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.

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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. 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.6,9 Long-term exposure to antidepressant, antipsychotic, anxiolytic, mood stabilising and other psychotropic drugs leads to neuropharmacological adaptations that include changes in postsynaptic receptor and auto-receptor sensitivity, neurotransmitter synthesis and release, and various downstream molecular and genetic mechanisms in multiple brain systems.6,9 Agents with long elimination half-lives appear to carry lower risk of withdrawal effects, including fluoxetine among antidepressants and long-acting antipsychotics.9 Effects of adaptive 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

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 as well as some antidepressants, particularly selective serotonin reuptake inhibitors. 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.6,5 Adverse clinical effects of discontinuing psychotropic drugs also can arise in changing from active drug to placebo in clinical trials.6,7

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
Effects of discontinuation rate

We have reported on adverse clinical effects of discontinuing long-term treatment with antidepressants and antipsychotics as well as lithium. Such effects may also occur in patients with bipolar disorder following discontinuation of maintenance treatments other than with lithium. 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. Similar risks also followed rapid discontinuation of antipsychotic drugs in patients with psychotic disorders, and antidepressants in those with major depression or other disorders. The impact of abrupt or rapid treatment discontinuation in these studies and that of Öhlund et al. was most apparent in initial months, with more similar risk × time rate functions thereafter than with lithium or antipsychotics. Hospital admission increased non-significantly after stopping lithium abruptly or rapidly in the new study by Öhlund et al., 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 as well as risk or severity of early withdrawal reactions 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. 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. 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. 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. 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
admission.\textsuperscript{14} Although Öhlund and her colleagues\textsuperscript{3} 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.\textsuperscript{6,14} In general, we recommend discontinue 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.

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

Funding
Supported by an award from the Areteaus 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.).

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