PERSISTENT TARDIVE REBOUND PANIC DISORDER, REBOUND ANXIETY AND INSOMNIA FOLLOWING PAROXETINE WITHDRAWAL: A REVIEW OF REBOUND-WITHDRAWAL PHENOMENA

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ABSTRACT

Objective
To describe tardive rebound anxiety phenomena (panic, anxiety and insomnia) following abrupt paroxetine discontinuation.

Method
Case report, with comprehensive literature review on rebound and withdrawal phenomena associated with psychotropic medications.

Results
Three different discontinuation syndromes with psychotropics are described: (1) new-onset CNS-depressant type withdrawal symptoms (minor and major); (2) rebound syndromes; and (3) supersensitivity symptoms. Abrupt paroxetine discontinuation has been well described and fits the first category. Tardive rebound panic disorder-phenomena with paroxetine has some features of the supersensitivity category.

Conclusion
Chronic paroxetine treatment may lead to 5-HT_2-receptor down regulation, with desensitization of 5-HT_{1A} and 5-HT_2 receptors, which may contribute to tardive rebound symptoms upon abrupt withdrawal. Early reports suggest that genetic factors may also contribute to withdrawal symptoms in susceptible individuals. Cholinergic rebound may also occur and could explain tardive insomnia and anxiety in paroxetine withdrawal.

Key Words: *Paroxetine; panic; tardive; rebound; discontinuation; withdrawal*

Rebound insomnia was first described by Kales and colleagues following the withdrawal of short beta half-life benzodiazepines.[1] Several years later, rebound anxiety associated with short beta half-life benzodiazepines was also observed by Chouinard and colleagues.[2,3] Since the introduction of the selective serotonin reuptake inhibitors (SSRIs), reports of acute symptoms of the CNS-depressant withdrawal minor type have emerged following abrupt discontinuation.[4-8] We present a case of delayed rebound syndrome consisting of tardive rebound panic attacks, rebound anxiety, and insomnia phenomena, all following abrupt paroxetine discontinuation after long-term therapy. We propose pharmacological mechanisms for this phenomenon, and an approach for distinguishing among the different clinical manifestations observed with abrupt psychotropic discontinuation.

Case Report
The patient is a 73–year-old female who presented to the emergency room (ER) two months

following abrupt paroxetine cessation. She reported a longstanding history of panic disorder along with generalized anxiety disorder and several recurrent episodes of major depression. The most recent episode of depression dated seven years previously, and the patient had been maintained on continuous paroxetine 20-mg daily since. She had been functioning well, including her usual activities of daily living and community participation. Relevant medical history included: hypothyroidism, hypertension, hypercholesterolemia, gastric ulcer, and abdominal artery aneurysm, all of which were stable. Pharmacotherapy regimen included L-thyroxine 0.05-mg daily (QD), losartan 50-mg QD, pravastatin 20-mg QD, omeprazole 20-mg QD, and aspirin 80-mg QD.

In the ER, she described a four-week history of persistent and worsening anxiety symptoms that had commenced one month following abrupt paroxetine discontinuation. The patient decided to stop paroxetine following reading media reports that suggested paroxetine to be "addictive". In the first month following the abrupt cessation, the patient denied any withdrawal symptoms. However, one month later, she began to have waves of anxiety and tension, all leading to further anticipatory anxiety. Rebound panic symptoms were elicited - shortness of breath, palpitations, and nausea, as well as feelings of depersonalization and derealization, combined with initial and middle insomnia. No depressive symptoms were elicited and the patient denied other somatic complaints such as paresthesias, dizziness, or autonomic symptoms. Despite an eight-week period following paroxetine cessation, rebound symptoms were not abating and were becoming worse than her original presentation.

Medical evaluation in the ER was noncontributory, and following psychiatric evaluation, a diagnosis of panic disorder (DSM-IV-TR) was made and the patient begun on clonazepam 2-mg/day, with outpatient follow-up. However, assessment four weeks later noted poor response to this strategy. Citalopram 20-mg daily for four additional weeks also led to no sustainable gains. Due to progressive disability (including agoraphobia and frequent ER visits), the patient eventually agreed to resume paroxetine 20-mg daily. Within two days, her symptoms started to abate and were completely remitted by two weeks. They did not recur during three months of follow-up.

