STOPPING MOOD STABILISERS AND ANTIDEPRESSANTS

Professor David Taylor
South London and Maudsley NHS Foundation Trust
King's College, London

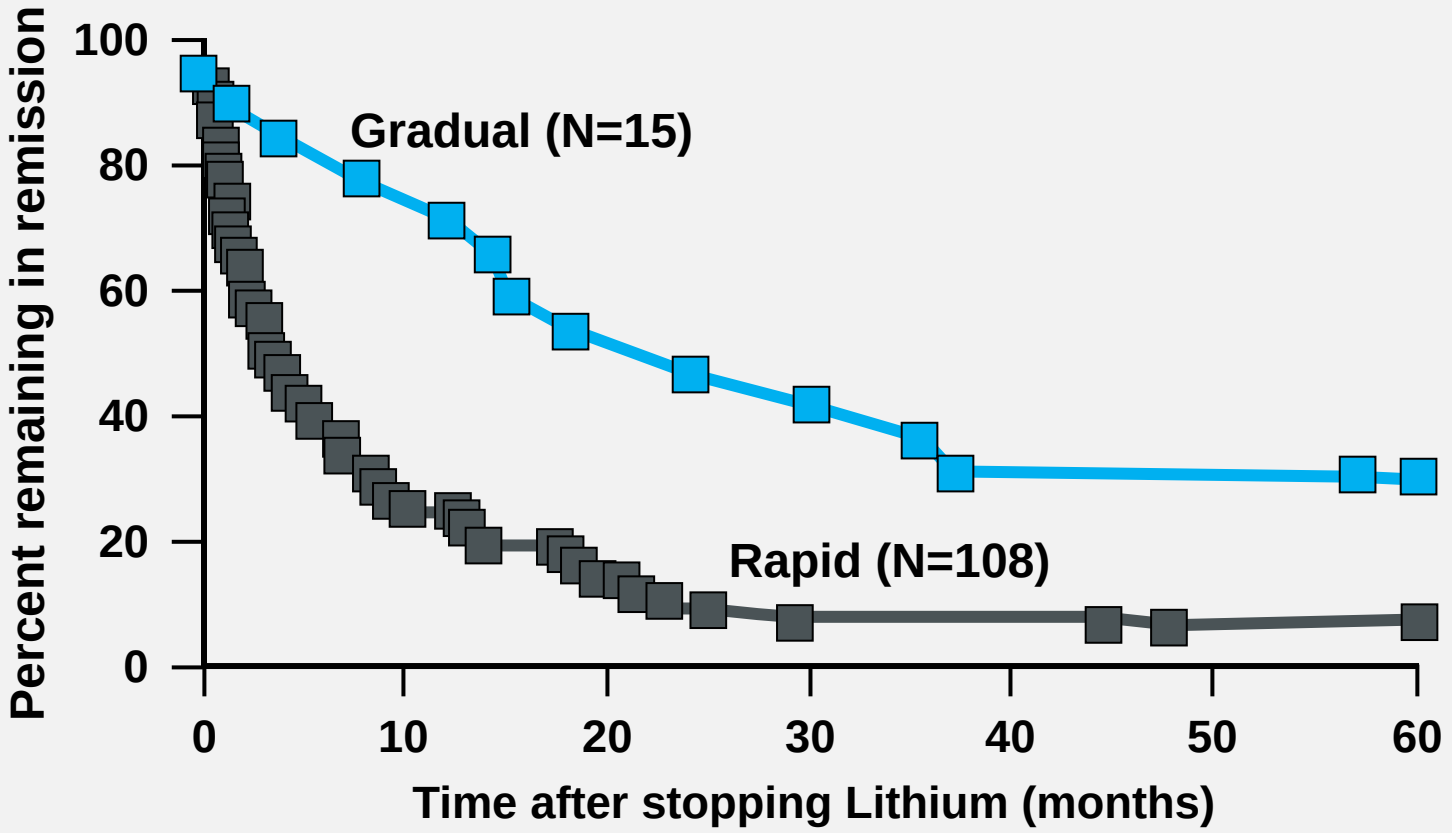
LITHIUM, WE KNOW ABOUT

Lithium withdrawal symptoms

Physical	Psychological
▪ Tremor ▪ Polyuria ▪ Muscular weakness ▪ Polydipsia ▪ Dryness of mouth	▪ Anxiety ▪ Nervousness ▪ Irritability ▪ Alertness ▪ Sleep disturbances ▪ Elated mood/mania ▪ Depressed mood

Baastrup PC, et al. Prophylactic lithium: double blind discontinuation in manic-depressive and recurrent-depressive disorders. Lancet 1970; **2**:326-330.
Klein E, et al. Discontinuation of lithium treatment in remitted bipolar patients: relationship between clinical outcome and changes in sleep-wake cycles. J Nerv Ment Dis 1991; **179**:499-501.

EFFECT OF DISCONTINUATION OF LITHIUM



From Suppes et al, Arch Gen Psych, 48, 1082-1088, 1991.

Outcome After Rapid vs Gradual Discontinuation of Lithium Treatment in Bipolar Disorders

Gianni L. Faedda, MD; Leonardo Tondo, MD; Ross J. Baldessarini, MD; Trisha Suppes, MD, PhD; Mauricio Tohen, MD, DrPH

Objective: Withdrawal of bipolar mood disorder (BP-I) patients from prolonged, stable lithium maintenance has a high risk of early recurrence, particularly of mania. We thus compared risks of stopping lithium rapidly vs gradually.

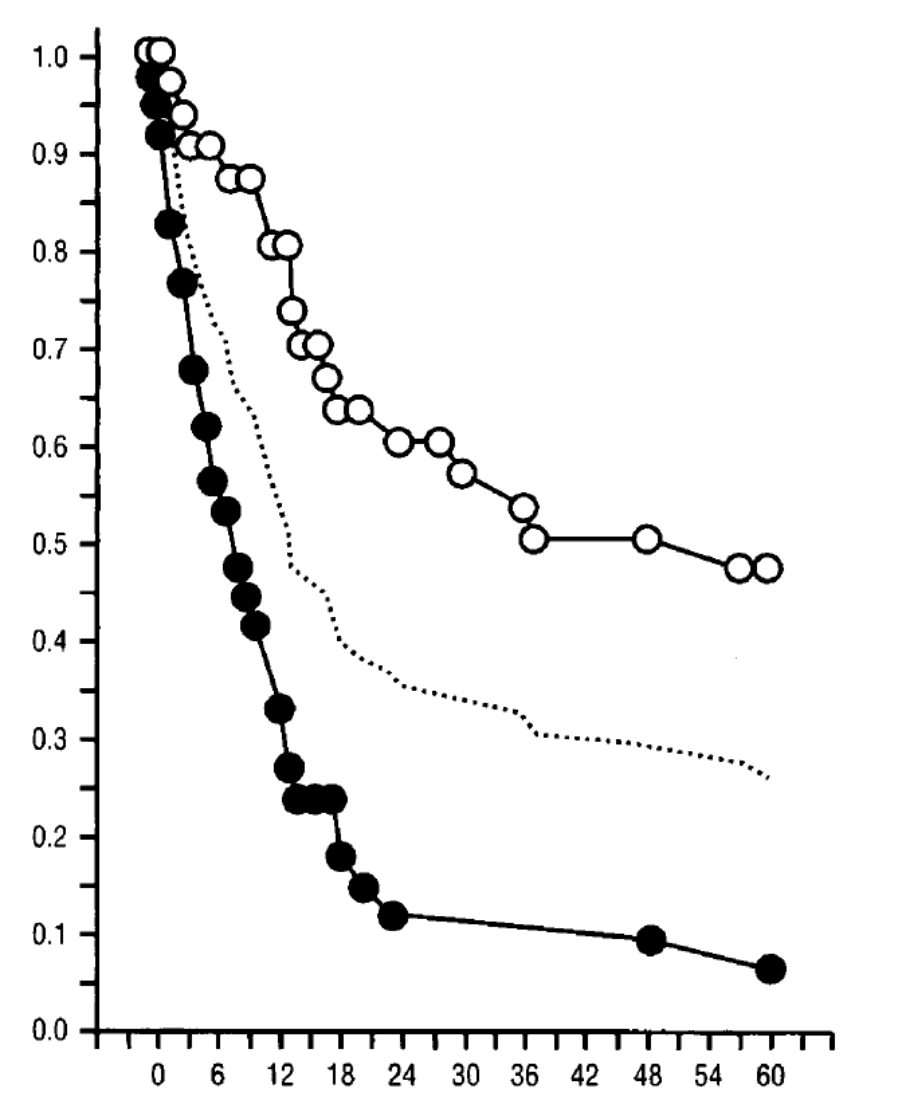
Design: Outpatients undergoing clinically determined discontinuation of lithium treatment at different rates were followed up prospectively to 5 years. Risks and timing of new episodes were analyzed.

Patients: Subjects (N=64) with a *DSM-III-R* BP disorder, previously stable on lithium monotherapy for 18 to 120 months (mean, 3.6 years) were followed up clinically after discontinuing lithium (elected in prolonged well-being in 67%). None was unavailable for follow-up, and subtyping (BP-I or BP-II) remained stable.

