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CASO CLÍNICO/CASE REPORT

Psychotic Symptoms Possibly Associated with an Increase in the Dose of Venlafaxine: A Report of a Rare Case

Sintomas Psicóticos Possivelmente Associados ao Aumento da Dose de Venlafaxina: Relato de um Caso Raro

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ABSTRACT
Venlafaxine, a serotonin–noradrenaline reuptake inhibitor (SNRI), predominantly inhibits serotonin reuptake at lower doses, while noradrenergic effects become more prominent at higher doses. At higher doses, a modest dopaminergic effect has also been described, particularly in the prefrontal cortex. Although generally well tolerated, venlafaxine has been associated with rare neuropsychiatric adverse effects, including psychotic symptoms.
We report the case of a 55-year-old woman with recurrent depressive disorder who developed auditory verbal hallucinations with commenting and imperative content following an increase in venlafaxine dose from 150 mg/day to 225 mg/day. Symptoms remitted following dose reduction of venlafaxine to 150 mg/day and short-term antipsychotic treatment. After seven months of follow-up, she remained free of psychotic symptoms.
The close temporal relationship between venlafaxine dose escalation and the onset of psychotic symptoms, together with their resolution following dose reduction and the absence of recurrence during follow-up, suggests a possible association between venlafaxine and the observed psychotic symptoms. However, the concomitant use of antipsychotic medication limits definitive attribution of causality.
This case highlights the importance of monitoring for perceptual disturbances and other psychotic symptoms following venlafaxine dose increases, even in patients without a previous history of psychosis.

Keywords: Antidepressive Agents, Second-Generation/adverse effects; Delusions/chemically induced; Hallucinations/chemically induced; Psychotic Disorders Selective/chemically induced; Serotonin Reuptake Inhibitors/adverse effects; Venlafaxine Hydrochloride/adverse effects

RESUMO
A venlafaxina, um inibidor da recaptação da serotonina e da noradrenalina (IRSN), inibe predominantemente a recaptação da serotonina em doses mais baixas, enquanto os efeitos noradrenérgicos se tornam mais pronunciados em doses mais elevadas. Em doses elevadas, foi também descrito um efeito dopaminérgico modesto, particularmente no córtex pré-frontal. Embora seja geralmente bem tolerada, a venlafaxina tem sido associada a efeitos adversos neuropsiquiátricos raros, incluindo sintomas psicóticos.
Apresentamos o caso de uma mulher de 55 anos com perturbação depressiva recorrente que desenvolveu alucinações auditivas verbais com conteúdo comentativo e imperativo, na sequência de um aumento da dose de venlafaxina de 150 mg/dia para 225 mg/dia. Os sintomas regrediram após a redução da dose de venlafaxina para 150 mg/dia e a instituição de tratamento antipsicótico de curta duração. Após sete meses de seguimento, a doente mantinha-se sem sintomas psicóticos. A estreita relação temporal entre o aumento da dose de venlafaxina e o aparecimento dos sintomas

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psicóticos, associada à sua resolução após a redução da dose e à ausência de recorrência durante o seguimento, sugere uma possível associação entre a venlafaxina e os sintomas psicóticos observados. Contudo, a utilização concomitante de medicação antipsicótica limita a possibilidade de estabelecer uma relação causal definitiva.
Este caso destaca a importância da vigilância de alterações da perceção e de outros sintomas psicóticos após o aumento da dose de venlafaxina, mesmo em doentes sem antecedentes de psicose.

Palavras-chave: Alucinações/induzidas quimicamente; Antidepressivos de Segunda Geração/efeitos adversos; Cloridrato de Venlafaxina/efeitos adversos; Delírios/induzidos quimicamente; Perturbações Bipolares/induzidas quimicamente; Perturbações Psicóticas/induzidas quimicamente.

INTRODUCTION

Venlafaxine is a serotonin–noradrenaline reuptake inhibitor (SNRI) widely used in the treatment of major depressive disorder and anxiety disorders.[1] Its pharmacological profile is dose-dependent, with serotonin reuptake inhibition predominating at lower doses and noradrenergic effects becoming more prominent at higher doses.[2] At higher doses, a modest dopaminergic effect has also been described, particularly in the prefrontal cortex.[1]

Although generally well tolerated, venlafaxine has been associated with rare neuropsychiatric adverse effects, including psychotic symptoms, mania, hypomania, and impulse control disorders such as kleptomania.[3-7] According to product information, hallucinations are classified as an uncommon adverse reaction (<1/100 and >1/1000), while mania and hypomania are classified as rare reactions (<1/1000). Delirium is classified as a very rare adverse reaction (<1/10 000).[8]

Psychotic symptoms associated with venlafaxine have been reported at both high and moderate doses.[3,9,10] We present the case of a 55-year-old woman with recurrent depressive disorder who developed auditory verbal hallucinations after an increase in venlafaxine dose from 150 mg/day to 225 mg/day.

