A Case Report of Onset of Tinnitus Following Discontinuation of Antidepressant and a Review of the Literature

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ABSTRACT

This case report describes a 46-year-old woman with long-standing episodic severe depression (*ICD-10* code F33) who discontinued venlafaxine over a 4-week taper after taking the antidepressant for 8 years. Severe discontinuation syndrome was experienced. Panic and relapse of depression occurred 2 months after achieving discontinuation, and the development of tinnitus took place concurrently to the discontinuation. The experience of the tinnitus as a side effect of discontinuation is different from cases reported in the literature in which the tinnitus was experienced when the antidepressant was started and ceased when the antidepressant was stopped. Here, the patient experienced the tinnitus as a discontinuation symptom, and it persisted even after the antidepressant was reintroduced. A review of the literature on antidepressant discontinuation syndrome is also provided.

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It is well established that discontinuation symptoms of most antidepressants are common.[1–6] It could be suggested that, for patients who have taken antidepressant medication for several years or more, a regimen of graded reduction of dosage toward discontinuation might be made over a period of months/years rather than weeks in order to mitigate against discontinuation syndrome including rebound anxiety and relapse difficulties. In this report, the case of a patient who experienced tinnitus following discontinuation of venlafaxine is presented. Also, a review of the literature on antidepressant discontinuation syndrome is provided.

CASE REPORT

Ms A, a 46-year-old woman with a history of a severe depressive episode (*ICD-10* code F33) 10 years prior, had been treated with various antidepressants (paroxetine 40 mg, lofepramine 280 mg) for 2 years and then was started on venlafaxine 150 mg (first, she was started on 75 mg twice a day, and she was later switched to extended-release 150 mg). The treatment was successful, and Ms A reported a good initial recovery and gradual improvement in function over the years.

Ms A had been maintained on venlafaxine 150 mg for 8 years and was functioning well, including her usual activities of full-time work and socializing. Feeling stable, Ms A decided it was time to discontinue the medication and was given a tapered reduction program by her general practitioner, with the dose to be cut by a 37.5-mg daily reduction on a weekly basis. Table 1 provides details on dates and doses used during the discontinuation period. Within 1 day, the lowered dose produced symptoms that were typical of discontinuation syndrome. Table 2 provides details of the symptoms described by Ms A and the dates on which they were reported.

One of the symptoms that Ms A experienced was tinnitus, and this symptom was still persistent over 2 years later and at the same intensity even after reinstatement of the venlafaxine. It is possible that the tinnitus may have been caused by the discontinuation of venlafaxine, as its onset was concurrent with the discontinuation. The tinnitus was described as a continuous buzzing in the head rather than a ringing in the ears, although Ms A did experience occasional ringing in the ears as well. The ringing and buzzing were slightly worse on the right side.

The general practitioner checked for other possible causes of the tinnitus. A course of ear spray eliminated the possibility of an ear infection. A referral was made to the ear, nose, and throat clinic, and a hearing test noted slight but insignificant hearing loss in the right ear; the pure tone audiometry was essentially normal. On examination, the lympanic membranes were normal. A diagnosis of minor tinnitus in both ears was made.

Two months after discontinuation of the antidepressant, Ms A experienced onset of persistent and worsening anxiety symptoms.

Clinical Points

- Antidepressant therapy is often associated with a side effect of tinnitus.
- Withdrawal from antidepressants should be tapered over a longer period (such as 6 to 24 months or more) when they have been taken for the longer term (a few years or more) in order to avoid withdrawal syndrome.
- Rebound panic/anxiety occurring 2 or 3 months following antidepressant withdrawal might be effectively treated by returning to the same antidepressant at the same dose.

Ms A was referred for consultation with a psychiatrist at the local community mental health center, and a diagnosis of episodic depression (*ICD-10* code F33) was made. Reinstatement of the venlafaxine (titrated over 2 weeks to the original dose of 150 mg) produced complete remittance of the anxiety symptoms. The anxiety symptoms did not recur during 12 months of follow-up. However, the tinnitus has been the same and continuous (same level 24 hours/day) and persists 2 years later at the time of writing.

REVIEW OF THE LITERATURE

Method

The databases AMED, BNI, CINAHL, EMBASE, MEDLINE, and PsychINFO were searched with no date limit using English language only and the keywords *antidepressant*, *discontinuation*, *withdrawal*, and *tinnitus*. Articles cited in reference lists from retrieved articles were also included.

Antidepressant Discontinuation

Several descriptions and lists of the various key symptoms that are characteristic of a discontinuation syndrome have been compiled (Table 3). Ms A suffered from symptoms in all of the categories described.