Results: Within 5 years, 75% had a recurrent episode; BP-I patients were 1.5-times less likely than BP-II to remain in remission. Polarity of first-recurrent and onset episodes was 80.8% concordant. Overall risk of a new episode of mania was significantly greater after rapid (<2) than gradual (2 to 4 weeks discontinuation (5-year hazard ratio=2.8); the difference in risk of depression was even greater hazard ratio=5.4). Recurrence rate was more elevated within months of rapid discontinuation (12-month hazard ratio=5.4). Recurrence rate was more elevated within months of rapid discontinuation (12-month hazard ratio=4.3) than at later times (2 to 5 years), when courses of "survival" over time were nearly parallel in both discontinuation groups.

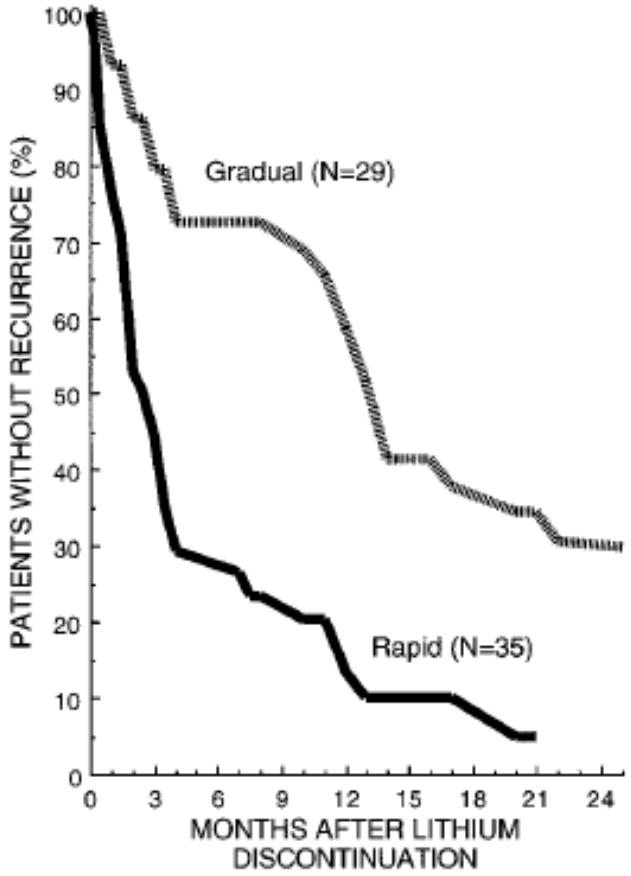
Conclusions: Risk of early recurrence of BP disorder following discontinuation of lithium maintenance is elevated, but may be both predictable (timing and polarity) and modifiable by gradual discontinuation.

(Arch Gen Psychiatry. 1993;50:448-455)


1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
6
12
18
24
30
36
42
48
54
60
Months off lithium
Gradual (2-4 weeks)
All
Rapid (< 2 weeks)

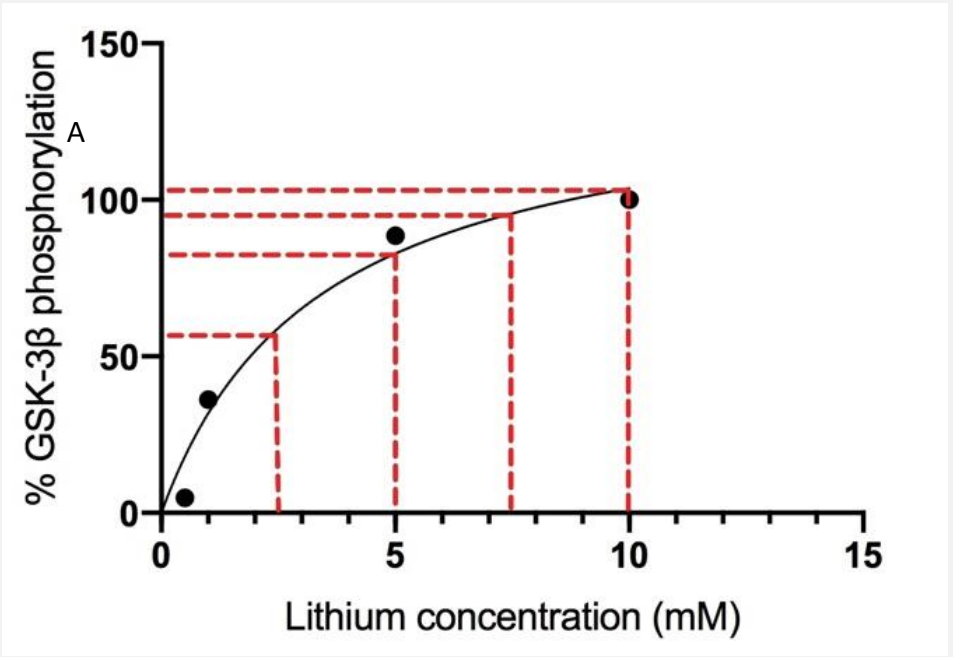
BALDESSARINI, R.J. ET AL. 1997. REDUCED MORBIDITY AFTER GRADUAL DISCONTINUATION OF LITHIUM TREATMENT FOR BIPOLAR I AND II DISORDERS: A REPLICATION STUDY. AM J PSYCHIATRY; 154: 551-553

FIGURE 1. Proportion of Patients Without Recurrence of Affective Episodes Over 24 Months After Gradual or Rapid Discontinuation of Lithium Treatment (Survival Analysis)[a]

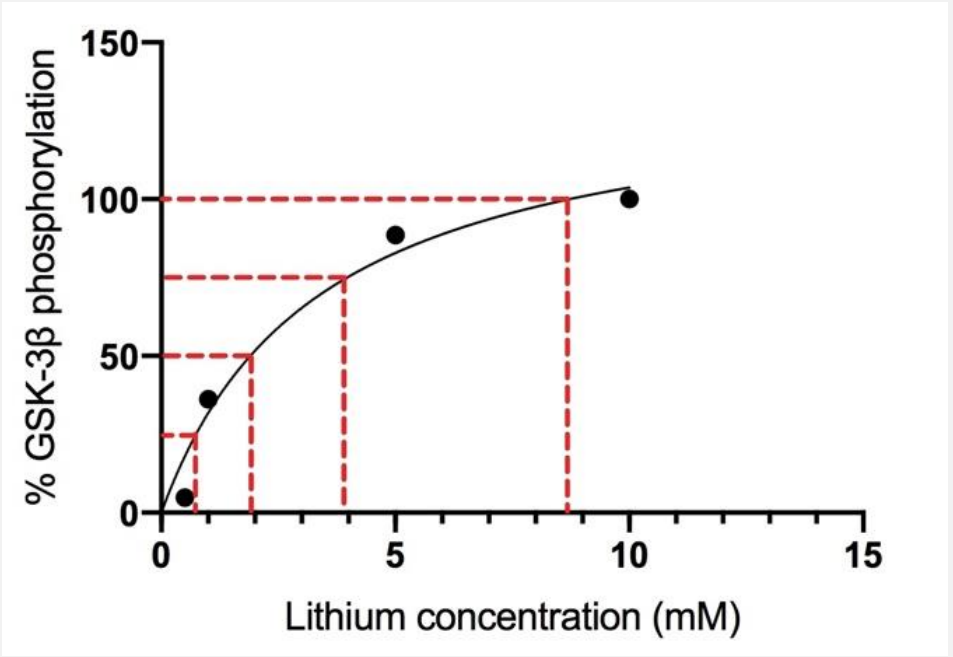


[a]Gradual–15–30 days; rapid–1–14 days.

A


% GSK-3β phosphorylation
150
100
50
0
0
5
10
15
Lithium concentration (mM)

B


% GSK-3β phosphorylation
150
100
50
0
0
5
10
15
Lithium concentration (mM)

Period	Lithium dose (mg)	Period	Lithium dose (mg)
1	1000	11	110
2	800	12	85
3	640	13	70
4	510	14	55
5	410	15	45
6	330	16	35
7	260	17	30
8	210	18	25
9	170	19	20
10	135	20	0

IT'S PROBABLY NOT JUST LITHIUM

Risk of Recurrence in Women With Bipolar Disorder During Pregnancy: Prospective Study of Mood Stabilizer Discontinuation

Adele C. Viguera, M.D.

Theodore Whitfield, Sc.D.

Ross J. Baldessarini, M.D.

D. Jeffrey Newport, M.D.

Zachary Stowe, M.D.

Alison Reminick, B.A.

Amanda Zurick, B.A.

Lee S. Cohen, M.D.

Objective: This study estimated the risk of recurrence of mood episodes among women with a history of bipolar disorder who continued or discontinued treatment with mood stabilizers during pregnancy.

Method: In a prospective observational clinical cohort study, the authors determined recurrence risk and survival-analysis-based time to recurrence of a new episode in 89 pregnant women with DSM-IV bipolar disorder. Eligible subjects were euthymic at conception and continued mood stabilizer treatment or discontinued treatment proximate to conception.

