in bipolar disorder,[1,12–14] antipsychotics in schizophrenia,[15] and antidepressants in patients with major depression.[16] For selective serotonin reuptake inhibitors these effects may last for periods varying between a few weeks to a year or more.[17]

Pregnancy is commonly associated with interruption of ongoing medicinal treatments – often abruptly, typically driven by fear of teratogenic or toxic effects on the fetus and associated liability. Discontinuing lithium maintenance treatment in women with bipolar disorder has been associated with 60% risk of a new episode of illness within 9 months in age-matched women, whether pregnant or not, and the risk was higher following abrupt or rapid (<15 days) discontinuation.[18] In addition, risk of new, mainly depressive or mixed, episodes of bipolar disorder was markedly increased after stopping various mood stabilisers with pregnancy, especially in the first trimester.[12] Increased recurrences even among women with bipolar disorder who had remained stable without treatment in the year prior to pregnancy suggest that pregnancy itself is an additional stressor.

Effects of discontinuation rate

We have reported on adverse clinical effects of discontinuing long-term treatment with antidepressants and antipsychotics as well as lithium.[6,9,12–14,18] Such effects may also occur in patients with bipolar disorder following discontinuation of maintenance treatments other than with lithium.[17] Of particular interest, abrupt or rapid (1–14 days) versus slower discontinuation of lithium was consistently associated with earlier recurrences of illness and increased risk or suicide attempts or fatalities in patients with bipolar disorder.[13,14] Similar risks also followed rapid discontinuation of antipsychotic drugs in patients with psychotic disorders,[16] and antidepressants in those with major depression or other disorders.[16,19] The impact of abrupt or rapid treatment discontinuation in these studies and that of Öhlund *et al*[1] was most apparent in initial months, with more similar risk × time rate functions thereafter that paralleled risk × time before treatment.[1] Hospital admission increased non-significantly after stopping lithium abruptly or rapidly in the new study by Öhlund *et al*,[1] although contrasts were limited by including conditions other than BD-I and late spontaneous recurrences probably unrelated to treatment discontinuation. The preponderance of available evidence supports the view that gradual discontinuation of most psychotropic drugs over at least several weeks is likely to reduce early risks of relapses[6,9,11–16,17] as well as risk or severity of early withdrawal reactions[6,9,17,19,20] and should be considered a preferred clinical practice.

Implications of treatment discontinuation for therapeutics research

In addition to its clinical importance, treatment discontinuation has important implications for the design, conduct and interpretation of clinical treatment trials. Instead of relying on long-term, randomised controlled trials, which are challenging to carry out, it has become common to study effects of treatment discontinuation following initial clinical improvement in randomised trials for acute psychiatric illnesses. Typically, such designs involve removing an apparently effective treatment, often relatively rapidly, to a placebo-control condition, often when patients may not be fully recovered from the index episode of illness.[21] Such circumstances make scientific interpretation of findings uncertain and also may raise ethical issues.

More generally, complications often arise in modern therapeutic trials in relation to previous treatments, to which most contemporary research participants have been exposed up to trial entry. Terminating preceding treatments can lead to both discontinuation and carry-over effects. That is, benefits of prior treatments can continue into the early days after randomisation to a new treatment. In addition, drug discontinuation effects can contaminate the outcome of placebo-control conditions, exaggerate comparisons with responses to a new active treatment, and complicate assessment of adverse effects.[9,22] Trial designs involving treatment discontinuation currently are prevalent, and can, potentially misleadingly, be considered to offer evidence of long-term treatment efficacy. In such trials, additional bias is introduced by 'enrichment,' or allowing only responders to a particular experimental treatment to continue into a more prolonged treatment-discontinuation trial phase.