DISCUSSION

Three different types of discontinuation syndromes with psychotropic agents have been described:

1. new-onset CNS-depressant-type withdrawal symptoms (minor and major);
2. rebound syndromes (e.g., insomnia and anxiety); and
3. supersensitivity symptoms (e.g., psychosis and dyskinesias).[9]

Clinicians ought to be able to distinguish between the recurrence of the underlying illness (e.g., pre-existing panic disorder) versus one of these three discontinuation phenomena when assessing patients.

The first syndrome consists of *new-onset* withdrawal symptoms following cessation of narcotics, barbiturates, benzodiazepines, various antidepressants, and low-potency antipsychotics.[3,10,11] The discontinuation syndrome associated with the SSRI agents, and in particular, paroxetine, appear to fit this category of minor withdrawal symptoms.[12,13] A review by Black and colleagues on discontinuation symptoms specific to SSRIs found that, of forty-six case reports and three studies reviewed, the most common minor new withdrawal symptoms included: physical (headache, dizziness, visual disturbances, vertigo, gait instability, tremor, nausea, emesis, and diarrhea); affective (anxiety and irritability); and psychomotor (agitation and paresthesias).[13] Symptoms generally commenced within 48 hours and lasted approximately one week.[13] Studies examining discontinuation reactions to SSRI agents are summarized in Table 1.

TABLE 1 Studies on SSRI Discontinuation Reactions

Study	Drug Withdrawn	N	Withdrawal Symptoms	
			N	%
Black et al. (14)	Fluvoxamine	14	12	86
Mallya et al. (15)	Fluvoxamine	17	4	24
Barr et al. (16)	Paroxetine	6	3	50
Keuthen et al. (17)	Paroxetine	13	5	39
Oehrberg et al (18)	Paroxetine	55	19	35
	Placebo	52	7	14
Bhaumik and Windgust (19)	Paroxetine	12	5	42
	Fluoxetine	?	0	0
Coupland et al. (20)	Clomipramine	13	4	31
	Paroxetine	50	10	20
	Fluvoxamine	43	6	14
	Sertraline	45	1	2
	Fluoxetine	20	0	0
Rosenbaum et al. (21)	Fluoxetine	81	11	14
	Sertraline	79	47	60
	Paroxetine	82	54	66
Bogetto et al. (22)	Paroxetine	52	22	85
	Fluoxetine	45	4	15

(Adapted and modified from Reference 12)

Major new-onset CNS-depressant discontinuation symptoms would include new-onset seizures, psychosis, or death.[3] Management of patients in these cases may include adding a similar agent with a longer half-life (e.g., fluoxetine or diazepam), and then gradual tapering of the offending agent.

The second syndrome consisting of *rebound* symptoms (such as insomnia and increased anxiety) following abrupt medication discontinuation has been noted with benzodiazepines, especially agents with short terminal half-life. This reversible syndrome consists of symptoms of greater intensity than prior to initiation of pharmacotherapy and remits quickly when the offending agent is reinstituted.[1-3] Unlike the first syndrome, using an alternate agent from the same class does not appear to have positive effects, and as a result, management should ideally include reinstituting the previously used agent.

The final supersensitivity syndrome likely results from chronic use of antipsychotic agents, appears acutely during dosage adjustments (either an increase or decrease), and manifests as *abrupt exacerbation* of positive psychotic symptoms without presence of negative symptoms. This phenomenon may also occur with antidepressant agents, including SSRI agents such as paroxetine. The syndrome has been postulated to result from chronic dopaminergic receptor changes in the mesolimbic areas, similar to chronic dopaminergic changes in the nigrostriatum for tardive dyskinesia.[23,24] Management here appears to be less definitive and may include substitution with a higher potency agent; combining pharmacotherapy with other agents; or temporarily increasing dosage of the offending agent.[3,23,24]

In our patient, panic symptoms became apparent one month following abrupt paroxetine discontinuation, unlike the minor withdrawal symptoms, which have a shorter onset and duration. In addition, unlike the underlying panic, anxiety, and depressive disorders that she had previously suffered from, her presenting symptoms of panic and anxiety were distinguished by their crescendo-like occurrence and occurring in absence of any obvious triggers. She denied the well-described typical acute withdrawal symptoms such as paresthesias, dizziness, or autonomic symptoms. Finally, her symptoms

remitted rapidly after resuming paroxetine and were not helped with either benzodiazepine or an alternative SSRI. This rebound phenomenon has also been noted by others with no clear explanation regarding the mechanism.[21] However, due to persistence and non-responsiveness to an alternative SSRI or benzodiazepine, and due to their tardive emergence, the symptoms noted in our patient mimic both rebound as well as supersensitivity syndromes.