Results: The overall risk of at least one recurrence in pregnancy was 71%. Among women who discontinued versus continued mood stabilizer treatment, recurrence risk was twofold greater, median time to first recurrence was more than fourfold shorter, and the proportion of weeks ill during pregnancy was five times greater. Median recurrence latency was 11 times shorter after abrupt/rapid versus gradual discontinuation of mood stabilizer. Most recurrences were depressive or mixed (74%), and 47% occurred during the first trimester. Predictors of recurrence included bipolar II disorder diagnosis, earlier onset, more recurrences/year, recent illness, use of antidepressants, and use of anticonvulsants versus lithium.

Conclusions: Discontinuation of mood stabilizer, particularly abruptly, during pregnancy carries a high risk for new morbidity in women with bipolar disorder, especially for early depressive and dysphoric states. However, this risk is reduced markedly by continued mood stabilizer treatment. Treatment planning for pregnant women with bipolar disorder should consider not only the relative risks of fetal exposure to mood stabilizers but also the high risk of recurrence and morbidity associated with stopping maintenance mood stabilizer treatment.

(Am J Psychiatry 2007; 164:1817–1824)

TABLE 1. Demographic and Clinical Characteristics Associated With Mood Stabilizer Treatment Status Among Pregnant Women With Bipolar Disorder

Characteristic	All Subjects (N=89)		Subjects Who Discontinued Treatment (N=62)		Subjects Who Maintained Treatment (N=27)		p[a]
	N	%	N	%	N	%	
Demographic							
Age ≥30 years	63/89	70.8	45/62	72.6	18/27	66.7	0.62
Caucasian	86/89	96.6	59/62	95.2	27/27	100.0	0.55
Single	16/89	18.0	13/62	21.0	3/27	11.1	0.37
Education ≥12 years	88/89	98.9	61/62	98.4	27/27	100.0	1.00
Not employed outside the home	21/87	24.1	17/60	28.3	4/27	14.8	0.28
Previous pregnancy	57/89	64.0	41/62	66.1	16/27	59.3	0.63
Unplanned current pregnancy	30/89	33.7	24/62	38.7	6/27	22.2	0.15
Clinical							
Bipolar type I	61/89	68.5	36/62	58.1	25/27	92.6	0.001
Early onset at age <15 years	43/89	48.3	36/62	58.1	7/27	25.9	0.006
Lifetime illness ≥5 years	41/89	46.1	34/62	54.8	7/27	25.9	0.02
Average episodes/year ≥1	26/89	29.2	21/62	33.9	5/27	18.5	0.21
Current psychiatric comorbidity[b]	35/89	39.3	26/62	41.9	9/27	33.3	0.49
Prior rapid cycling	36/89	40.5	30/62	48.4	6/27	22.2	0.03
Prior psychiatric hospitalization	63/89	70.8	41/62	66.1	22/27	81.5	0.21
Prior psychotic features	58/89	65.2	36/62	58.1	22/27	81.5	0.05
Prior suicide attempt	31/88	35.2	25/61	41.0	6/27	22.2	0.10
≥12 months since last episode	53/88	60.2	33/61	54.1	20/27	74.1	0.10
Prior episodes in pregnancy or postpartum	42/47	89.4	31/34	91.2	11/13	84.6	0.61
Treatment							
Lithium as primary mood stabilizer	55/89	61.8	32/62	51.6	23/27	85.2	0.004
Anticonvulsant as primary mood stabilizer	32/89	36.0	29/62	46.8	3/27	11.1	0.001
Current adjunctive antidepressant use[c]	46/89	51.7	41/62	66.1	5/27	18.5	<0.001
Current adjunctive antipsychotic use[c]	24/89	27.0	13/62	21.0	11/27	40.7	0.07
≥Two psychotropics	63/89	70.8	50/62	80.7	13/27	48.2	0.004

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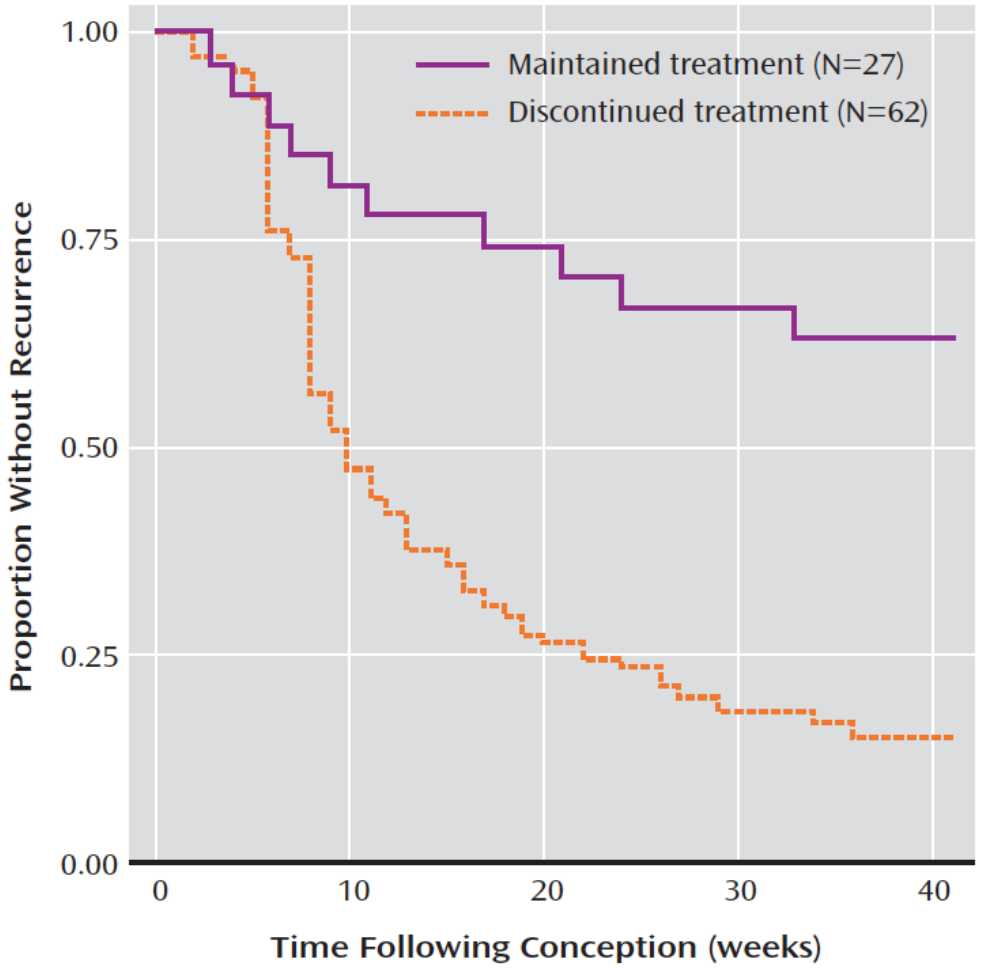
≥Two psychotropics	63/89	70.8	50/62	80.7	13/27	48.2	0.004

FIGURE 1. Kaplan-Meier Survival Functions for Pregnant Patients With Bipolar Disorder Who Maintained or Discontinued Treatment[a]



[a] Median time to first recurrence from the estimated date of conception was >41 weeks (95% CI=indeterminate) when mood stabilizer treatment was *maintained* (N=27) and only 9.0 weeks (95% CI=8.0–13.0) when treatment was *discontinued* (N=62; $\chi^2 \geq 17.9$, df=1, $p<0.0001$), a 4.6-fold difference.

Short report

Psychopharm

Journal of Psychopharmacology
22(4) (2008) 452–456
© 2008 British Association
for Psychopharmacology
ISSN 0269-8811
SAGE Publications Ltd,
Los Angeles, London,
New Delhi and Singapore
10.1177/0269881107085238

Bouncing back: is the bipolar rebound phenomenon peculiar to lithium? A retrospective naturalistic study

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T Mahmood *Consultant Psychiatrist, Leeds Mental Health Teaching NHS Trust, Malham House, Hyde Terrace, Leeds, UK.*

AH Young *Professor of Psychiatry, Department of Psychiatry, University of British Columbia, Vancouver BC, Canada.*

Abstract

In bipolar disorder the discontinuation of lithium prophylaxis is associated with early episode precipitation. Is this 'rebound' phenomenon peculiar to lithium? This naturalistic retrospective case note review investigated the frequency of immediate recurrence after discontinuation of any prophylactic treatment. Bipolar patients who stopped at least one medication after at least 6 months of remission were studied. A total of 310 case notes were examined in a systematic search. A total of 53 cases of discontinuation in 48 subjects were found. Discontinued medications included lithium, valproate, carbamazepine, typical and atypical antipsychotics and antidepressants. Recurrence occurred within 3 months of medication withdrawal in 39 cases (74%). Over half of the discontinuation episodes involved lithium: recurrence occurred in 86% of these cases. In the groups stopping other prophylactic agents, a majority of subjects suffered recurrence: anticonvulsants (89%), antipsychotics (64%) and antidepressants (58%). However, these groups were small and the clarity of the data was undermined by the simultaneous withdrawal of other agents. Manic and hypomanic episodes were the most common form of recurrences. Depressive episodes occurred proportionately most frequently following antidepressant withdrawal. More than half of recurrences required hospital admission. This study provides preliminary naturalistic evidence that early episode recurrence in bipolar disorder is not peculiar to lithium withdrawal but may occur following withdrawal of medication from all classes recommended in prophylaxis. These findings, if replicated, have important implications for clinical practice and for research.