According to Haddad, "… the severity of discontinuation reactions varies across a spectrum; some patients manifest an isolated symptom, others a cluster of symptoms, and symptoms vary from mild to severely disabling. This raises a 'threshold' issue for defining a discontinuation syndrome."[3(p185)] Some researchers have found that the use of the Discontinuation Emergent Signs and Symptoms Scale (DESS) checklist is helpful.[16–18] For example, Fava et al[19] classified patients as experiencing a discontinuation syndrome "if the number of DESS checklist events increased by 4 or more during the interruption period."[(p836)]

Symptoms can be mild to severe[20–22] and usually abate within a few weeks.[13,23–27] To avoid these symptoms, antidepressant discontinuation should be tapered.[2,7,28,29] Most of the recommended time periods for tapered discontinuation are over several weeks (eg, 7–4 days,[12] a 4-week period,[7,23] and 4 weeks or more[29]).

Table 1. Discontinuation Regimen of Ms A

Timing	Dose, mg	Dates
Before discontinuation	150	Approximately 8 years up to September 26, 2008
Week 1	112.5	September 27, 2008–October 2, 2008
Week 2	75	October 3, 2008–October 10, 2008
Week 3	37.5	October 11, 2008–October 19, 2008
Week 4	No dose	October 20, 2008–onward

Those who are considered to be perhaps most at risk for encountering more severe discontinuation symptoms include the following:

1. Females[30]
2. Those with underlying anxiety and dysthymic disorders[30]
3. Those with earlier age at onset of dysthymia[30]
4. Those taking higher doses of antidepressants[21]
5. Those who have been on longer courses of treatment[2,3,7,19,21,22,30,31]
6. Those reducing treatment more abruptly than more gradually[2,12,18,32–34]
7. Those discontinuing from particular antidepressants, including medications with a shorter half-life such as paroxetine and venlafaxine[7,35–40]
8. Those who have a history of difficulties in discontinuation or dose reduction[3,7]
9. The elderly.[9]

For these patients, it may be advisable to use a very slow, long taper of over 6 months' duration.[29]

In the case presented here, Ms A had a number of the factors that placed her at risk for experiencing more severe symptoms of discontinuation. She was female, with underlying early onset dysthymia, and she had been taking venlafaxine for the long-term. Ms A experienced a reaction similar to that of the patient in the case report by Bhanji et al,[30] who had a relapse and onset of panic a few months after the commencement of discontinuation. Thus, on reflection, a very slow taper over more than 6 months or more would have been advisable for Ms A.

On occasion, individuals encounter longer-term discontinuation problems and/or relapse symptoms. For example, in the case reported by Bhanji et al,[30] the female patient described a 4-week history of persistent and worsening anxiety symptoms that began 1 month following abrupt paroxetine discontinuation. The patient's presenting symptoms of panic and anxiety were distinguished by a crescendo-like occurrence in the absence of any obvious triggers, unlike the underlying panic, anxiety, and depressive disorders that she had previously experienced, and waves of anxiety and tension led to further anticipatory anxiety.[30] Rebound panic symptoms included shortness of breath, palpitations, nausea, feelings of depersonalization and

Table 2. Symptoms Described by Ms A

Event	Dates	Patient Described Symptoms
Discontinuation (on sick leave)	September 27, 2008–October 2, 2008 October 3, 2008–November 18, 2008	Loud buzzing noise in head and feeling dizzy, exhaustion, no sleep (lying awake as if taking amphetamines), crying/sobbing, short tempered, nausea and diarrhea, sensation of shaking all over inside, sensations of an evil being/evil presence in the room (incubus) when half asleep in bed, vivid disturbing nightmares, intermittent tinnitus (ringing)
Returned to work	November 19, 2008–December 23, 2008	Constantly felt about to cry and often did, gradual tapering of the buzzing at the back of the head, waking in early hours, low energy, tinnitus (ringing) more persistent
Week of Christmas and New Year's day	December 24, 2008–January 3, 2009	Vomiting, free-floating anxiety, panic, nausea, feeling of high blood pressure in the head, insomnia, difficulty getting to sleep, waking in the early hours, self-loathing, low energy, constantly felt about to cry and often did, palpitations, shame, felt hopeless (but not actively suicidal), unable to enjoy anything/feel pleasure, loss of appetite, exhaustion, continuous tinnitus
Recommenced 75 mg venlafaxine	January 4, 2009–January 13, 2009	Edge taken off panic surges, continued nausea and loss of appetite (and consequent weight loss), difficulty getting to sleep and staying asleep throughout the night, constantly felt about to cry and often did, felt bad about self, exhaustion, continuous tinnitus
Increased to 150 mg venlafaxine	January 14, 2009–January 29, 2009	Gradual recovery, tinnitus continued with constant buzzing in head and intermittent ringing (mainly in or worse in right ear)
Continued on 150 mg venlafaxine	January 30, 2009 onward	Functional and well, tinnitus continued with unremitting buzzing in head and intermittent ringing (mainly in or worse in right ear)

