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Combination of venlafaxine and phentermine/topiramate induced psychosis: A case report

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Abstract

Background: Various publications have noted increases in dopamine, specifically in the mesolimbic region of the brain, to have a direct correlation to psychotic-like symptoms. Venlafaxine, a first-line medication for depression, inhibits the reuptake of both serotonin and norepinephrine. Additionally, venlafaxine weakly inhibits the reuptake of dopamine. Phentermine/topiramate (Qsymia®), specifically the phentermine component, functions by blocking the dopamine and norepinephrine transporter, similar to amphetamine.

Case Report: A 40-year-old Hispanic woman was admitted to the inpatient mental health unit based on reports of delusional thinking and several attempts of self-harm. Past medical history was significant for major depressive disorder, posttraumatic stress disorder, anxiety, irritable bowel syndrome, and migraines. The patient was started on venlafaxine (75 mg extended-release by mouth once daily) for depression approximately 1 month prior to admission. Furthermore, the patient was restarted on a previously prescribed medication, oral phentermine/topiramate for weight loss, in combination with venlafaxine, approximately 1 week prior to the bizarre behavior. The patient denied any psychosis or changes in behavior when medications were taken individually prior to the combination. The patient was treated with lurasidone (40 mg by mouth daily) with resolution of psychosis.

Discussion: A PubMed search revealed no current literature or case reports on psychosis induced by the combination of venlafaxine and phentermine/topiramate. Individual case reports of psychosis in patients on venlafaxine alone and the phentermine component of phentermine/topiramate alone have been reported.

Keywords: venlafaxine, phentermine/topiramate, psychosis

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Background

Venlafaxine, a commonly prescribed antidepressant, inhibits the presynaptic reuptake of both serotonin and norepinephrine in the brain.[1,2] In addition to the commonly known mechanism of action, according to Stahl and colleagues,[1] venlafaxine is a weak inhibitor of dopamine uptake, specifically in the prefrontal cortex at high doses greater than 375 mg/d. As venlafaxine does not strongly inhibit the dopamine transporter, venlafaxine is commonly recognized as a "dual-action" medication, often disregarding the action on dopamine. The prefrontal cortex correlates with executive function, specifically the making of memories, perception, and cognitive processes. Decreased dopamine in the prefrontal cortex has been linked to symptoms of depression and, in theory, adds another advantage to the use of venlafaxine for depression.[3]

Phentermine/topiramate (Qsymia®, VIVIS Inc, Mountain View, CA) is a combination medication approved for the treatment of obesity.[4] Phentermine exhibits its function

by blocking the dopamine transporter and the norepinephrine transporter, similar to amphetamine. The phentermine component of phentermine/topiramate increases dopamine and affects many areas of the brain. The mechanism of action for phentermine, specifically in reducing appetite, appears to be the stimulation of the hypothalamus to release norepinephrine.[4] Topiramate is added to allow for lower doses of phentermine and to provide a synergistic effect to the appetite-suppressing pathway; however, the exact mechanism on weight management is unknown.

The clinical definition of psychosis is a mental disorder in which perception, thought, and emotion are disoriented and includes falsification of reality.[5] It has been noted in the literature that increases in dopamine, specifically in the mesolimbic area of the brain, can induce or exacerbate psychotic symptoms.[1] Stimulant drugs, such as amphetamine, are known to increase the release of dopamine and have the potential to cause delusions or hallucinations.[6-8]

The combination of venlafaxine and phentermine/topiramate and the risk of psychosis has yet to be determined. Based on the above-mentioned mechanisms of action, psychotic-like features may be possible. Additionally, careful consideration is warranted in a patient population already prone to psychosis or those with a past history of a mental health disorder.

Case Report

A 40-year-old Hispanic woman veteran with a past medical history significant for major depressive disorder, posttraumatic stress disorder, anxiety, irritable bowel syndrome, and migraines was admitted to an inpatient psychiatry unit from a walk-in clinic referral. The patient's psychologist, psychiatrist, and husband all encouraged inpatient admission as they had noticed acute changes in behavior and self-injurious behavior. Medications on admission included venlafaxine extended-release 75 mg by mouth daily, clonazepam 0.5 mg by mouth daily, and phentermine 7.5 mg/topiramate 46 mg by mouth once daily. The complete blood count, comprehensive metabolic panel, liver function panel, and urinalysis upon admission all were within normal limits. Additionally, the patient had a negative urine drug screen and pregnancy test. The patient described her recent mood as having a depressed affect, with no suicidal ideation. She also admitted to recently displaying abnormal behaviors, such as self-harm by cutting her wrists multiple times. The patient denied racing thoughts, decreased need for sleep, irritable mood, impulsivity (except for the above-mentioned cutting), or grandiosity. Furthermore, the patient displayed delusional thinking, in which she believed that the military should allow her to become an assassin and that a portal to death/afterlife actually exists. The patient denied any past medical history of delusional thoughts or psychosis.