Key words

bipolar disorder; naturalistic; rebound episode; retrospective

Table 2 The nature of the affective episode occurring following discontinuation of agents from each class. Episodes in which more than one agent was stopped are included in the data of each index agent and other discontinued agents are described

Medication discontinued	*n*	Manic/hypomanic episodes	Depressive episodes	Mixed episodes
Lithium	25	17 (68%) Two subjects also discontinued an anticonvulsant, one discontinued an antipsychotic	7 (28%) One subject also discontinued an antidepressant and an antipsychotic	1 (4%) This subject stopped lithium only
Anticonvulsants	8	5 (62.5%) Two subjects who stopped valproate also discontinued lithium. Two subjects who stopped carbamazepine also discontinued an antipsychotic and an antidepressant	2 (25%) One subject also stopped an antidepressant	1 (12.5%) This subject discontinued carbamazepine with no other maintenance agent
Antipsychotics	10	7 (70%) One subject also stopped lithium, two also stopped an anticonvulsant and an antidepressant	2 (20%) One subject also stopped lithium and an antidepressant	1 (10%) This subject stopped an antipsychotic but continued other prophylaxis
Antidepressants	7	2 (28.6%) These two subjects also stopped anticonvulsant and antipsychotic agents	5 (71.4%) One subject also stopped an anticonvulsant, another also stopped lithium and an antipsychotic	0 (0%)

Franks, et al, J Psychopharm 2008

ANTIDEPRESSANTS

Number of calls received (by drug)

Antidepressant	Number of calls	%
Paroxetine	690	39.36
Venlafaxine	252	14.38
Citalopram	141	8.04
Fluoxetine	133	7.59
Sertraline	84	4.79
Dothiepin/dosulepin	76	4.34
Mirtazapine	76	4.34
Amitriptyline	46	2.62
Parstelin (tranylcypromine+trifluoperazine)	39	2.22
Lofepramine	27	1.54
Clomipramine	25	1.43
Nefazodone	19	1.08
Moclobemide	19	1.08
Imipramine	17	0.97
Escitalopram	16	0.91
Phenelzine	14	0.80
Trazodone	13	0.74
Motival (fluphenazine+nortriptyline)	13	0.74
Flupentixol	11	0.63
Fluvoxamine	9	0.51
St John's Wort	9	0.51
Reboxetine	8	0.46
Trimipramine	4	0.23
Tranylcypromine	4	0.23
Isocarboxazid	3	0.17
Doxepin	2	0.11
Mianserin	1	0.06
Nortriptyline	1	0.06
Duloxetine	1	0.06
Amoxapine	0	0

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Journal of Affective Disorders 95 (2006) 129–133

JOURNAL OF AFFECTIVE DISORDERS

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Brief report

Antidepressant withdrawal symptoms—Telephone calls to a national medication helpline

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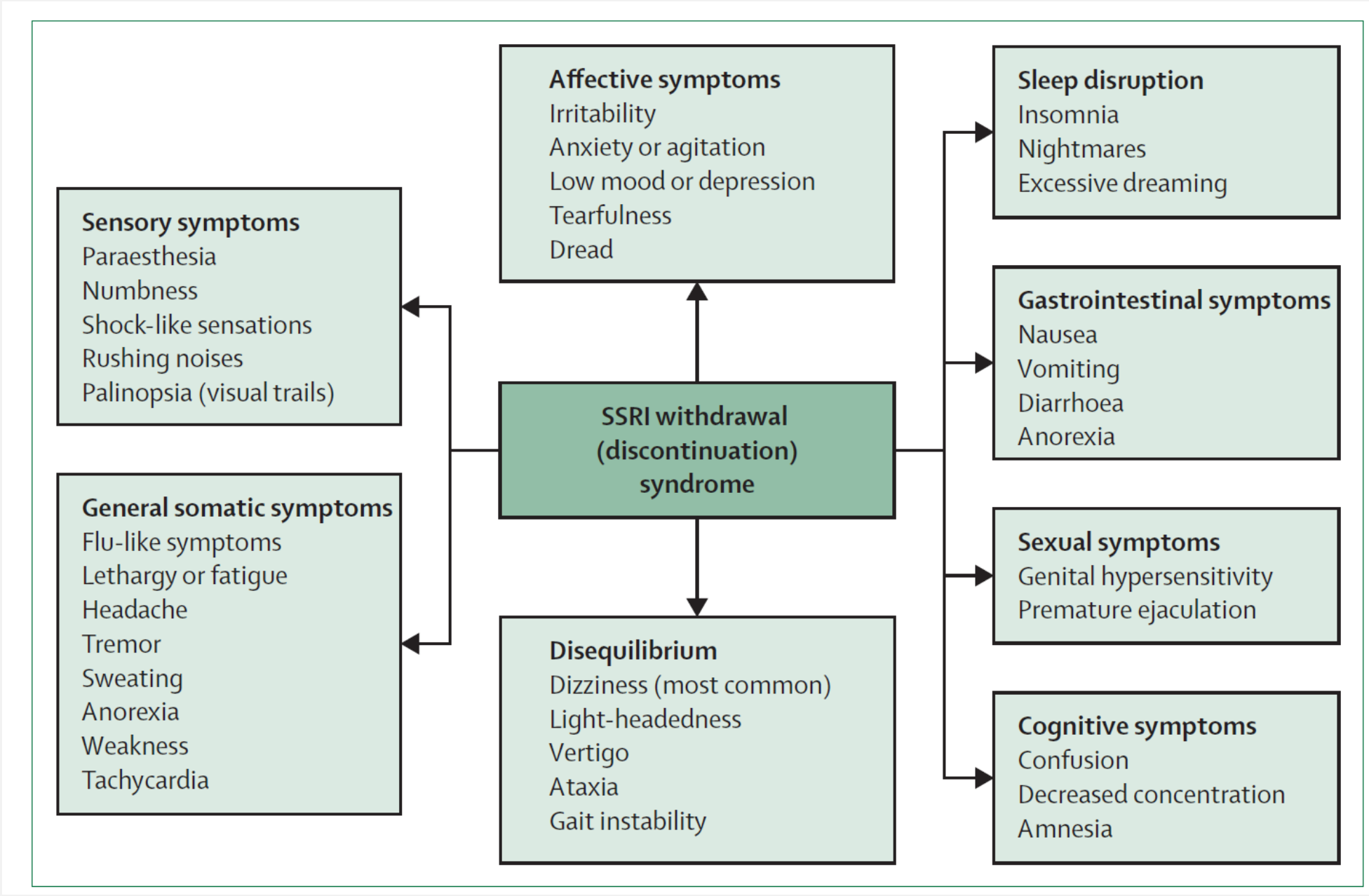
Received 19 December 2005; received in revised form 13 April 2006; accepted 18 April 2006
Available online 22 June 2006


Affective symptoms
Irritability
Anxiety or agitation
Low mood or depression
Tearfulness
Dread
Sleep disruption
Insomnia
Nightmares
Excessive dreaming
Sensory symptoms
Paraesthesia
Numbness
Shock-like sensations
Rushing noises
Palinopsia (visual trails)
Gastrointestinal symptoms
Nausea
Vomiting
Diarrhoea
Anorexia
SSRI withdrawal (discontinuation) syndrome
General somatic symptoms
Flu-like symptoms
Lethargy or fatigue
Headache
Tremor
Sweating
Anorexia
Weakness
Tachycardia
Sexual symptoms
Genital hypersensitivity
Premature ejaculation
Disequilibrium
Dizziness (most common)
Light-headedness
Vertigo
Ataxia
Gait instability
Cognitive symptoms
Confusion
Decreased concentration
Amnesia

	Number of patients	Medication	Tapering period	Lowest dose before zero	Outcome (% with discontinuation syndrome or DESS score)	Odds ratio AD versus taper	Comment
Groot and van Os (2018)[14]	895; antidepressant use median 2–5 years	Paroxetine, venlafaxine	Median 56 days (IQR 28–84 days)	0·5 mg (paroxetine); 1·0 mg (venlafaxine)	71% able to cease	N/A	Included patients who had had severe withdrawal syndrome previously
Tint and colleagues (2008)[16]	28	SSRI, venlafaxine	3 days; 14 days	Unknown	46% (3 days); 46% (14 days)	N/A	No difference between 3 day and 14 day taper
Baldwin and colleagues (2006)[30]	249	Paroxetine (N=115) or escitalopram (N=134)	7 days; 14 days	10 mg (paroxetine); 5 mg (escitalopram)	DESS 5·4 (SD 8·3) for paroxetine; DESS 3·2 (SD 4·8) for escitalopram; no difference between 7 and 14 days	N/A	No difference between 7 day and 14 day taper (but both slightly better than AD when compared with other studies)
Himei and Okamura (2006)[33]	385	Paroxetine	AD (N=80); taper, reducing by 10 mg every 2 weeks (N=305)	10 mg	33·8% (AD); 4·6% (taper)	7·4	36 patients with withdrawal syndrome were recommenced on paroxetine and tapered at 5 mg every 2–4 weeks with no re-emergence of symptoms
van Geffen (2005)[34]	74	Fluvoxamine, fluoxetine, paroxetine, citalopram	AD (N=14); taper, 2 weeks–4 months (N=52)	Unknown	86% (AD); 52% (taper)	1·65	Significant reduction in withdrawal symptoms with tapering compared with AD
Murata and colleagues (2010)[35]	56	Paroxetine	AD (N=23); taper, average 38·6 weeks, range 2–197 weeks (N=33)	10 mg	78·2% (AD); 6·1% (taper)	12	Odds ratio of 55·8 by univariate logistic regression of tapering compared with AD

DESS=Discontinuation-Emergent Signs and Symptoms. AD=abrupt discontinuation. N/A=not applicable.