Table 3. Discontinuation Symptoms Described in the Literature

Disequilibrium	Dizziness (exacerbated by movement or postural changes),[5] light-headedness,[7] vertigo,[5,7,8] ataxia,[5,7] and headaches[5,7] (less common: disequilibrium in brief bursts when patients move their head or eyes[7])
Gastrointestinal	Nausea,[5,7,8] vomiting,[5,7] loose stools,[5,7] dry mouth,[5] anorexia[7]
Flu-like symptoms[8]	Myalgia,[5] fatigue/lethargy,[5,7] shaking chills,[5] rhinorrhea,[5] tremor,[7] sweating[7]
Sensory disturbances[8]	Vivid dreams,[5] nightmares,[7] excessive dreaming,[7] initial and middle insomnia,[5,7,8] paresthesia,[7] numbness,[7] electric shock–like sensations,[7] rushing noise in head,[7] and palinopsia (visual trails)[7] (less common: visual hallucinations,[9] auditory hallucinations,[10,11] visual phenomena similar to the fortification spectra associated with migraines,[12] shock-like sensations,[13] and stroke-like symptoms[14])
Psychological	Anxiety,[5,7,8] agitation,[5,7,8] irritability,[7] mania,[5,15] crying spells,[5,7] cognitive disturbances,[5] low mood,[7] and slowed thinking[5] (less common: confusion[9])

derealization, and initial and middle insomnia. The patient denied other somatic complaints such as paresthesias, dizziness, or autonomic symptoms, and there were no depressive symptoms. Rebound symptoms were not abating and were becoming worse despite an 8-week period since stopping paroxetine.[30]

Discontinuation symptoms can be severe and chronic and can seriously impact the patient's lifestyle.[20] Symptoms can on occasion last for months.[41] Fava et al[19] found that patients who had discontinuation syndrome also had a relapse of panic disorder. Baldessarini et al[42] and Freedman[43] noted the likelihood of relapse particularly when discontinuation was abrupt and with the shorter half-life antidepressants.

For those who experience severe discontinuation syndrome, alleviation can be found (as was the case of Ms A) by reintroducing the original antidepressant[2,3,13,15,21,29,32,44] at the same dose as before discontinuation.[1,7] Other medications have been found to be ineffective for discontinuation syndrome (eg, benzodiazepines[45] and switching to a different antidepressant in some cases).[19,46] One strategy to avoid discontinuation symptoms when reducing antidepressants with a shorter half-life is to switch to a medication that has a longer half-life during the tapering phase.[7]

Antidepressants and Tinnitus

The literature has produced evidence to associate the use of antidepressants with the onset of tinnitus. These reports indicate a causal relationship between antidepressant use and onset of tinnitus. Paradoxically, antidepressants are one line of treatment for tinnitus[47–49] though studies have not yet established an understanding of their efficacy for treating this condition.[50,51] Case reports (Table 4) indicate that the onset of tinnitus coincides with the taking of rather than the discontinuation of antidepressants (except in 1 case[51]). These results are different from the case of Ms A, who experienced the onset of tinnitus when discontinuing the antidepressant and continued to experience tinnitus after the reinstatement of the antidepressant 3 months after the start of the discontinuation regimen.

There are studies that conclude that the perception of tinnitus is the result of neural activity in the brain and/or auditory system.[59–64] Given that, in the present case, Ms A had been taking venlafaxine for a long time (8 years) it is quite possible that some changes in the patterns of neural activity and/or concentrations of neural transmitters and receptors within her brain would have taken place over that time. The discontinuation of the antidepressant may have caused biochemical reactions affecting Ms A's brain, including the auditory regions.

