Supplementary Material

Withdrawal confounding in randomized controlled trials of antipsychotic, antidepressant, and stimulant drugs, 2000-2017

Alexander Recalt & David Cohen

Onset and Duration of Withdrawal Symptoms

Withdrawal symptoms are likely to occur following the discontinuation of most CNS agents that have relatively short half-lives (hours to days), but onset and duration of symptoms, and their presentation, may vary considerably [1].

For antidepressants, the onset of discontinuation symptoms following drug reduction or cessation has been stated to occur from a few hours to 3 weeks [2], "within hours or days" [3], 1 day to 2 weeks [4], 1 to 3 days [5], a few days to 1 week [6], 2 to 14 days [7], a few days to 1 month [8], and 36 to 96 hours typically but up to six weeks [9]. In cases of slower or gradual discontinuation, symptoms have been reported to appear during such a taper [4]. The symptoms have been reported to last from 1 to 2 weeks [1], from 5 days to "six weeks or even longer" [8], "resolve within ten days" [5], 2 to 14 days [7], 1 to 52 days [6], 1 to "after 7 days" [10], 9 to 198 days [11], 6 weeks to "several months" [9], or "many months" [2].

For antipsychotics, onset is stated to occur from "soon after" [12], 48 hours [13], days 7 to 10 days during cross-titration of two drugs [14], "promptly after" discontinuation [15], and up to six weeks after discontinuation for oral antipsychotics and three months for depot (injection) formulations [9,18,15]. In the case of specific withdrawal-related movement disorders such as rebound akathisia, parkinsonism, and dyskinesia, onset can range from "suddenly" after dose reduction [18] and the first few days to a month post-discontinuation [15]. Syndromes such as tardive dyskinesia (TD) and supersensitivity psychosis (SP), both associated with the discontinuation of antipsychotic drugs, can persist for "several months or years" and can in some cases be irreversible [9].

Little recent literature discusses onset or duration of withdrawal reactions from prescribed stimulants. The DSM-5 Criterion B for Stimulant Withdrawal states that the symptoms develop "within a few hours to several days" after cessation or reduction in prolonged stimulant use [19]. A literature review cites reports of stimulant rebound and withdrawal reactions lasting up to two weeks [20].

Given the heterogeneity in reported onset and duration of withdrawal phenomena, the limited empirical exploration of the potential withdrawal confound so far, and the variability of the duration of randomized withdrawal phases in selected RCTs, this analysis planned to examine both shorter and longer timepoints after discontinuation: 1 and 2 weeks for stimulant trials, 3 and 6 weeks for antidepressant trials, and 6 and 12 weeks for antipsychotic trials, respectively.

Table 1

Drugs and drug classes of 80 RCTs employing a drug discontinuation procedure and 30 RCTs eligible for withdrawal confounding analysis

		Pre-Analysis (n=80)	Withdrawal Confound Analysis (n=30)
Drug Class	Drug	*n*	*n*
Antidepressants	Multiple	12	3
	Escitalopram	4	2
	Agomelatine	1	1
	Citalopram	1	1
	Desvenlafaxine	1	
	Imipramine	1	
	Mirtazapine	1	1
	Sertraline	1	
	Not Reported	1	
Antipsychotics	Multiple	13	5
	Haloperidol	3	2
	Risperidone	3	3
	Quetiapine	2	1
	Lurasidone	1	1
	Fluphenazine	1	
	Olanzapine	1	
	Perphenazine	1	
	Zuclopenthixol	1	1
Benzodiazepines	Multiple	14	
	Not Reported	5	
	Diazepam	1	
	Zolpidem	1	
Non-BZD Anxiolytics	Pregabalin	1	1
Mood Stabilizers	Lamotrigine	1	
Lithium	Lithium	1	1
Stimulants	Lisdexamfetamine	2	2
	Modafinil	2	2
	Methylphenidate	2	2
	Amphetamine	1	1

Table 2

Disposition of study subjects in included trials (n=14)