Table 1: **Studies that measured withdrawal symptoms in patients tapered off antidepressants**

Therapeutic Advances in Psychopharmacology *Original Resear*

Protracted withdrawal syndrome after stopping antidepressants: a descriptive quantitative analysis of consumer narratives from a large internet forum

Ther Adv Psychopharma

2020, Vol. 10: 1–13

DOI: 10.1177/2045125320980573

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Michael P. Hengartner, Lukas Schulthess, Anders Sorensen and Adele Framer

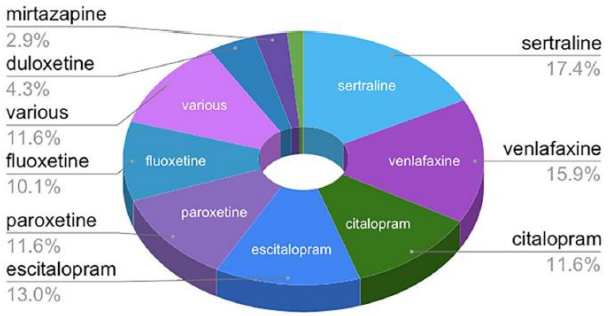
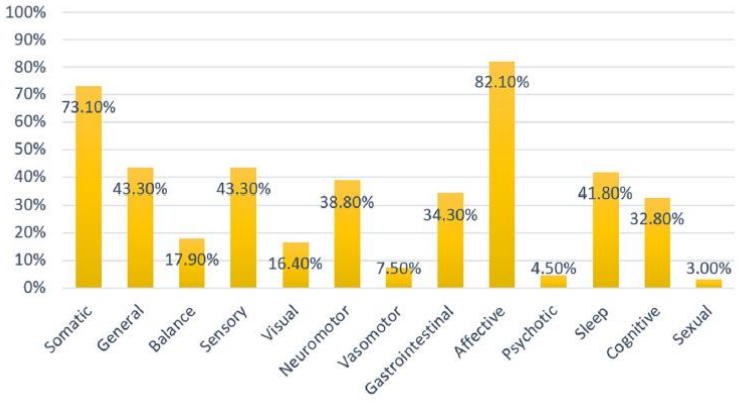
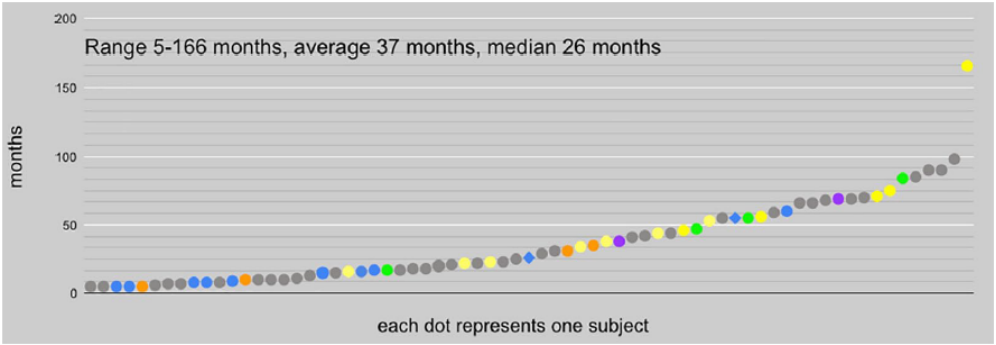
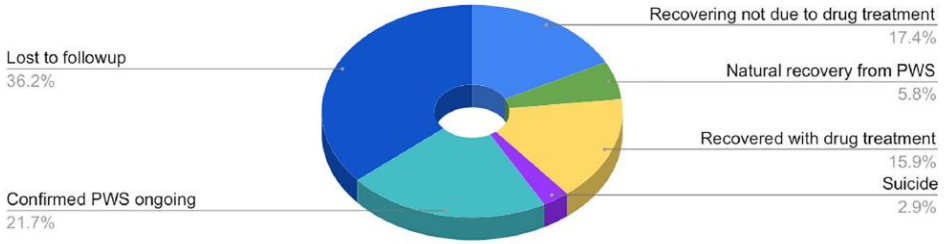


Figure 1. Antidepressants suspected to precipitate PWS.
PWS, protracted withdrawal syndrome.







Therapeutic Advances in Psychopharmacology *Review*

What I have learnt from helping thousands of people taper off antidepressants and other psychotropic medications

Ther Adv Psychopharmacol

2021, Vol. 11: 1–18

DOI: 10.1177/2045125321991274

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Adele Framer

***Abstract*:** Although psychiatric drug withdrawal syndromes have been recognized since the 1950s – recent studies confirm antidepressant withdrawal syndrome incidence upwards of 40% – medical information about how to safely go off the drugs has been lacking. To fill this gap, over the last 25 years, patients have developed a robust Internet-based subculture of peer support for tapering off psychiatric drugs and recovering from withdrawal syndrome. This account from the founder of such an online community covers lessons learned from thousands of patients regarding common experiences with medical providers, identification of adverse drug reactions, risk factors for withdrawal, tapering techniques, withdrawal

Article

Illness Risk Following Rapid Versus Gradual Discontinuation of Antidepressants

Ross J. Baldessarini, M.D.

Leonardo Tondo, M.D., M.S.

Carmen Ghiani, M.D.

Beatrice Lepri, Psy.D.

Objective: Rapid discontinuation of some psychotropic medications is followed by discontinuation symptoms as well as an increased risk of early illness recurrence. Recurrence occurs earlier after rapid than after gradual discontinuation with lithium and antipsychotics. The authors compared illness recurrence after rapid versus gradual discontinuation of antidepressants.

Method: The authors compared 398 patients with a DSM-IV diagnosis of recurrent major depressive disorder (N=224), panic disorder (N=75), bipolar II disorder (N=62), or bipolar I disorder (N=37). Two-thirds were women, the mean age was 42 years, and patients were treated with antidepressants for a mean of 8.5 months. Antidepressants were discontinued clinically, either rapidly (over 1–7 days; N=188) or gradually (over 14 days or more; N=210), with a mean follow-up duration of 2.8 years; patients who were ill at discontinuation were excluded from the analysis. The authors compared latency to first new illness episodes using survival analysis and Cox multivariate modeling.

Results: The latency to first illness with rapid discontinuation was 0.4 times that with gradual discontinuation, and the latency after rapid discontinuation was one-fourth the estimated average previous interepisode interval in the same patients. The effect was similar across antidepressant classes and across years; the pace of discontinuation had less effect with drugs of prolonged half-life. The effect also varied by diagnosis (bipolar I ≥ panic > bipolar II ≥ major depressive disorder) but not by episodes per year, duration of index illness, use of concomitant treatment, or antidepressant dose or duration.

Conclusions: The recurrence risk for depression or panic was much shorter after rapid than after gradual discontinuation of antidepressants. These findings have implications for both clinical management and the design and interpretation of clinical trials.

