The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column is a composite with characteristics of several real patients.

Recognition and management of antidepressant discontinuation syndrome

Venkat Bhat, MD; Sidney H. Kennedy, MD

A 22-year-old woman presented to the emergency department during the flu season with flu-like symptoms that had persisted for 3 days and reported intense anxiety and sadness, dizziness with movement, insomnia, nausea, periodic "electric shock" sensations and seeing flashes of light. A week prior, she had stopped taking 150 mg venlafaxine. Her symptoms resolved when venlafaxine was reintroduced. It was then tapered over 4 weeks and switched to 5 mg vortioxetine. One year following remission, vortioxetine was discontinued over 2 weeks without onset of discontinuation symptoms.

Antidepressant discontinuation syndrome (ADDS) is a new entity in DSM-5 in the category of medication-induced movement disorders and other adverse effects of medication.[1] Symptoms generally begin 2–4 days after abrupt discontinuation of antidepressants taken continuously for at least 1 month.[1] ADDS is often seen during taper or after missed doses with short half-life agents, such as paroxetine and venlafaxine.[2–4]

Up to 70% of patients prescribed antidepressants occasionally skip doses.[5] For diagnosis, ADDS symptoms should not be present before dose reduction and should not be better explained by another psychiatric disorder.[1] Symptoms that fit the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), can be experienced by up to 40% of patients upon abrupt antidepressant discontinuation.[2,6–8] The Discontinuation Emergent Signs and Symptoms Scale (DESS) can be used to quantify symptoms.[2] ADDS can also include worsening symptoms of the original illness and can be mistaken for a relapse.[1,2] In addition, misdiagnosing the physical symptoms of ADDS can lead to unnecessary medical and laboratory workup.[9]

Patients must be informed of ADDS when starting treatment and of the differences between ADDS and withdrawal associated with addiction.[10] Although withdrawal symptoms and ADDS could have neurobiological similarities, such as a "receptor rebound" phenomenon upon sudden discontinuation,[2,7,11,12] there are important differences. Unlike antidepressants, use of drugs of abuse include reinforcing/euphoric effects of the drug and associated drug-seeking behaviour.[1] Symptoms of ADDS are associated with short half-life agents, and symptoms are usually mild and short-lived.[1]

Risk for ADDS is highest with short half-life agents, high doses and rapid taper.[1,10] The risk also appears to be higher for those who have taken antidepressants for 8 weeks or longer,[13] experience anxiety symptoms when starting a selective serotonin reuptake inhibitor (SSRI), are taking other centrally acting medications (e.g., antipsychotics, antihypertensives, antihistamines), are children/adolescents, or have a history of ADDS episodes.[2,10] ADDS has been reported with all monoamine oxidase inhibitors (MAOIs) and commonly presents with agitation, movement disorders, and sleep and speech problems.[10] ADDS has most commonly been reported for amitriptyline and imipramine among tricyclic antidepressants (TCAs) and paroxetine and venlafaxine among SSRIs.[10] Neonatal venlafaxine discontinuation syndrome upon maternal venlafaxine discontinuation before childbirth has been reported.[14] ADDS with TCAs and SSRIs commonly presents with flu-like symptoms, insomnia and vivid dreams, and with additional "shock-like" sensations with SSRIs.[10] Movement disorders have occasionally been reported with both TCAs and SSRIs.[10] Symptoms of ADDS have not been reported with abrupt discontinuation of agomelatine[10,15,16] or vortioxetine.[10,17]

Prevention of ADDS, particularly for short half-life agents, includes a gradual discontinuation over 4 weeks with a slow rate of taper at the end,[2,6,7] and a longer taper for those on MAOIs. Importantly, patients need reassurance that ADDS is common, self-limited and often mild.[2] If symptoms are severe, restarting the original antidepressant or another antidepressant with a long half-life in the same class can be followed by gradual taper.[2] When ADDS symptoms persist despite slow taper,[18] abrupt withdrawal options could be considered, particularly when patients prefer a short period of intense symptoms to a longer period of mild symptoms associated with a gradual taper.[10] Importantly, there is limited evidence on ADDS management; some studies suggest benefits with fluoxetine for ADDS associated with venlafaxine[19] or clomipramine[20] and anticholinergic agents in TCA withdrawal.[21] Although one recommendation is to switch patients to long-acting antidepressants like fluoxetine before withdrawal of venlafaxine, there are no controlled studies to identify the best option (taper v. substitution).[22]

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Competing interests: V. Bhat is supported by the Canadian Biomarker Integration Network for Depression. S. Kennedy reports grants from BMS, Janssen, Lundbeck, Pfizer, Servier, St. Jude Medical, the Ontario Brain Institute, Canadian Institutes of Health Research, Brain Canada, the Ontario Mental Health Foundation and the Ontario Research Fund; is on the advisory boards of and has received personal fees from Allergan, AstraZeneca, BMS, Janssen, Lundbeck, Pfizer, Servier, St. Jude Medical and Sunovion; has received speaker fees from Xian-Janssen; and has received research support from Brain Cells Inc and Clera.

