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Effects of Treatment Discontinuation in Clinical Psychopharmacology

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Introduction

Reports in this issue of *Psychotherapy and Psychosomatics* by Drs. Cohen and Recalt document the occurrence of treatment discontinuation in therapeutic trials involving most types of drugs used for psychiatric disorders [1, 2]. They conclude that treatment discontinuation has broad implications rarely acknowledged in published reports. The precise prevalence of treatment discontinuation in therapeutic trials is not known, but it is commonplace clinically and is often associated with trials aimed at testing for both short-term effects and long-term, preventive or prophylactic effects of psychotropic drugs [1, 2]. Effects associated with discontinuing psychotropic drugs include several types that have been described elsewhere [3].

First are early reactions arising within hours or first days following discontinuation of many psychotropic drugs. They include apparently physiological withdrawal-like syndromes but can also include rapid emergence of other new symptoms [3–7]. A description of such reactions (Discontinuation-Emergent Signs and Symptoms [DESS] scale) includes 43 signs and symptoms [8]. In addition to physical and sensory phenomena, reactions sometimes include symptoms also found in the illnesses being treated (especially depression and anxiety), as well as other novel syndromes. Examples of the latter include: withdrawal-emergent dyskinesias [9] or catatonia [10], emergence or worsening of tardive dyskinesia [11, 12], and a proposed tardive psychosis syndrome [13] – all on removal of antipsychotic drugs; new panic symptoms and worsening or new depression or mania after removing an antidepressant [3, 8, 14–16]; and new or increased suicidal behavior after discontinuing lithium [17] and possibly antidepressants [15, 16]. Second and usually somewhat later, symptoms of illnesses being treated can recur more often, sometimes more severely, and much more rapidly than predicted by the natural history of untreated illness, including by comparison to a patient's own history. Usually such episodes arise over weeks rather than the hours or days characteristic of initial withdrawal-emergent reactions. Post-discontinuation relapse or recurrence has been documented after discontinuing antidepressants [18], mood stabilizers [19–21], and antipsychotics [22], particularly following abrupt or rapid discontinuation over a few days [18–22]. The average time to a relapse after rapid discontinuation of antidepressants and lithium is about 3 months, whereas it ex-

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tends to 6 months after gradual discontinuation [18, 20]. Of note, none of these iatrogenic complications was mentioned in a new, large national survey of morbid conditions associated with major psychiatric disorders, probably owing to lack of categorical designations for such conditions in national health information registries [23]. Overall, there seems to be a lack of consensus about a well-defined distinction between the sometimes overlapping characteristics of the effects of medication withdrawal and discontinuation.

Withdrawal Reactions

Withdrawal-like syndromes occur with most sedatives and antianxiety agents, as well as opioids, alcohol, and other psychoactive agents [24–28]. Similar reactions also have been observed following discontinuation of various antidepressants [29] but are especially strongly associated with serotonin reuptake inhibitors (SRIs) [16, 30] and some serotonin-norepinephrine reuptake inhibitors (SNRIs) [31]. Typically, in adults and juveniles, they arise after discontinuing treatment that has been ongoing for many weeks or months and appear to be more likely if relatively high doses of short half-life agents are removed or reduced suddenly or rapidly [4, 5, 7, 9, 30, 31]. Such withdrawal reactions appear to be especially likely with paroxetine and venlafaxine, probably less with most other SRIs or SNRIs other than venlafaxine [4, 5, 7, 9, 30, 31], and still less with older antidepressants [16]. Among SRIs, the risk is especially low with the very long-acting antidepressant-anxiolytic fluoxetine, which sometimes has been substituted for short-acting SRIs in efforts to manage withdrawal symptoms by slow removal of the more slowly cleared agent [4, 5, 7]. To some extent, relative risks of withdrawal reactions appear to correlate with drug elimination half-life, particularly among SRIs [32]. Half-life of modern antidepressants can be categorized as: *short* (<20 h: bupropion, desvenlafaxine, duloxetine, paroxetine, venlafaxine), *intermediate* (20–30 h: escitalopram, fluvoxamine, mirtazapine, viloxazine), and *slow* (>30 h: citalopram, fluoxetine, sertraline) [33, 34].