Conclusions

Adverse clinical effects of discontinuing psychotropic drug treatment include early, but potentially persisting, withdrawal syndromes, as well as typically increased later risk of relapse or recurrence of a treated illness – sometimes with increased suicidal risk in addition to increased psychiatric morbidity.[6] Furthermore, effects of discontinuing treatment with psychotropic drugs can influence the outcome of studies aimed at assessing the severity and course of a psychiatric illness, and confound the outcome of randomised treatment trials. Both clinical and experimental treatments are especially likely to be influenced by treatment discontinuation when preceding treatment is changed to a new clinical treatment, at entry into an experimental trial, or following a later change from an apparently effective experimental treatment to placebo. Such possibilities should be considered when treatment is withdrawn or changed clinically, as well as when reviewing risks in the informed consent process for experimental treatments, and interpreting the outcome of experimental trials involving treatment discontinuation. Remedies for the problems involved may include: (a) providing more 'lead-in', drug 'washout' time before initiating a controlled trial to seek freedom from preceding treatments, although with some risk of provoking clinical worsening, and (b) by allowing longer time for recovery before changing treatment to a placebo condition. Treatment-discontinuation syndromes for psychotropic medicines may be worth considering for inclusion as distinct disorders in standard international diagnostic systems including DSM and ICD.

Currently, research designed to test for the impact of the rate of discontinuing particular psychotropic treatments and effects of their doses remains uncommon. Most previous research has supported the view that abrupt or rapid discontinuation of long-term lithium maintenance treatment leads to risk of early relapses and recurrences exceeding that expected from the previous course of illness in the same individuals. The new study by Öhlund *et al*.[1] adds findings indicating that discontinuation of lithium, even rapidly, was much less likely to be followed by admission to hospital in those with BD-II or other unspecified types of bipolar disorder than those with BD-I and schizoaffective disorder. Such an outcome is consistent with the generally much lower risk of psychiatric hospital admission in patients with BD-II, although it is not in accord with a previous comparison of patients with BD-I and BD-II based on risk of new illness episodes rather than hospital

https://doi.org/10.1192/bjo.2020.6 Published online by Cambridge University Press

admission.[14] Although Öhlund and her colleagues[1] did not find a statistically significant effect of rapid discontinuation of lithium, there was substantially more early hospital admission following rapid discontinuation, at least in patients with BD-I and schizoaffective disorder, within the initial few months following lithium discontinuation (see their Fig. 2(c)), when discontinuation would be expected to exert major effects.[6,14] In general, we recommend discontinuing psychotropic medicines, including lithium, as slowly as circumstances permit as a prudent clinical and research policy as further research on this important topic is pursued.

Leonardo Tondo, MD, MS, Department of Psychiatry, Harvard Medical School USA; International Consortium for Mood & Psychotic Disorders Research, McLean Hospital, USA; Director, Lucio Bini Mood Disorder Center, Italy; **Ross J. Baldessarini**, MD, MA (Hon), DSc (Hon), DLFAPA, FACP, FACNP, FCINP, Professor of Psychiatry (Neuroscience), Department of Psychiatry, Harvard Medical School; and International Consortium for Mood & Psychotic Disorders Research, McLean Hospital, USA

Correspondence: Leonardo Tondo. Email: Ltondo@aol.com

First received 8 Dec 2019, final revision 20 Jan 2020, accepted 25 Jan 2020

Funding

Supported by an award from the Aretaeus Foundation of Rome (to L.T.) and a grant from the Bruce J. Anderson Foundation and the McLean Hospital Private Donors Psychiatry Research Fund (to R.J.B.).

References

1 Öhlund L, Ott M, Berqvist M, Oja S, Lundqvist R, Sandlund M, et al. Clinical course and need for hospital admission after lithium discontinuation in patients with bipolar disorder type I or II: mirror-image study based on the LiSIE retrospective cohort. *BJPsych Open* 2019; **5**: e101.

2 Fluyau D, Revadigar N, Monobianco BE. Challenges of the pharmacological management of benzodiazepine withdrawal, dependence, and discontinuation. *Ther Adv Psychopharmacol* 2018; **8**: 147–168.

3 Fava GA, Gatti A, Belaise C, Guidi J, Offidani E. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: systematic review. *Psychother Psychosom* 2015; **84**: 72–81.