The patient was started on venlafaxine extended-release 37.5 mg by mouth daily for 7 days in April 2015 and was titrated to 75 mg daily. According to the patient, she was taking venlafaxine consistently for a month prior to admission. Upon further questioning, it was discovered the patient was restarted and prescribed her previous medication phentermine/topiramate for weight loss approximately 1 week prior to admission by an alternative prescriber. The patient was previously taking the medication in April 2014 for weight loss with no concomitant psychotropic drugs at the time. The patient denied any suicidal ideation or behavioral changes prior to taking the combination of venlafaxine and phentermine/topiramate, specifically during the first couple weeks of venlafaxine therapy. Additionally, the patient denied any behavioral changes occurring while taking phentermine/topiramate in the past. The patient was started on lurasidone 40 mg by mouth in the evening for psychosis, while venlafaxine and phentermine/topiramate were discontinued. Total duration of inpatient stay was approximately 1 week. Upon discharge, the patient reported improvements in her bizarre behavior, no impulses to self-harm, and no suicidal ideation. The patient was discharged on lurasidone 40 mg by mouth every evening, and her previous outpatient medication clonazepam 0.5 mg by mouth daily was continued. The patient was continued on lurasidone for a total of 4 weeks without recurrence of symptoms.

Discussion

Case reports of psychotic behavior have been documented in the literature for venlafaxine and phentermine alone (see the Table); however, no specific data have been published on the combination of venlafaxine and phentermine/topiramate causing psychosis.

One specific case study[9] published in the *Indian Journal of Psychiatry* reported psychotic symptoms induced by venlafaxine. A 32-year-old patient was diagnosed with social phobia and venlafaxine was initiated. Oral doses of venlafaxine, titrated to 150 mg/d, were used initially until the patient developed delusions that his coworkers were deliberately trying to sabotage his career. Venlafaxine was stopped, and oral olanzapine 5 mg, a second-generation antipsychotic, was started. The delusional psychosis stopped when olanzapine was further increased to 10 mg. Resolution of symptoms occurred 1 month after initiation of olanzapine. Over the next 2 months, olanzapine was discontinued. Venlafaxine was then retrialed for social phobia; however, the psychotic features

TABLE: Case reports of venlafaxine- and phentermine-induced psychotic symptoms

	Safeekh and Pinto[9] (2009)	Adamou and Hale[10] (2003)	Alexander et al[6] (2011)	Cleare[7] (1996)
Drug	Venlafaxine	Venlafaxine	Phentermine	Phentermine
Dose	150 mg	225 mg	Patient A: 40 mg Patient B: Not available Patient C: 30 mg Patient D: 60-90 mg	30-60 mg
Length of treatment	1 mo and 2 wk	20 wk	Patient A: 6 d Patient B: 1 wk Patient C: 2 wk Patient D: 6 d	4 mo
Disease state	Social phobia	Treatment-resistant depression	Patient A: Poor self-image and with weight → given diet pill Patient B: Not available Patient C: Bought on street for symptoms of lethargy Patient D: Weight concerns/recreational purposes	Obese
Adverse event	Delusions	Delusions	Patient A: Hallucinations Patient B: Psychosis Patient C: Psychosis Patient D: Paranoid delusions and auditory hallucinations	Psychosis
Type of psychosis produced	Persecutory delusion	Erotomania	Patient A: Hallucinations → pressured speech and argumentative behavior Patient B: Paranoid delusions Patient C: Auditory hallucinations and delusions Patient D: Referential, being bugged, persecution	Isolation, agitation, hallucinations
Outcome	Treated with olanzapine 10 mg, and symptoms resolved	Venlafaxine decreased to 150 mg over 5-wk period, and symptoms resolved	Patient A: Stopped phentermine, and symptoms abated Patient B: Use of antipsychotic (no drug given) and discontinuation of phentermine produced rapid resolution of symptoms Patient C: Symptoms resolved with cessation of phentermine Patient D: Not available	Phentermine stopped for 10 d with no symptom improvement; given haloperidol 5 mg 3 times daily; symptoms improved in 10 d

began to reappear approximately 2 months later. The patient was once again treated with olanzapine 10 mg, and the psychosis disappeared. According to the case report, the final hypothesis attributed the psychosis to the dopamine reuptake inhibition of venlafaxine.