Typical symptoms of withdrawal syndromes associated with SRIs and SNRIs include nausea, lethargy, insomnia, headache, impaired balance, tremor, abnormal sensations such as electric-shock-like sensations, and sometimes irritable and even aggressive behavior [4, 5, 7, 9, 30, 31]. In the DESS, at least 10 of 43 signs and symptoms associated with withdrawal reactions are also found in depressive or anxiety disorders [9]. As noted, such overlap can tend to obscure the distinction of withdrawal-emergent reactions and re-emergence of illnesses being treated. In a survey based on nine reports of such reactions, among 632 patients treated with an SRI, withdrawal-emergent reactions were identified in an average of 33.2% (95% CI: 31.3–35.1), indicating a substantial but minority prevalence [14]. Such reactions typically emerge within hours or a few days after major reductions of dose or complete removal of the suspect agent and can persist for widely different times from days or a few weeks, and less often, to many weeks [4, 7, 9, 15, 16]. A reassuring finding is that evidence of withdrawal symptoms in neonates born to mothers taking SRIs was not found in one study [35]. Abrupt discontinuation of psychotropic drugs is very common in pregnancy, with greatly increased risk of adverse clinical effects on the mother and unknown impact on the fetus [36, 37]. Additional potential complications include shifts in the metabolic elimination of other prescribed medicines with which SRIs can interact pharmacokinetically [10, 34].

Efforts to explain mechanisms underlying withdrawal reactions to various psychotropic agents have been unsatisfying. Some of the many, complex pharmacodynamic changes induced by long-term exposure to antipsychotic, antidepressant, anxiolytic, mood-stabilizing and other psychotropic drugs have been investigated. However, many more changes in receptor and autoreceptor sensitivity, neurotransmitter synthesis and release, and various downstream molecular and genetic mechanisms and secondary effects on multiple brain systems are emerging [34]. They include supersensitivity of dopamine receptors in forebrain following prolonged exposure to antipsychotic and other antidopaminergic agents [38], as well as desensitization of serotonin receptors and autoreceptors after prolonged exposure to SRIs and SNRIs, additional adaptive changes in noradrenergic mechanisms with SNRIs and tricyclic antidepressants, and responses to antimuscarinic effects of paroxetine and tricyclic antidepressants [39]. How such neuroadaptive changes may produce specific withdrawal-emergent symptoms remains unclear.

Optimal treatment for drug withdrawal-emergent reactions remains uncertain. Characteristically, restarting the withdrawn medicine, even temporarily and at lower doses, usually leads to reduction or remission of symptoms, supporting their classification as withdrawal-associated reactions [4, 7]. A widely accepted clinical practice is gradual reduction of doses of psychotropic drugs including SRIs to improve the safety of treatment discontinuation [4, 7, 9, 40]. However, studies aiming to test the