Authors & year	Number entering study	Are non-responders randomized?	Number entering randomized discontinuation phase	Number randomized to drug discontinuation	Drug discontinuation completers	Number randomized to drug maintenance	Drug maintenance completers
Ulfvarson et al., 2003 [23]	70	NR*	70	35	18	35	27
Ruths et al., 2008 [25]	55	NR*	55	27	23	28	25
Bergh et al., 2012 [24]	128	Y	128	63	36	65	47
Brams et al., 2012 [35]	123	N	116	60	13	56	50
Chen et al., 2010 [22]	178	N	178	89	15	89	34
Devanand et al., 2012a ‡ [26]	180	N	110	38	14	32	10
Devanand et al., 2012b ‡ [26]	-	N	-	40	10	-	-
Devanand et al., 2011 [27]	44	N	20	10	2	10	6
Goodwin et al., 2009 [2]	492	N	339	174	91	165	115
Coghill et al., 2014 [13]	276	N	157	79	21	78	55
Res. Units on Ped. Psychopharm., 2005 [30]	101	N	32	16	6	16	14
Troost et al., 2005 [28]	36	N	24	12	4	12	9
Arnold et al., 2004 [3]	89	N	75	40	15	35	28
Haessler, et al. 2007 [36]	49	N	39	20	1	19	7
Tandon et al., 2016 [29]	676	N	285	141	20	144	28
Total	***2497***	**-**	***1628***	***844***	***289***	***784***	***455***

**Not reported ‡ 2 analyses from Devanand et al., 2012, which used 2 discontinuation groups*

Table 3

Qualitative review of potentially confounded symptoms in eligible studies (n=14)

Authors & year	Drug class (drug)	Short DCT – Confound detected?	Long DCT – Confound detected?	Potentially confounded symptoms	Rationale
Ulfvarson et al., 2003	AD (citalopram, sertraline)	-	Inconclusive	"[Investigators] re-started treatment in seven patients in the [discontinuation] group after 4-6 weeks. […] *five patients complained of increased sadness*."* (737)	Affective symptoms of SSRI withdrawal include depression, mood swings, and bouts of crying. [9, 23]
Ruths et al., 2008	AP (haloperidol, olanzapine, risperidone)	Y	-	"However, behavioural symptoms increased in one of three [discontinuation group] patients during the blinded study."	This study used the NPI to measure behavioral and psychological changes. The questionnaire measures symptoms such as hallucinations, agitation / aggression, depression, anxiety, and irritability, all of which have been identified as withdrawal symptoms of AP [21].
Bergh et al., 2012	AD (escitalopram, citalopram, sertraline, paroxetine)	-	Y	"Thirteen (20%) patients in the discontinuation group and four (6%) in the continuation group withdrew from the study prematurely because of increased depressive or neuropsychiatric symptoms (P=0.019; table 2)." (4) Significant differences were detected in NPI affective subscale scores, and more subjects dropped out due to increased neuropsychiatric symptoms in the disc group than in the maintenance group.	This study used the NPI to measure behavioral and psychological changes. The questionnaire measures symptoms such as hallucinations, agitation / aggression, depression, anxiety, and irritability, all of which have been identified as withdrawal symptoms of SSRI ADs [9].
Brams et al., 2012	Stimulants (lisdexamfetamine)	Y	Y	"One [serious adverse event] was reported during the randomized withdrawal phase in a male aged 18 years who was randomly assigned to placebo […]. In this participant, *suicidal ideation* occurred 14 days after randomized treatment commenced. No previous history of suicidal thoughts was reported. The investigator considered this event mild and unrelated to study medication."* (980)	Suicidal ideation, dysphoric mood, and depression are known potential features of withdrawal from stimulants [19, 22].
Chen et al., 2010	AP (quetiapine)	N	Y	"In relapses, specific symptoms that scored at or above the threshold included *delusions* (72%; 58/81), *hallucinations* (54%; 44/81), *suspiciousness* (38%; 31/81), *conceptual disorganization* (30%;24/81), and *unusual thought content* (23%; 19/81); 68% (55/81) of patients had two or more types of psychotic symptom. The most common co-occurring psychotic symptoms were *delusions* and *hallucinations* (37%; 30/81) and *delusions* and *suspiciousness* (31%; 25/81)."*	Strong evidence of iatrogenic dopamine supersensitivity psychosis (DSP) upon antipsychotic withdrawal, especially in patients treated with APs for at least 3 months [21,23]. DSP consists of rapid onset of positive symptoms of psychosis, such as hallucinations and delusions. Quetiapine, the drug being discontinued in this study, can induce SP without producing detectable drug-induced movement disorders [21].
Devanand et al., 2012	AP (risperidone)	N, Y †	Y, Y †	AEs listed in Table 2 (p. 1505): EPS, akathisia or restlessness, sedation, insomnia, confusion, agitation-aggression, falling, nausea or vomiting.	Agitation and aggression are potential withdrawal symptoms common to all CNS drugs, as are nausea and sleep disturbances like insomnia [21]. In drugs with serotonergic action like risperidone, serotonergic withdrawal effects include confusion and restlessness.