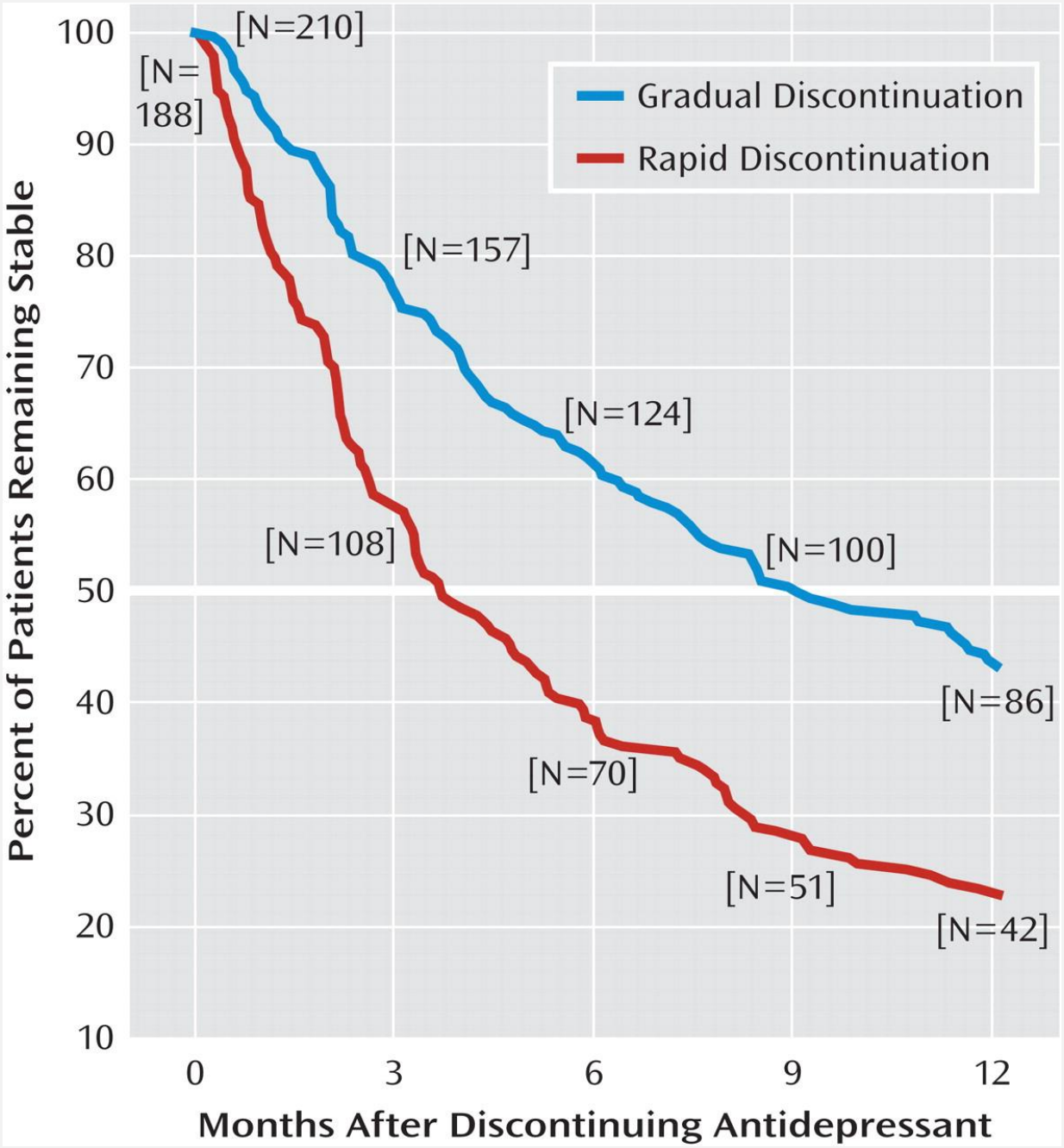
(Am J Psychiatry 2010; 167:934–941)

In addition to the use of antidepressants to treat acute depression or anxiety, prolonged antidepressant treatment is widely used to limit the high risk of relapse or recurrence (1–5). Overall, antidepressant sales rank third worldwide among all drugs (6) and are the leading prescription drug class in the United States among patients 18–64 years of age (7). They are prescribed more frequently by primary care physicians than by mental health specialists (8, 9). The effects of antidepressant withdrawal are of clinical and public interest. Stopping antidepressant treatment, especially abruptly, can provoke physiological withdrawal reactions, especially with short-acting serotonin reuptake inhibitors, and perhaps also with tricyclic antidepressants (10–19). Such reactions include somatic symptoms (gastrointestinal and other general somatic distress, including dysesthesias and paresthesias), movement disorders (bradykinesia and akathisia), and neuropsychiatric distress (typically anxiety and agitation, sleep disturbances, impaired cognition, and activation or mania) (10–18, 20).

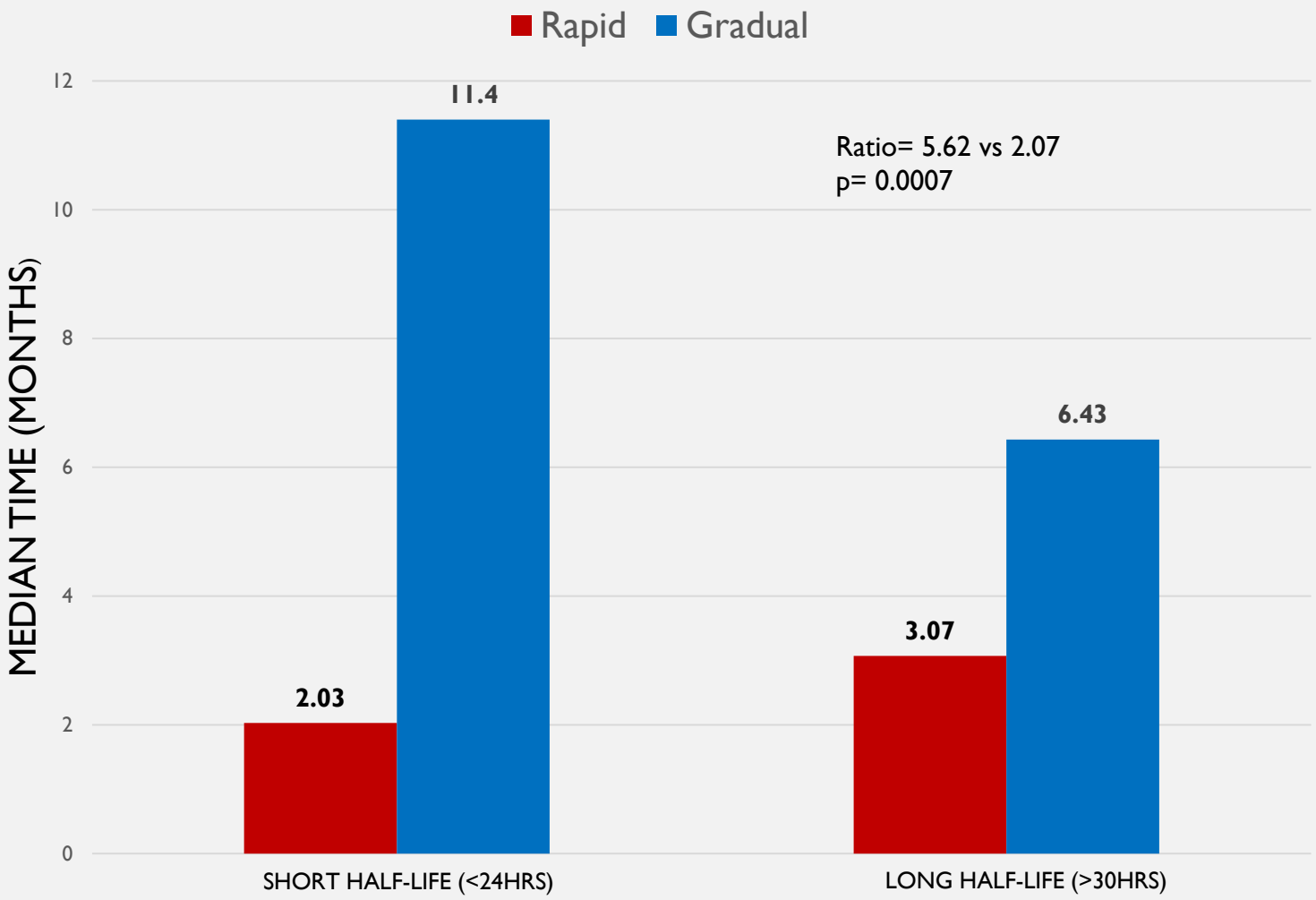
In addition to physiological withdrawal syndromes associated with some antidepressants, stopping long-term treatment with some agents can increase the risk of new episodes of illness and reduce the time to new episodes (1). Evidence for such an effect has been found for lithium in bipolar disorder (21, 22) and neuroleptics in psychotic disorders (23). Also, in a review comparing discontinued and continued long-term antidepressant treatment (1), we found that the overall 12-month recurrence risk was 2.3 times higher among patients who discontinued treatment, and the median time to a first depressive recurrence was one-third that of those who continued. Such contrasts may reflect loss of long-term prophylactic effectiveness or a confounding impact of treatment discontinuation itself (1, 21).

We found much shorter latency to occurrence of new mania or bipolar depression after stopping lithium abruptly versus gradually (24, 25) and earlier exacerbations of schizophrenia after discontinuing antipsychotics rapidly versus gradually (23). It is also noteworthy that physiological syndromes associated with antidepressant withdrawal appear to be more likely to occur with relatively rapidly cleared serotonin reuptake inhibitors (e.g., paroxetine and venlafaxine, as opposed to citalopram and fluoxetine),

This article is featured in this month's AJP Audio and is discussed in an editorial by Dr. Freedman (p. 886).