prediction that slow removal of drugs can reduce risk of withdrawal reactions are rare and most have major design limitations. For SRIs, these sometimes include lack of adequate controls, small numbers of subjects, multiple drugs with major pharmacokinetic differences, and short discontinuation times with few downward steps in dose, or lack of matching of the presence and severity of DESS outcome items at baseline [15, 40–42]. Despite such limitations, some findings suggest that gradual reduction of doses of SRIs may *not* provide important reduction of withdrawal symptoms. One study found symptoms considered to represent withdrawal in 45% of subjects being treated for panic disorder after 2 or more weeks of discontinuing a variety of SRIs, though without a comparison group involving abrupt or rapid discontinuation [40]. Another trial evaluated withdrawal symptoms after discontinuing desvenlafaxine in older women treated for menopausal vasomotor instability, with randomization to abrupt discontinuation or to various stepwise reductions of doses over 2 weeks; the findings supported a reduction of risk of withdrawal symptoms with more gradual discontinuation [41]. A third study of anxiety disorder patients found that antidepressants could be discontinued, even very slowly over 4 months, in only 37%, and that two-thirds became newly anxious [42]. A fourth study found little difference in risks of DESS-defined withdrawal symptoms after discontinuing various SRIs or venlafaxine given for depression over 3 versus 14 days, and that drugs of long half-life (mainly fluoxetine) and those of short half-life had similar risks of DESS-based withdrawal symptoms; however, depressive symptoms were more likely with rapidly eliminated agents, with associated new suicidal preoccupations and behaviors [32]. Finally, a trial involving desvenlafaxine given for depression and discontinued abruptly, over 2 weeks gradually, or not at all found that the risk of DESS withdrawal symptoms did not differ between those who continued the SRI or underwent rapid dose-lowering, although there was a highly significantly lower risk with gradual versus abrupt discontinuation [15]. In short, evidence concerning the value of slow discontinuation of drugs including modern antidepressants to minimize or avoid withdrawal reactions is limited, inconsistent, and often based on less-than-optimal study designs. Beneficial effects might be found with even slower discontinuation over at least several weeks. Suggested alternative treatment strategies, in addition to switching to, and then removing the very slowly eliminated SRI fluoxetine, include use of an anticonvulsant or clonazepam, a long half-life, anxiolytic-anticonvulsant benzodiazepine [4, 17]. However, none of these options has undergone rigorous testing for efficacy and safety. In addition, psychotherapy may or may not be helpful [16, 42]. Finally, the safe management of discontinuation of increasingly prevalent combinations of psychotropic drugs presents a challenge [10]. One study found that changing from one antipsychotic to another, at least, could be done as safely with immediate drug-switching as with widely employed "cross-tapering" of doses downward of a discontinued, and upward of a replacement antipsychotic [43].

Post-Discontinuation Relapse or Recurrence

Also of great clinical importance is the phenomenon of treatment discontinuation-associated increase in risk and earlier relapse (re-emergence of a most recent, and possibly not fully remitted, episode) or recurrence (new episode) of illnesses being treated. We have described this phenomenon following discontinuation of lithium [19–21, 44, 45], antipsychotics [22], and antidepressants [18, 46]. It is probably only partly a reflection of the return of illness without treatment and seems to involve treatment discontinuation itself as a significant stressor. That is, discontinuing treatment is evidently *not* equivalent to being untreated. Support for earlier, more frequent, and possibly more severe relapse or recurrence as an effect of treatment discontinuation includes comparisons with the same patients prior to the start of treatment to evaluate the natural history of their untreated illness [19, 44], as well as major differences in risk of new or early illness with gradual versus abrupt or rapid discontinuation of treatment [29–21, 44, 45]. Of note, the reduction of post-discontinuation relapse and recurrence by very gradual discontinuation and use of slowly cleared agents supports the expectation that the risk or severity of earlier-occurring withdrawal reactions might also be modified by slow discontinuation.

Implications of Treatment Discontinuation-Associated Relapse

Withdrawal reactions and post-treatment-discontinuation clinical worsening are very likely to affect the findings of randomized therapeutic trials, particularly when a placebo control is involved, in addition to complicating clinical treatment involving drug discontinuation, major dose reductions, or repeated changes of treatment. Regarding experimental therapeutic trials, most human

subjects entering a trial in a developed country will have been treated previously and so undergo a change in treatment status. It follows that effects of previous treatment and its discontinuation may impact the findings of most controlled trials. These effects can include both *carry-over* and *discontinuation* effects. That is, the benefits and adverse effects of prior treatment, even after it is discontinued, are likely to continue into the early days or even weeks of a new treatment trial – respectively, exaggerating the apparent benefits of a new treatment and either blunting (carry-over effect) or increasing (discontinuation effect) the impact of randomization to an inactive placebo, as well as misleadingly increasing ratings of adverse effects for a time. In addition, shifting from either previous or new active treatment to placebo, such as in "continuation" trials, can make for particular problems, including an inflated risk of relapse.