CASE REPORT

A 55-year-old married woman with four years of formal education, working as a home care assistant in a community support facility, had been followed in Psychiatry since 2002 for recurrent depressive disorder. She had been treated for approximately nine years with venlafaxine 150 mg/day, trazodone 150 mg/day, and lorazepam 2.5 mg/day, with consistent adherence to the prescribed medication regimen. She had previously been treated with fluoxetine, titrated up to 40 mg/day, and was switched to venlafaxine 150 mg/day in September 2016 because of persistent depressed mood. She had no other psychiatric history, no relevant family psychiatric history, and no substance use.

Approximately four months before admission, she experienced a worsening of her depressive symptoms, characterized by depressed mood, anhedonia, reduced energy, and impaired concentration. There was associated impairment in occupational and social functioning, and she had been on medical leave for two months.

In view of the clinical deterioration, venlafaxine was increased from 150 mg/day to 225 mg/day. Sixteen days after this dose increase, she developed auditory verbal hallucinations (AVH), hearing two voices that she identified as two deceased neighbors who had died by suicide. The voices commented on her behavior in the third person, insulted her, and made derogatory remarks about her sisters and mother-in-law, while also alleging that her husband was being unfaithful. She additionally described imperative auditory hallucinations instructing her to perform certain actions. For example, she was instructed to refuse food that she believed to be spoiled, and she occasionally followed these commands. She also reported possible concomitant olfactory hallucinations, describing a foul odor emanating from food that was not perceived by others.

On mental status examination, she was alert and oriented to time, place, and person. She became progressively more cooperative throughout the interview. Personal hygiene was maintained. Contact was superficial. Mood was euthymic, with some emotional lability and occasionally incongruent affect. Speech was fluent and coherent, without syntactic or semantic abnormalities. AVH with pejorative and imperative content was present. No formal thought disorder was identified. Insight was preserved. No disturbances of self-boundaries were identified. Appetite was maintained. There was no evidence of apathy, anhedonia, abulia, or adynamia. She denied suicidal ideation and had no previous history of psychotic symptoms.

Given the late onset of the psychotic symptoms and the absence of a previous history of psychosis, an organic cause was investigated. Complementary investigations included a complete blood count, serum electrolytes, renal and liver function, thyroid function, vitamin B12, folate, and serological screening for HIV and syphilis. All laboratory results were within normal limits. Brain computed tomography and electroencephalography showed no abnormalities suggestive of an organic cause.

At admission, amisulpride 400 mg/day was initiated. On day six of hospitalization, venlafaxine was reduced from 225 mg/day to 150 mg/day. Over the following days, a progressive reduction in the frequency and intensity of the hallucinations was observed, with complete resolution of the perceptual disturbances within four days of the venlafaxine dose reduction. Amisulpride was subsequently reduced to 200 mg/day after seven days. She also presented with initial and middle insomnia, which improved with sleep hygiene measures and the initiation of quetiapine 50 mg/day and mirtazapine 15 mg/day.

At admission, the Positive and Negative Syndrome Scale (PANSS) was administered, with a Positive Symptom

subscale score of 16/49. Following clinical remission, at discharge, the Positive Symptom subscale score had decreased to 7/49.

She was discharged on day 12 with venlafaxine 150 mg/day, amisulpride 200 mg/day, lorazepam 2.5 mg/day, quetiapine 50 mg/day, and mirtazapine 15 mg/day.

During seven months of outpatient follow-up, she remained asymptomatic regarding psychotic symptoms, with no recurrence of hallucinations and no recurrence of depressive symptoms. The dose of amisulpride was progressively reduced to 50 mg/day. She returned to work and was able to derive satisfaction from her work.

DISCUSSION

The emergence of perceptual disturbances in a patient without a personal history of psychosis, no relevant family psychiatric history, and no substance use led to consideration of several diagnostic hypotheses, including dissociative symptoms, psychotic decompensation associated with recurrent depressive disorder, and a pharmacological adverse reaction.

The close temporal relationship between the increase in venlafaxine dose to 225 mg/day and the onset of AVH, together with symptom remission following reduction to 150 mg/day, suggests a possible association between venlafaxine and the observed psychotic symptoms.

Several aspects of the clinical course support this hypothesis. First, the patient had been treated with venlafaxine 150 mg/day for approximately nine years without psychotic symptoms. Second, the hallucinations emerged 16 days after the dose was increased to 225 mg/day. Third, the perceptual disturbances progressively decreased in frequency and intensity following reduction of venlafaxine to 150 mg/day and completely resolved within four days. Finally, there was no recurrence of psychotic symptoms during seven months of follow-up, despite maintenance of venlafaxine at 150 mg/day.

Nevertheless, a psychotic episode related to the underlying depressive disorder cannot be fully excluded. The patient had experienced worsening depressive symptoms during the four months preceding admission, including depressed mood, anhedonia, reduced energy, and impaired concentration. However, at the time of psychiatric assessment, her mood was euthymic, and there was no evidence of ongoing anhedonia, apathy, abulia, or adynamia. Insight was preserved, and there was no formal thought disorder. These findings make an ongoing psychotic depressive episode less clearly supported, although they do not completely exclude a relationship between the psychotic symptoms and the underlying mood disorder.