Possible mechanisms have been discussed, and serotonin (5-HT) neurotransmitters appear to be involved. It could be

Table 4. Reported Cases of Tinnitus Coinciding With Antidepressant Treatment

Author	Presentation	Outcome	Summary
Robinson et al[51]	A 32-year-old woman abruptly discontinued venlafaxine 100 mg 3 times/d; tinnitus and other discontinuation symptoms occurred within 36 hours	Restarting the medication at 100 mg resulted in resolution of all symptoms within 2 hours	Tinnitus occurred at abrupt discontinuation of the antidepressant; tinnitus resolved at recommencement of the antidepressant
Ahmad[52]	The patient appeared to have experienced severe tinnitus as a side effect of venlafaxine; no organic cause for the tinnitus was identified	Venlafaxine was discontinued, and the patient's tinnitus disappeared over the next 7 days; the patient's tinnitus recurred when rechallenged with venlafaxine 75 mg/d; the patient stopped taking venlafaxine, and the tinnitus again subsided and did not recur	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was discontinued
Feder[53]	The patient was started on a dose of amitriptyline 50 mg at bedtime that was increased to 100 mg at bedtime at the end of the first week and increased to 150 mg at bedtime at the end of the second week; onset of bilateral tinnitus occurred 2 days later	Amitriptyline treatment was discontinued at the end of the third week because of tinnitus; within 1 week of stopping the medication, the tinnitus resolved; amitriptyline 50 mg at bedtime was started again 3 weeks later; within 2 weeks, the tinnitus recurred; the medication was again discontinued, and the tinnitus resolved within 4 days	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was discontinued
Pondrom and Brahm[54]	The patient started venlafaxine; at 4-week reevaluation, the patient reported the new onset of tinnitus and described the sensation as a bilateral constant ringing in the ears that was extremely bothersome but not disabling and occurred in episodes throughout the day with no clear pattern	The patient was switched to decenlafaxine succinate and reported decreased frequency and duration of tinnitus with nearly complete resolution within 7 days	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was changed to an alternative medication
Racy and Ward-Racy[55]	A 37-year-old woman was prescribed imipramine 50 mg/d; after 1 week, she reported that ringing in her ears had started 2 to 3 days after starting imipramine; the tinnitus was so unpleasant that she did not want to continue treatment	The patient's tinnitus stopped when the imipramine dose was lowered to 25 mg/d as advised by her therapist	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was reduced to a lower dose
Racy and Ward-Racy[55]	A 15-year-old girl was prescribed imipramine on a graduated regimen of up to 150 mg/d; when the imipramine dose reached 150 mg/d, she complained of ringing in her ears	The patient's medication was reduced to 125 mg/d, and the tinnitus stopped	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was reduced to a lower dose
Racy and Ward-Racy[55]	A 30-year-old woman was prescribed imipramine 100 mg/d; when the dosage was increased to 150 mg/d, she began to complain of nausea and a buzzing sound in her ears	When the medication was reduced to 100 mg/d, her nausea and tinnitus subsided, but she again became depressed; her therapist attempted to find a therapeutic level, increasing the dosage by 10-mg increments; the tinnitus and nausea returned at 120 mg/d; she achieved clinical improvement with 110 mg/d and suffered no further tinnitus	Tinnitus with onset of antidepressant treatment Tinnitus subsided when the antidepressant was reduced to a lower dose
Racy and Ward-Racy[55]	A 31-year-old man was prescribed imipramine 150 mg/d and complained of distinct ringing in his ears	When the medication was reduced to 75 mg/d, the ringing was still present but somewhat milder; the patient's therapist discontinued imipramine and substituted desipramine at a dosage of 100–150 mg/d; the patient's tinnitus did not return, and he found the medication helpful	Tinnitus with onset of antidepressant treatment Tinnitus reduced when the antidepressant was reduced to a lower dose Tinnitus subsided when the antidepressant was changed to an alternative medication
Evans and Golden[56]	A 45-year-old woman began treatment with protriptyline 15 mg/d (divided dose) and increased the dose every 2 days until a dose of 45 mg/d (divided dose) was reached on day 10; she complained of tinnitus (ringing in both ears) 2 days later	Tinnitus persisted for the next 21 days as protriptyline was decreased to 30 mg/d (divided dose); the patient noted moderate amelioration of side effects, but due to continued subjective discomfort, protriptyline was replaced with desipramine at a dose of 75 mg/d, and she experienced only occasional mild tinnitus; desipramine was increased 2 days later to 100 mg/d with no increase of side effects; while taking protriptyline 45 mg/d, the patient subjectively rated the severity of her tinnitus as 6 on a 10-point scale; with dosage reduction, the severity decreased to 4, and with the change to desipramine, she rated her tinnitus as 1 to 2 on the same 10-point scale	Tinnitus with onset of antidepressant treatment Tinnitus reduced when the antidepressant was reduced to a lower dose Tinnitus reduced further when the antidepressant was changed to an alternative medication
Mendis and Johnston[57]	A 40-year-old woman developed persisting tinnitus after 3 days' intake of 10 mg amitriptyline, which had been prescribed for neuralgic foot pain; after starting amitriptyline, the patient complained of sudden-onset severe unilateral left-sided tinnitus	Medication was stopped; however, when the foot pain resolved, the tinnitus persisted; at follow-up 4 months later, the tinnitus had made some gradual improvement and 7 months later was shown to persist at the same level	Tinnitus with onset of antidepressant treatment Tinnitus reduced when the antidepressant was discontinued
Langguth et al[58]	A 39-year-old man experienced the onset of intense bilateral tinnitus after 3 days of trimipramine intake; he had experienced short episodes of transient tinnitus 8 years previously	Trimipramine was increased from 50 mg to 100 mg and then changed at 6 weeks to amitriptyline 50 mg, but the tinnitus worsened; the patient was switched to citalopram 20 mg, but the depressive episode was not alleviated; the patient was switched to mirtazapine 30 mg, which was augmented with lithium carbonate 900 mg 8 months later	Tinnitus with onset of antidepressant treatment
The present case	A 46-year-old woman experienced tinnitus when venlafaxine was discontinued	Tinnitus continued despite reintroduction of venlafaxine	Tinnitus onset coincided with discontinuation of the antidepressant Tinnitus continued after the antidepressant was reintroduced