Devanand et al., 2011	AP (haloperidol)	N	N	No symptoms described	N/A
Goodwin et al., 2009	AD (agomelatine)	N	N	This study specifically measured "adverse events suggestive of withdrawal symptoms" within 4-weeks post-discontinuation in Table 5 (1134). Those were: asthenia, aggravated depression, diarrhea, headache, insomnia, irritability, muscle spasms, musculoskeletal pain, nausea/vomiting, heart palpitations.	All have been cited as AD withdrawal symptoms [9, 21].
Coghill et al., 2014	Stimulants (lisdexamfetamine)	Y	Y	Table 2 (652) summarizes treatment-emergent adverse events, but not comprehensively. AEs found in ≥10% of subjects: decreased appetite, headache, decreased weight, nasopharyngitis, anorexia, insomnia, vomiting. Elsewhere: "One patient in the placebo group discontinued treatment because of 2 TEAEs (*restlessness* and an *increase in ADHD behavior*)."* (653)	Headache and nausea/vomiting are withdrawal symptoms common to all CNS drugs [21]. Insomnia, psychomotor agitation (i.e. restlessness) are known stimulant withdrawal symptoms [19].
Res. Units on Ped. Psychopharm., 2005	AP (risperidone)	Y	-	"On one hand, the return of aggression, tantrums, and agitation was five times as great in the placebo-substitution group as in the subjects who continued to take risperidone." (1366)	Aggression and agitation are withdrawal symptoms common to all CNS drugs. In addition to its serotonergic effects, risperidone acts on several adrenergic, and histaminic receptors; agitation and irritability are known symptoms of adrenergic and histaminic withdrawal syndromes [21].
Troost et al., 2005	AP (risperidone)	Y	-	"All side effects were in the mild to moderate range. No significant changes in [AIMS] and Simpson-Angus scores were encountered. Neurological side effects included *tremor* (once), *muscle rigidity* (twice), and *restlessness* (twice). No withdrawal effects, such as dyskinesias, were observed."* (1141)	Restlessness and muscle rigidity are symptoms of serotonin withdrawal syndrome [21]
Arnold et al., 2004	Stimulants (dexmethylphenidate)	Y	-	From Table 4: Headache, insomnia, rhinitis, pain (Table 4, p. 550)	Headache and insomnia are general CNS withdrawal symptoms; insomnia is a symptoms of stimulant withdrawal [19, 21].
Haessler, et al. 2007	AP (zuclopenthixol)	Y	-	"The number of adverse events and possible symptoms of withdrawal, such as *nausea*, *insomnia*, and *diarrhoea*, were recorded and did not differ between the groups."* (448) "[…] it was the withdrawal of zuclopenthixol that caused an increase in *aggressive behaviour*."* (448)	This study acknowledges that AEs may be withdrawal symptoms. Nausea, insomnia, and aggression are common CNS drug withdrawal symptoms, while diarrhea is a symptom of serotonin withdrawal (zuclopenthixol acts on serotonin receptors) [21]. In adrenergic and histaminic withdrawal syndromes, agitation is a known symptom [21]
Tandon et al., 2016	AP (lurasidone)	Y	Y	Criteria for relapse (Table 2) include: aggressive behavior, delusions, and hallucinatory behavior (p. 74).	Dopamine supersensitivity psychosis consists of rapid onset of psychotic symptoms including delusions and hallucinations. Aggression is a potential withdrawal symptom common to CNS drugs [21].