Such trial designs are currently prevalent and often considered to offer evidence of long-term beneficial effects. However, they risk exaggerating contrasts in morbidity between subjects continuing on a treatment that has just proved effective for them versus being withdrawn to an inactive placebo when they are still recovering from an index episode of acute illness. Such designs are commonly considered "enrichment" trials (selecting subjects who responded initially to a treatment of scientific or commercial interest) or "continuation" trials. Those designations tend to obscure biasing based on removing treatment from subjects selected for "responding" initially (partial reduction of symptom ratings) and then having treatment removed, sometimes relatively rapidly and when an index episode of illness had not yet fully resolved, so as to increase the risk of relapse [34]. For example, such effects are especially likely in the weeks following initial partial improvement ("treatment response") in a trial of antidepressant treatment for an acute episode of major depression that goes on to a "continuation" with the same agent or *discontinuation* to a placebo [47, 48]. With some medicines, the risk of inducing post-discontinuation relapse may require several months of clinical recovery to fall to a stable baseline level [47]. As such, discontinuation trials that follow soon after an acute episode of illness are likely to provide inadequate and potentially confounded evidence of potential long-term or prophylactic benefit [47, 48]. A related question is whether returning to a discontinued treatment may involve a compromised future benefit. The general answer to this question is unknown, but at least for lithium in bipolar disorder, we have found evidence of minimal loss of benefit from treatment on a second or even later re-trials [49].

Discontinuing ongoing treatment with a psychotropic medicine is especially likely and may occur abruptly in anticipation of or during early pregnancy, typically driven by fear of fetal teratogenic effects and associated concern about legal liability. For example, the risk of relapse of major depression during pregnancy was much greater after discontinuing treatment with an antidepressant [36]. In addition, we found that discontinuing lithium maintenance treatment in women with bipolar disorder led to a similar risk of a new episode of illness of about 60% within 9 months, in age-matched, both pregnant and nonpregnant women evaluated during the same period of time, with a higher risk following rapid discontinuation [50]. The similarity of risk with and without pregnancy suggests treatment discontinuation itself as the greater risk factor. Moreover, a markedly increased risk of new episodes of bipolar disorder during pregnancy followed discontinuation of various mood stabilizers. Most of this risk was depressive or mixed, highest in the first trimester, and was followed by an even more severe risk of new affective or psychotic illness soon after delivery without mood-stabilizing treatment through pregnancy [37].

Conclusions

The various effects of discontinuing treatment with psychotropic drugs, encountered both clinically and in therapeutic trials, raise important clinical and possible ethical concerns. They can also compromise the scientific soundness of research, especially in trials that involve discontinuing a previous or current active treatment to a placebo. They may also challenge the content and conduct of the informed consent process, particularly when a consequence of trial design or change of clinical treatment may include risks of provoking relapse or recurrence of clinically significant illness. Trials involving discontinuation of an effective treatment are especially likely to produce exaggerated differences in morbidity between continuing treatment versus discontinuing it to an inactive placebo. An exaggerated risk of relapse with placebo can be minimized by allowing sufficient time of treatment to reach full clinical remission.

Current needs include refinement of the distinction between early withdrawal-associated reactions and later, post-treatment-discontinuation re-emergence of psychiatric illness, and evidence-supported means of avoiding or managing them. Treatment discontinuation syndromes for psychotropic medicines may be worth considering for inclusion as disorders in DSM and ICD. They are specific syndromes requiring optimized treatment, similar to cur-

rently classified withdrawal syndromes of abused substances. Available research designed to test for the impact of various rates of discontinuing psychotropic treatments is rare, inconsistent, and inconclusive with respect to early withdrawal reactions commonly encountered with short half-life SRIs and venlafaxine. Findings are more consistent with respect to the later risk of discontinuation-associated re-emergence of the illness being treated, including both mood and psychotic disorders. Accordingly, we recommend discontinuing psychotropic medicines as slowly as circumstances permit as a prudent clinical and research policy as we await adequate investigations aimed at testing for ways of conducting drug discontinuations.

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