A possible pharmacological mechanism has been proposed for venlafaxine-associated psychotic symptoms. At higher doses, venlafaxine produces greater noradrenergic effects, and modest effects on dopaminergic neurotransmission have also been described. Norepinephrine transporter (NET) blockade may influence dopaminergic transmission because dopamine is also cleared through NET in some cortical regions, particularly the prefrontal cortex.[3,7] Increased dopaminergic activity has therefore been proposed as one possible mechanism contributing to psychotic symptoms in susceptible individuals. However, this mechanism remains hypothetical, and the exact neurobiological basis of venlafaxine-associated psychotic symptoms is not established.

Previous case reports provide additional support for the possibility of such an association. Adamou and Hale[9] reported a patient who developed erotomanic delusions on two separate occasions while receiving high doses of venlafaxine, between 225 and 300 mg/day. On both occasions, the symptoms remitted after reduction of the venlafaxine dose. Safeekh *et al*[3] described a patient with social phobia who developed persecutory delusions on two occasions while receiving venlafaxine 150 mg/day; the delusions resolved after withdrawal of venlafaxine and a short course of antipsychotic treatment. These reports suggest that psychotic symptoms may occur not only at high doses but also at moderate doses.

Another report described a patient who developed persecutory delusions and auditory and visual hallucinations while receiving venlafaxine 150 mg/day, despite concomitant antipsychotic treatment, with resolution following discontinuation of venlafaxine.[10]

The present case has several similarities with these previous reports, particularly the temporal relationship between venlafaxine exposure and psychotic symptoms and the improvement following reduction or discontinuation of the drug. However, unlike a complete discontinuation, the present case involved a reduction from 225 mg/day to 150 mg/day, which was followed by sustained remission despite continued exposure to venlafaxine. This observation may suggest a possible dose-dependent relationship.

The concomitant use of amisulpride during hospitalization is an important limitation in establishing causality, as clinical improvement may have been partially influenced by antipsychotic treatment. The temporal sequence nevertheless remains suggestive: the symptoms emerged after venlafaxine dose escalation, venlafaxine was subsequently reduced, and the hallucinations resolved within four days. The sustained absence of psychotic symptoms during follow-up while venlafaxine was maintained at 150 mg/day further supports a possible dose-related association.

The absence of drug rechallenge is another limitation. Rechallenge would theoretically provide stronger evidence of causality, but it would not be ethically appropriate given the severity and imperative nature of the patient's hallucinations. Therefore, the absence of rechallenge should be considered an inherent limitation rather than a weakness specific to the management of this case.

The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 6, indicating a possible relationship between venlafaxine and the psychotic symptoms observed.[11]

This case adds to the limited literature on venlafaxine-associated psychotic symptoms and highlights the importance of monitoring perceptual disturbances and other psychotic symptoms, particularly following dose increases. Clinicians should be aware that such symptoms may occur even in patients without a previous history of psychosis and after prolonged exposure to a previously tolerated dose.

CONCLUSION

This case suggests a possible association between an increase in venlafaxine dose from 150 mg/day to 225 mg/day and the subsequent onset of psychotic symptoms in the form of auditory verbal hallucinations.

Several features support this association, including the long period of treatment with venlafaxine 150 mg/day without psychotic symptoms, the emergence of hallucinations 16 days after dose escalation, the progressive improvement following reduction to 150 mg/day, complete resolution of the perceptual disturbances within four days, and the absence of recurrence during seven months of follow-up despite continued treatment with venlafaxine 150 mg/day.

However, causality cannot be considered definitive because amisulpride was initiated before the venlafaxine dose was reduced, and a psychotic episode associated with the underlying depressive disorder cannot be completely excluded. The absence of rechallenge is an additional limitation.

Although rare, previous case reports and the present case suggest that venlafaxine may be associated with psychotic symptoms, potentially in a dose-related manner. Clinicians should therefore remain vigilant for the emergence of perceptual disturbances and other psychotic symptoms in patients treated with venlafaxine, particularly following dose increases and even in the absence of a previous psychotic history.

Early recognition of this potentially rare adverse reaction may allow timely intervention, including dose reduction or discontinuation when clinically appropriate, while avoiding unnecessary investigations and reducing patient morbidity.

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JRR, TFF, MA e SRF: Redação do artigo.
Todos os autores contribuíram para este trabalho, aprovaram a versão final do manuscrito para publicação e concordam em assumir a responsabilidade por todos os aspetos do trabalho, garantindo a exatidão e a integridade dos dados apresentados.

CONTRIBUTORSHIP STATEMENT

JRR, TFF, MA, and SRF: Writing of the article.
All authors contributed to this work, approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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