4 Rosenbaum JF, Fava M, Hoog SL, Ascroft RC, Krebs WB. Selective serotonin reuptake inhibitor discontinuation syndrome: randomized clinical trial. *Biol Psychiatry* 1998; **44**: 77–87.

5 Chouinard G, Chouinard V-A. New classification of selective serotonin reuptake inhibitor withdrawal. *Psychother Psychosom* 2015; **84**: 63–71.

6 Baldessarini RJ, Tondo L. Effects of treatment discontinuation in clinical psychopharmacology. *Psychother Psychosom* 2019; **88**: 65–70.

7 Récalt AM, Cohen D. Withdrawal confounding in randomized controlled trials of antipsychotic, antidepressant, and stimulant drugs, 2000–2017. *Psychother Psychosom* 2019; **88**: 105–13.

8 Blier P, Trembley P. Physiologic mechanisms underlying the antidepressant discontinuation syndrome. *J Clin Psychiatry* 2006; **67** (Suppl 4): 8–13.

9 Baldessarini RJ. *Chemotherapy in Psychiatry (3d edition)*. Springer Press, 2013.

10 Franks MA, Macritchie KAN, Mahmood T, Young AH. Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? Retrospective naturalistic study. *J Psychopharmacol* 2008; **22**: 452–6.

11 Suppes T, Baldessarini RJ, Faedda GL, Tondo L, Tohen M. Discontinuing maintenance treatment in bipolar manic-depression: risks and implications. *Harv Rev Psychiatry* 1993; **1**: 131–44.

12 Viguera AC, Whitfield T, Baldessarini RJ, Newport DJ, Stowe Z, Cohen LS. Recurrences of bipolar disorder in pregnancy: prospective study of mood-stabilizer discontinuation. *Am J Psychiatry* 2007; **164**: 1817–24.

13 Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M. Outcome after rapid vs. gradual discontinuation of lithium treatment in bipolar mood disorders. *Arch Gen Psychiatry* 1993; **50**: 448–55.

14 Baldessarini RJ, Tondo L, Floris G, Rudas N. Reduced morbidity after gradually discontinuing lithium in bipolar I and II disorders: a replication study. *Am J Psychiatry* 1997; **154**: 551–3.

15 Viguera AC, Baldessarini RJ, Hegarty JM, Van Kammen D, Tohen M. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Arch Gen Psychiatry* 1997; **54**: 49–55.

16 Baldessarini RJ, Tondo L, Ghiani C, Lepri B. Discontinuation rate vs. recurrence risk following long-term antidepressant treatment in major depressive disorder patients. *Am J Psychiatry* 2010; **167**: 934–41.

17 Horowitz MA, Taylor D. Tapering of SSRI treatment to mitigate withdrawal symptoms. *Lancet Psychiatry* 2019; **6**: 538–46.

18 Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of discontinuing lithium maintenance in pregnant vs. nonpregnant women with bipolar disorders. *Am J Psychiatry* 2000; **157**: 179–84.

19 Khan A, Musgnung J, Ramey T, Messig M, Buckley G, Ninan PT. Abrupt discontinuation compared with one-week taper regimen in depressed outpatients treated for 24 weeks with desvenlafaxine 50 mg/day. *J Clin Psychopharmacol* 2014; **34**: 365–8.

20 Fava GA, Bernardi M, Tomba E, Rafanelli C. Effects of gradual discontinuation of selective serotonin reuptake inhibitors in panic disorder with agoraphobia. *Int J Neuropsychopharmacol* 2007; **10**: 835–8.

21 Baldessarini RJ, Lau WK, Sim J, Sum MY, Sim K. Duration of initial antidepressant treatment and subsequent relapse of major depression. *J Clin Psychopharmacol* 2015; **35**: 75–6.

22 Gallagher JC, Strzinek RA, Cheng R-FJ, Ausmanas MK, Asti D, Seljan P. Effect of dose titration and dose tapering on the tolerability of desvenlafaxine in women with vasomotor symptoms associated with menopause. *J Womens Health* 2012; **21**: 188–98.

https://doi.org/10.1192/bjo.2020.6 Published online by Cambridge University Press