Gradual Discontinuation
Rapid Discontinuation
Percent of Patients Remaining Stable
100
90
80
70
60
50
40
30
20
10
0
3
6
9
12
Months After Discontinuing Antidepressant
[N=210]
[N=188]
[N=157]
[N=124]
[N=100]
[N=86]
[N=108]
[N=70]
[N=51]
[N=42]

Time to first recurrence



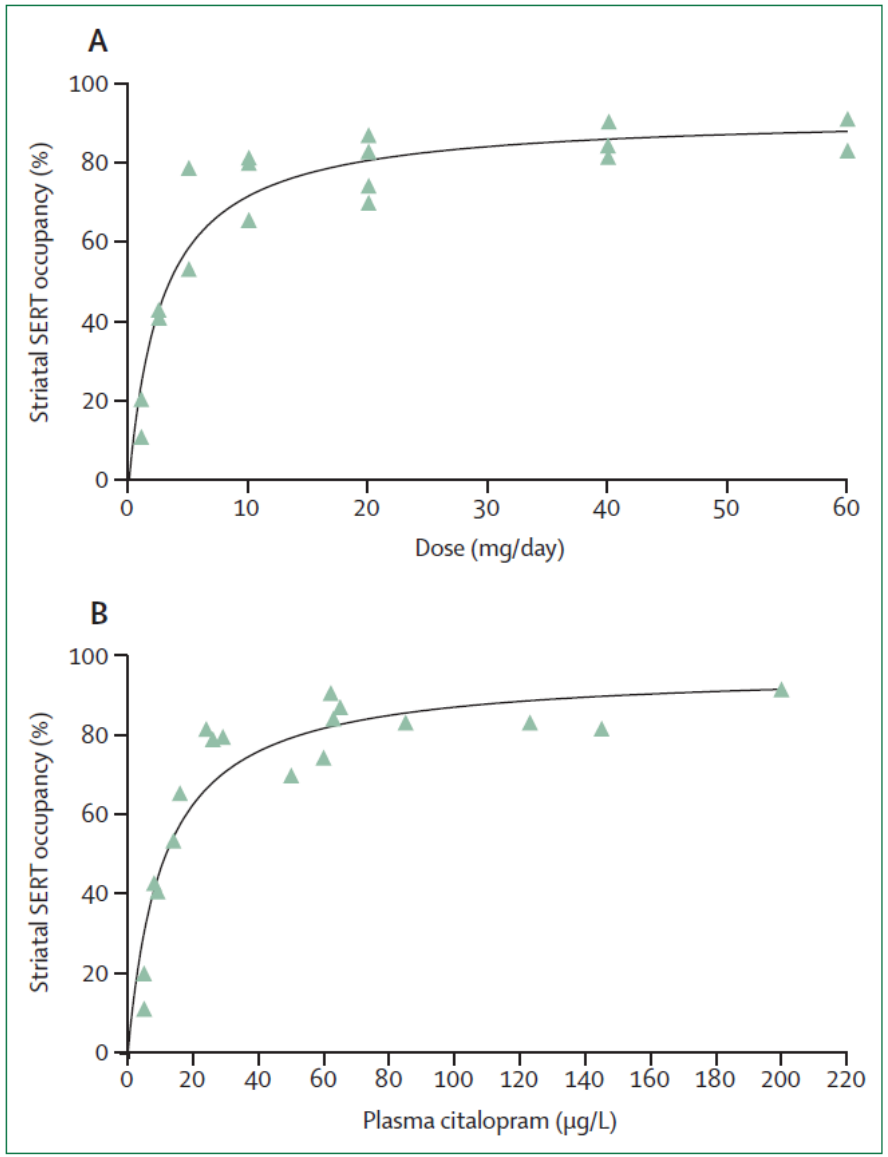


Figure 3: **Hyperbolic relationship between SERT and dose or plasma concentration of citalopram**

(A) Relationship between dose of citalopram and SERT occupancy (%). (B) Relationship between plasma level of citalopram and SERT occupancy (%). SERT=serotonin transporter. Reproduced from Meyer and colleagues,[60] by permission of the *American Journal of Psychiatry*.

Personal View

Tapering of SSRI treatment to mitigate withdrawal symptoms

Mark Abie Horowitz, David Taylor

All classes of drug that are prescribed to treat depression are associated with withdrawal syndromes. SSRI withdrawal syndrome occurs often and can be severe, and might compel patients to recommence their medication. Although the withdrawal syndrome can be differentiated from recurrence of the underlying disorder, it might also be mistaken for recurrence, leading to long-term unnecessary medication. Guidelines recommend short tapers, of between 2 weeks and 4 weeks, down to therapeutic minimum doses, or half-minimum doses, before complete cessation. Studies have shown that these tapers show minimal benefits over abrupt discontinuation, and are often not tolerated by patients. Tapers over a period of months and down to doses much lower than minimum therapeutic doses have shown greater success in reducing withdrawal symptoms. Other types of medication associated with withdrawal, such as benzodiazepenes, are tapered to reduce their biological effect at receptors by fixed amounts to minimise withdrawal symptoms. These dose reductions are done with exponential tapering programmes that reach very small doses. This method could have relevance for tapering of SSRIs. We examined the PET imaging data of serotonin transporter occupancy by SSRIs and found that hyperbolically reducing doses of SSRIs reduces their effect on serotonin transporter inhibition in a linear manner. We therefore suggest that SSRIs should be tapered hyperbolically and slowly to doses much lower than those of therapeutic minimums, in line with tapering regimens for other medications associated with withdrawal symptoms. Withdrawal symptoms will then be minimised.

Lancet Psychiatry 2019

Published Online March 5, 2019 http://dx.doi.org/10.1016/S2215-0366(19)30032-X

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Introduction

Many medications are associated with withdrawal syndromes, most commonly those that act on the cardiovascular system and CNS.[1] All major classes of antidepressants—monoamine oxidase inhibitors, tricyclic antidepressants, SSRIs, and SNRIs—are associated with withdrawal symptoms on cessation.[2,3] The term discontinuation syndrome was coined to refer to the withdrawal syndrome related to antidepressants.[4] SSRI discontinuation syndrome, as outlined in DSM-5,[5] and captured in the Discontinuation-Emergent Signs and Symptoms checklist,[6] comprises a wide variety of somatic and psychological symptoms (figure 1).

SSRI withdrawal symptoms can, in part, resemble the symptoms of anxiety or depression for which the medication was originally given.[5] However, the withdrawal syndrome can be distinguished from a relapse or recurrence of the underlying disorder by its quickness of onset (days rather than weeks),[1,7,8] rapid response to reintroduction of the SSRI (generally within hours, certainly within days),[1,7,9] and the presence of somatic and psychological symptoms quite distinct from the original illness (including dizziness, nausea, and shock-like sensations).[7,10] The withdrawal syndrome can be misdiagnosed as depressive recurrence, leading to prolonged treatment for patients who might not require it,[11–13] but it is not clear how often this occurs.[14]

SSRI withdrawal symptoms occur in many patients, with reported incidence varying from 42% to 100% for paroxetine,[4,15–18] and from 9% to 77% for fluoxetine,[4,15,17,18] with a mean rate of 53·6% for SSRIs across 14 studies that examined antidepressant withdrawal.[19] The incidence and severity appear to be influenced by half-life and receptor affinities, treatment duration and dose, method of tapering, and individual patient characteristics, potentially including anticipation effects.[1,9,20] A systematic review identified five studies that evaluated the severity of withdrawal effects and reported that nearly half of participants who had experienced withdrawal effects chose the most extreme option in the scale offered to them to describe the severity of those effects.[19] The discontinuation period (14 days after cessation) is also associated with a 60% increase in suicide attempts compared with previous users of antidepressants (the increased risk therefore attributed to the process of withdrawal and not to being untreated).[20]

SSRI withdrawal syndrome can last substantially longer than the period of 1–2 weeks[21] that has been previously suggested.[4] In one study, withdrawal symptoms generally lasted for up to 6 weeks, with a quarter of patients reporting symptoms that lasted more than 12 weeks.[18] Another study reported that for 86·7% of respondents the syndrome had lasted at least 2 months, for 58·6% it had lasted at least 1 year, and for 16·2% it had lasted for more than 3 years.[22] Case reports identify symptoms lasting for a year or longer.[22,23]

The increasingly long-term use of SSRIs (with nearly half of the patients in the UK who take antidepressants [usually SSRIs] doing so for more than 2 years)[10,24] has arisen in part because patients are unwilling to stop due to the aversive nature of the withdrawal syndrome,[19,25] and a scarcity of information on how to mitigate the syndrome.[19,22] Doctors feel that there is not enough guidance on how to proceed with discontinuation.[19]

Tapering SSRIs

Guidelines recommend short tapers of SSRIs, rather than abrupt discontinuation, to avoid withdrawal symptoms. The National Institute for Health and Care Excellence,[26] the British Association for Psychopharmacology,[27] the Monthly Index of Medical Specialities,[27] and UpToDate[28] suggest tapering periods of between 2 weeks and 4 weeks, with linear reductions of dose down to the minimum therapeutic dose, or half of the minimum therapeutic

Citalopram dose (mg)	SERT occupancy (%)
60·0	87·8%
40·0	85·9%
20·0	80·5%
19·0	80·0%
9·1	70·0%
5·4	60·0%
3·4	50·0%
2·3	40·0%
1·5	30·0%
0·8	20·0%
0·37	10·0%