that with longer-term administration of an antidepressant, the 5-HT receptors down-regulate, and the abrupt cessation may result in stores of 5-HT having insufficient amounts for neuronal signaling, initiating the onset of withdrawal symptoms,[30] or it may be that the neurotransmitter receptors undergo changes in their sensitivity during antidepressant treatment.[4] Serotonin is considered to play a role in subjective tinnitus, such as tinnitus caused by the effect of some drugs such as antidepressants.[60,61,64]

COMPARISON OF THE CASE OF MS A WITH THE LITERATURE

Ms A experienced the usual immediate onset of withdrawal symptoms as reported in the literature[4,42] despite tapering. The British National Formulary has been updated in recent years from stating that the withdrawal symptoms are "avoidable" if the discontinuation is "tapered over a few weeks"[65(p206)] to "…the dose should be tapered over a few weeks to avoid these effects. For some patients, it may be necessary to withdraw treatment over a longer period; consider obtaining specialist advice if symptoms persist."[28(p232)] The British National Formulary[65] included some of the usual symptoms from each of the categories, such as disequilibrium, gastrointestinal symptoms, flu-like symptoms, sensory disturbances, and psychological symptoms. These symptoms continued through the 4 weeks of tapered discontinuation from 150 mg venlafaxine to none in the case of Ms A.

After the antidepressant was out of Ms A's system, some symptoms continued that impacted her functioning in daily life (see Table 4). This experience is not always mentioned in the literature that covers antidepressant discontinuation. At the 3-month point following commencement of the reduction regimen, Ms A experienced rebound anxiety and a number of additional symptoms on top of those that had continued, which could be considered a relapse. This experience is, perhaps, underreported in the literature and was described by Ms A as almost identical to the report of the patient of Bhanji et al.[30]

The tinnitus onset in the case of Ms A was concurrent with the discontinuation of antidepressants. This onset contrasts with what has been reported in the literature, wherein the tinnitus onset has been associated with the commencement of an antidepressant and cessation of the antidepressant has been followed by cessation of the tinnitus (except for the authors of 1 article who found that tinnitus was associated with withdrawal of antidepressants [venlafaxine and sertraline][51]). In the case of Ms A, the antidepressant was reintroduced and the tinnitus continued.

CONCLUSION

Antidepressant withdrawal symptoms are not always mild, transitory, and tolerable so that patients can successfully cease antidepressant therapy. In increasing numbers of field cases and reports, it has been shown that withdrawal effects do not necessarily disappear spontaneously or in the short-term and can be so disabling that patients have to return to taking the antidepressant that enables withdrawal symptoms to disappear (otherwise they can last for years and can worsen).

This single case study reflects many of the findings of recent research into antidepressant discontinuation syndrome: the case was of a severe and long-term treated depression and the original depression was associated with anxiety. This indicated that a much slower (months or years rather than weeks) discontinuation would have been preferred to the standard few weeks of tapered discontinuation that was undertaken. Even with long-term gradual tapering of dose, the withdrawal syndrome can still occur.[6,19] The discontinuation may be a cause of the concurrent onset of long-term tinnitus experienced in this case.

Drug names: citalopram (Celexa and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), protriptyline (Vivactil and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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