** Emphasis added † 2 analyses from Devanand et al., 2012, which used 2 discontinuation groups*

References

[1] Ogle NR, Akkerman SR: Guidance for the discontinuation or switching of antidepressant therapies in adults. J Pharm Pract 2013;26:389-396.
[2] Castberg I: Seponeringssyndrom etter behandling med antidepressiver [Discontinuation syndrome after treatment with antidepressants]. Tidsskrift for den Norske Laegeforening 2004;124:2493-2494.
[3] Montgomery SA, Fava M, Padmanabhan SK, Guico-Pabia CJ, Tourian KA: Discontinuation symptoms and taper/poststudy-emergent adverse events with desvenlafaxine treatment for major depressive disorder. Int Clin Psychopharmacol 2009;24:296-305.
[4] Black K, Shea C, Dursun S, Kutcher S: Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. J Psychiatry Neurosci 2000;25:255.
[5] Maixner SM, Greden JF: Extended antidepressant maintenance and discontinuation syndromes. Depress Anxiety 2000;8:43-53.
[6] Haddad PM: Antidepressant discontinuation syndromes. Drug Safety 2000;24:183-197.
[7] Shelton RC: The nature of the discontinuation syndrome associated with antidepressant drugs. J Clin Psychiatry 2006;67:3.
[8] Fava GA, Gatti A, Belaise C, Guidi J, Offidani E: Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. Psychother Psychosom 2015;84:72-81.
[9] Chouinard G, Chouinard VA: New classification of selective serotonin reuptake inhibitor withdrawal. Psychother Psychosom 2015;84:63-71.
[10] Perahia DG, Kajdasz DK, Desaiah D, Haddad PM: Symptoms following abrupt discontinuation of duloxetine treatment in patients with major depressive disorder. J Affect Disord 2005;89:207-212.
[11] Narayan V, Haddad PM: Antidepressant discontinuation manic states: a critical review of the literature and suggested diagnostic criteria. J Psychopharmacol 2011;25:306-313.
[12] Lambert TJ: Switching antipsychotic therapy: what to expect and clinical strategies for improving therapeutic outcomes. J Clin Psychiatry 2007;68:10-13.
[13] Shields MK, Bastiampillai T, Mohan T: Managing clozapine discontinuation–acute and chronic maintenance strategies. Aust N Z J Psychiatry 2012;46:1104-1105.
[14] Buckley PF, Correll CU: Strategies for dosing and switching antipsychotics for optimal clinical management. J Clin Psychiatry 2008;69:1-14.
[15] Cerovecki A, Musil R, Klimke A, Seemüller F, Haen E, Schennach R, Kuhn KU, Volz HP, Riedel M: Withdrawal symptoms and rebound syndromes associated with switching and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs 2013;27:545.
[17] Constant É: Enjeux cliniques du passage d'un antipsychotique à l'autre. L'Encéphale 2013;39:439-444.
[18] Salomon C, Hamilton B: Antipsychotic discontinuation syndromes: a narrative review of the evidence and its integration into Australian mental health nursing textbooks. Int J Ment Health Nurs 2014;23:69-78.
[19] American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC: American Psychiatric Association; 2013
[20] Breggin, PR, Cohen D. Your drug may be your problem: How and why to stop taking psychiatric medications. Cambridge: Da Capo Press; 2007
[21] Chouinard G, Samaha AN, Chouinard VA, Peretti CS, Kanahara N, Takase M, Iyo M: Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. Psychother psychosom 2017;86:189-219.
[22] Barr AM, Markou A, Phillips AG: A 'crash' course on psychostimulant withdrawal as a model of depression. 2002;20:475-482
[23] Schatzberg AF, Haddad P, Kaplan EM, Lejoyeux M, Rosenbaum JF, Young AH, Zajecka J: Serotonin reuptake inhibitor discontinuation syndrome: A hypothetical definition. J Clin Psychiatry 1997;58(Suppl. 7):5-10.
[23] Moncrieff J: Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. Acta Psychiatr Scand 2006;114:3-13.