DOI: 10.1503/jpn.170022

References

1. American Psychiatric Association. DSM 5. Arlington (Va): APA; 2013.
2. Fava GA, Gatti A, Belaise C, et al. Withdrawal symptoms after selective serotonin reuptake inhibitor discontinuation: a systematic review. *Psychother Psychosom* 2015;84:72-81.
3. Rosenbaum JF, Fava M, Hoog SL, et al. Selective serotonin reuptake inhibitor discontinuation syndrome: a randomized clinical trial. *Biol Psychiatry* 1998; 44:77-87.
4. Michelson D, Fava M, Amsterdam J, et al. Interruption of selective serotonin reuptake inhibitor treatment. *Br J Psychiatry* 2000;176:363-8.
5. Meijer WE, Bouvy ML, Heerdink ER, et al. Spontaneous lapses in dosing during chronic treatment with selective serotonin reuptake inhibitors. *Br J Psychiatry* 2001;179:519-22.
6. Kennedy SH, Lam RW, McIntyre RS, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *Can J Psychiatry* 2016;61:540-60.
7. Renoir T. Selective serotonin reuptake inhibitor antidepressant treatment discontinuation syndrome: a review of the clinical evidence and the possible mechanisms involved. *Front Pharmacol* 2013; 4:45.
8. Berber MJ. FINISH: remembering the discontinuation syndrome. *J Clin Psychiatry* 1998;59:255.
9. Haddad PM. Antidepressant discontinuation syndromes. *Drug Saf* 2001;24:183-97.
10. Taylor D, Paton C, Kapur S. *The Maudsley prescribing guidelines in psychiatry*. Hoboken (NJ): Wiley; 2015.
11. Blier P, Tremblay P. Physiologic mechanisms underlying the antidepressant discontinuation syndrome. *J Clin Psychiatry* 2006;67:8-13.
12. Delgado PL. Monoamine depletion studies: implications for antidepressant discontinuation syndrome. *J Clin Psychiatry* 2006;67:22-6.
13. Kramer JC, Klein DF, Fink M. Withdrawal symptoms following discontinuation of imipramine therapy. *Am J Psychiatry* 1961;118:549-50.
14. Holland J, Brown R. Neonatal venlafaxine discontinuation syndrome: a mini-review. *Eur J Paediatr Neurol* 2017;21:264-8.
15. Goodwin GM, Emsley R, Rembry S, et al. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2009;70:1128-37.
16. Montgomery SA, Kennedy S, Burrows G, et al. Absence of discontinuation symptoms with agomelatine and occurrence of discontinuation symptoms with paroxetine: a randomized, double-blind, placebo-controlled discontinuation study. *Int Clin Psychopharmacol* 2004;19:271-80.
17. Jain R, Mahableshwarkar AR, Jacobsen PL, et al. A randomized, double-blind, placebo-controlled 6-wk trial of the efficacy and tolerability of 5 mg vortioxetine in adults with major depressive disorder. *Int J Neuropsychopharmacol* 2013;16:313-21.
18. Tint A, Haddad P, Anderson IM. The effect of rate of antidepressant tapering on the incidence of discontinuation symptoms: a randomised study. *J Psychopharmacol* 2008;22:330-2.
19. Giakas WJ, Davis JM. Intractable withdrawal from venlafaxine treated with fluoxetine. *Psychiatr Ann* 1997;27:85-92.
20. Benazzi F. Mirtazapine withdrawal symptoms. *Can J Psychiatry* 1998;43:525.
21. Dilsaver SC, Kronfol Z, Sackellares JC, et al. Antidepressant withdrawal syndromes: evidence supporting the cholinergic overdrive hypothesis. *J Clin Psychopharmacol* 1983;3:157-64.
22. Wilson E, Lader M. A review of the management of antidepressant discontinuation symptoms. *Ther Adv Psychopharmacol* 2015; 5:357-68.