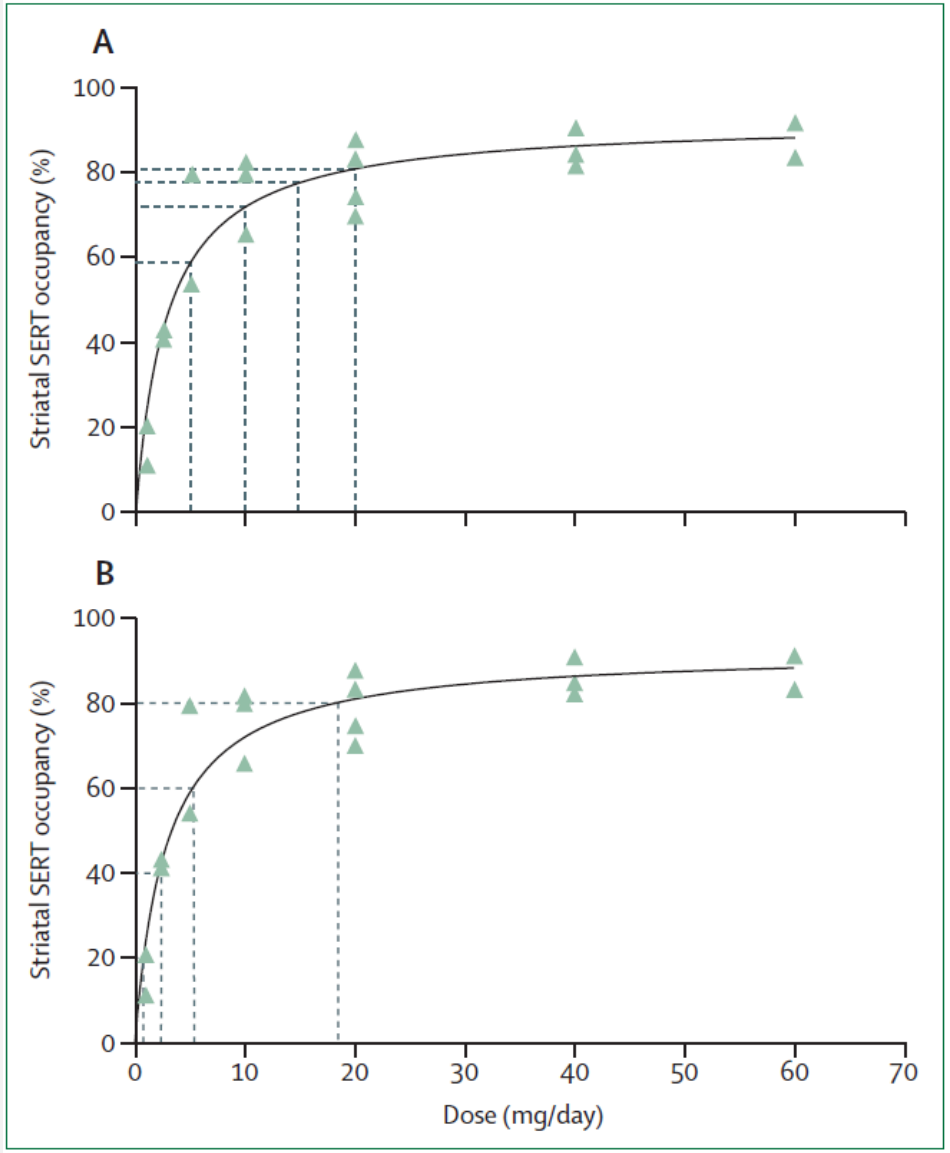
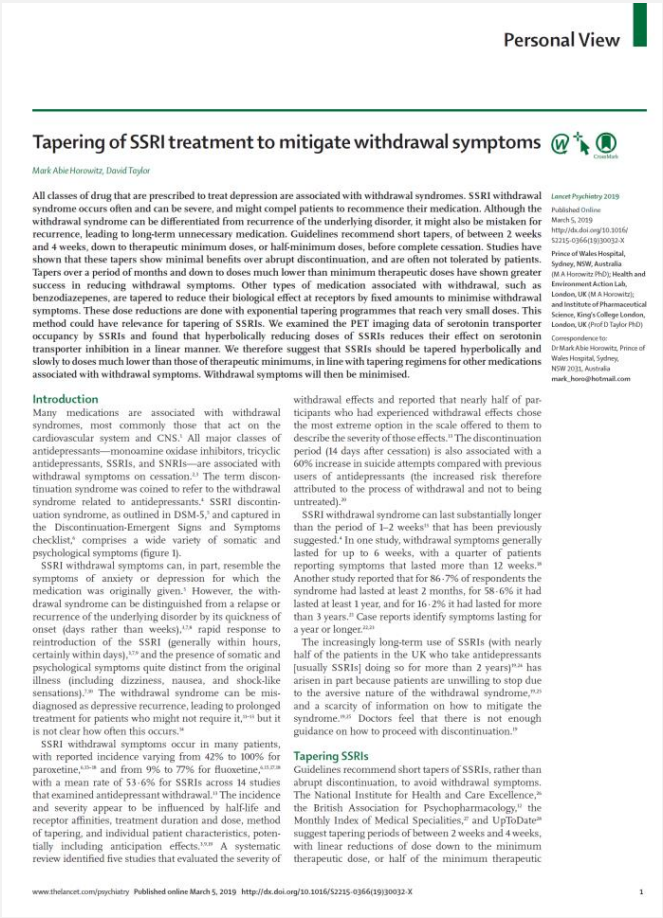


Figure 4: **Effect of linear and hyperbolic citalopram dose reductions on SERT occupancy**

(A) Linear dose decrements of citalopram (eg, intervals of 5 mg) produce exponentially increasing changes in SERT occupancy. (B) Hyperbolic dose decreases of citalopram produce linear changes in SERT occupancy (eg, intervals of 20% SERT occupancy). SERT=serotonin transporter. Reproduced from Meyer and colleagues,[60] by permission of the *American Journal of Psychiatry*.



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Therapeutic Advances in Psychopharmacology

Original Research

Outcome of antidepressant drug discontinuation with taperingstrips after 1–5 years

Peter C. Groot and Jim van Os

Ther Adv Psychopharmacol

2020, Vol. 10: 1–8

DOI: 10.1177/2045125320954609

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Medication	Frequency	Percentage
Amitriptyline	7	1.7
Bupropion	5	1.2
Citalopram	19	4.7
Duloxetine	1	0.3
Escitalopram	3	0.7
Fluoxetine	8	2.0
Fluvoxamine	3	0.7
Mirtazapine	14	3.4
Paroxetine	142	34.8
Sertraline	14	3.4
Venlafaxine	192	47.1
Total	408	100

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Total	408	100

Medication		Age	Years of use	Previous attempts	Previous withdrawal*	Current withdrawal**		Female sex	First attempters‡	Dichotomous success†
Venlafaxine (*n* = 192)	Mean	52.0	6.4	1.0	3.6	1.2	%	72.3%	37.0%	68.8%
	SD	14.6	5.8	1.1	1.8	1.5				
	Median	54	5	1	3	1				
	Min	18	0	0	1	0				
	Max	85	25	4	8	8				
Paroxetine (*n* = 142)	Mean	53.7	7.6	1.2	3.3	1.1	%	63.6%	39.4%	64.8%
	SD	13.5	6.9	1.2	1.8	1.6				
	Median	56	5	1	3	0				
	Min	21	0	0	0	0				
	Max	80	25	4	8	8				
Other antidepressant (*n* = 74)	Mean	48.8	6.3	1.0	3.2	1.0	%	77.0%	41.9%	70.3%
	SD	15.7	7.2	1.2	2.0	1.5				
	Median	49	3	1	3	0				
	Min	19	0	0	0	0				
	Max	82	35	4	8	8				
Total (*n* = 408)	Mean	52.0	6.8	1.1	3.4	1.1	%	70.1%	38.7%	67.6%
	SD	14.5	6.5	1.1	1.8	1.5				
	Median	54	4	1	3	1				
	min	18	0	0	0	0				
	max	85	35	4	8	8				

Medication		Age	Years of use	Previous attempts	Previous withdrawal*	Current withdrawal**		Female sex	First attempters‡	Dichotomous success†
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	Min	18	0	0	1	0				
	Max	85	25	4	8	8				
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	SD	13.5	6.9	1.2	1.8	1.6				
	Median	56	5	1	3	0				
	Min	21	0	0	0	0				
	Max	80	25	4	8	8				
Other antidepressant (*n* = 74)	Mean	48.8	6.3	1.0	3.2	1.0	%	77.0%	41.9%	70.3%
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	min	18	0	0	0	0				
	max	85	35	4	8	8				

“I had one sixteenth of an ounce of junk with me. I figured this was enough to taper off, and I had a reduction schedule carefully worked out. It was supposed to take 12 days. I had the junk in solution, and in another bottle distilled water. Every time I took a dropper of solution out to use it, I put the same amount of distilled water in the junk solution bottle. Eventually I would be shooting plain water. This method is well known to all junkies.”

William Burroughs (1953), Junkie, p. 72

Thank you

Special thanks to Dr Mark Horowitz