Unlike the tardive panic syndrome described in our patient, acute new withdrawal anxiety symptoms following abrupt cessation have been well described.[4-8,14-22] Among the published reports comparing the SSRIs, paroxetine appears to be the most commonly implicated SSRI in leading to new minor withdrawal symptoms.[13] Compared to fluoxetine, paroxetine users were more likely to suffer withdrawal effects, including increased depressive symptoms and greater global impairment.[22,23] A prospective placebo-controlled double-blind trial of SSRI discontinuation also noted that the paroxetine-treated group experienced the highest rate of new discontinuation symptoms compared to sertraline or fluoxetine.[25] More cognitive difficulties have been reported with paroxetine discontinuation than other SSRIs in a comparative trial.[26] Finally, paroxetine use during the third trimester of pregnancy has been reported to cause perinatal withdrawal symptoms including respiratory distress, hypoglycemia, and jaundice.[27] Taken together, these reports caution clinicians and patients that SSRI agents (particularly paroxetine) should be gradually tapered when stopping the agent.

Several mechanisms could explain paroxetine-induced discontinuation syndromes.[28] At risk appear to be females; those with underlying anxiety and dysthymic disorders; and those with earlier age of onset of dysthymia.[7,22] Pharmacologically, paroxetine possesses high affinities for both serotonin (5-HT) and norepinephrine transporters,[29] and chronic administration in susceptible individuals may result in 5-HT_2 receptor down regulation following continuous relative serotonin excess. Desensitization of the 5-HT_2 receptor transmembrane signaling system and desensitization of 5-HT_{1A} autoreceptors may also occur. Therefore, abrupt cessation of paroxetine would result in reduction of central 5-HT stores to levels insufficient for adequate neuronal signaling, leading to the observed withdrawal-like symptoms.

Unique among SSRIs, paroxetine also possesses affinity for cholinergic receptors similar to tricyclic antidepressants (TCAs)[8,29], which could further lead to both new withdrawal and rebound symptoms as well as cognitive difficulties.[26] Thus, following abrupt cessation, a cholinergic rebound phenomenon may also occur, leading to excess cholinergic rebound activity characterized by sedation, headaches, nausea, vomiting, and diarrhea, all usually of short duration, but which can persist and result in tardive insomnia and anxiety.

Finally, to further elucidate the mechanisms underlying the clinical observations of withdrawal phenomena discussed above, Murphy and colleagues recently completed a pharmacogenetic study of antidepressant discontinuation.[30] Patients with major depressive disorder were genotyped and then treated with either paroxetine (n=124) or mirtazapine (n=122), followed by monitoring during antidepressant discontinuation. Genetic variations in cytochrome 2D6 activity failed to reveal differences in discontinuation-related adverse effects in both treatment groups. However, survival analysis showed paroxetine-induced discontinuation to be strongly associated with the HTR2A C/C genotype (a measure of serotonergic receptor activity in the brain), which could further explain the adverse effects observed with paroxetine discontinuation.[30] Side effect severity in paroxetine-treated patients with the C/C allele genotype was greater, whereas HTR2A genotyping had no effect on the mirtazapine-treatment group. The researchers further suggested that these observations could be accounted for by pharmacologic differences between the two agents[30] –as mirtazapine has additional blockade of the 5-HT_{2A} receptors unlike paroxetine[31], and thus could negate the deleterious effects of serotonin functional variation following medication discontinuation. Pharmacogenetics, while still developing in clinical psychiatry, will likely revolutionize therapeutic choices as more becomes known about genetic variations and treatment outcomes. In the meantime, clinicians, given the accumulating evidence of new, intense, and continued withdrawal rebound symptoms

upon paroxetine discontinuation, should maintain ongoing vigilance for possible tardive rebound panic attacks after chronic paroxetine administration.

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