In addition, a case report[10] published in 2003 found erotomania (excessive sexual desire) was induced by oral venlafaxine in a 39-year-old female. The occurrence of erotomania appeared twice, on separate occasions, when taking venlafaxine. The excessive sexual desire disappeared upon reduction of the venlafaxine dose to ≤150 mg/d. The authors concluded that an increase in stimulation to the postsynaptic D_2/D_3 located in the mesolimbic system may be responsible for this erratic behavior. This theory, however, differs from Stahl's theory,[1] as he states venlafaxine is increased only in the prefrontal cortex. Further investigation into the specific areas of the brain in which dopamine is affected by venlafaxine is warranted. This investigation, however, is beyond the scope of this article.

Regarding phentermine, case reports of psychosis have been reported since the late 1960s.[6] One specific article reported 4 different patients' experiences of psychosis from the use of oral phentermine. First, a 30-year-old woman with a history of bipolar affective disorder suffered from a manic relapse with hallucinations, pressured speech, and argumentative behavior (patient A). Next, a 30-year-old woman reported paranoid delusions 1 week after starting phentermine (patient B). In addition, a 52-year-old man developed auditory hallucinations and delusions upon initiating phentermine (patient C). Last, a 39-year-old woman developed paranoid delusions and auditory hallucinations after using phentermine for only 6 days (patient D). Three out of 4 cases were resolved upon discontinuation of phentermine; however, because of a lack of information about the 39-year-old, it is undetermined at this time whether symptoms resolved upon discontinuation of phentermine. Returning to the mechanism of action mentioned above, the increase in dopamine likely contributes to the onset of psychosis.[6]

Finally, a case[7] published in the *Journal of Clinical Psychopharmacology* reported psychosis induced by phentermine administration in a 32-year-old woman with no previous psychiatric history. The woman was taking 30 to 60 mg oral phentermine daily for 4 months prior to this episode. The patient isolated herself, became extremely agitated, and was convinced she had a transmitter placed in her head. The woman presented to the mental health clinic as these symptoms continued to persist, despite stopping phentermine 10 days prior. She was treated with haloperidol 5 mg by mouth 3 times daily. Approximately 10 days after initiation of the antipsychotic, symptoms resolved, despite the fact that phentermine has an elimination half-life of approximately 20 hours. This specific article discussed the remission timeline, in which the 10 days of recurrent psychosis after discontinuation of phentermine was consistent with previously published data on phenylpropanolamine, a similar stimulant.[7,8] The reported average number of days to remission for phenylpropanolamine is 17 days.

Conclusion

Previous cases have been reported on psychosis induced by venlafaxine alone and by phentermine alone, but not in combination. The proposed mechanisms of each of the medications are consistent with the development of psychotic-like features. When estimating the probability of the adverse drug reaction using the Naranjo Adverse Drug Reaction Probability Scale, the total score is equal to 3, indicating the reaction was possible.[11] To further support the evidence, each of the medications, when taken individually, did not cause a psychotic-like reaction to occur; whereas, psychosis was observed when the medications were taken in combination. Additional information is needed regarding venlafaxine and the increase in dopamine, specifically in the prefrontal cortex versus various areas of the brain. Additionally, further information is needed on specific doses of venlafaxine and increases in dopamine, as this patient case demonstrates effects at doses of 75 mg/d. Last, specific data on topiramate's mechanism of action, specifically in appetite suppression, is lacking, and thus the potential for topiramate's contribution to the development of psychosis cannot definitively be excluded. Health care professionals should carefully consider the potential for psychosis with the combination of venlafaxine and phentermine/topiramate in a patient population with a mental health history. Increased monitoring is needed to confirm psychosis induced by the combination of venlafaxine and phentermine/topiramate, as is increased emphasis on publication of such case reports.

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