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Acute hypertensive crisis and severe headache after concurrent use of armodafinil and tranylcypromine: case report and review of the literature

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Abstract

Concurrent use of modafinil or armodafinil with monoamine oxidase inhibitors (MAOIs) is contraindicated due to a theoretical risk of drug synergism and acute hypertensive episodes. However, few data are available to substantiate that risk, and several case studies have suggested that the combination is safe. To our knowledge, we present the first case of a patient treated concurrently with armodafinil and tranylcypromine. The patient developed an acute hypertensive crisis with severe headache, nausea, blurry vision, and neck stiffness. Her symptoms corresponded with the predicted pharmacokinetic and pharmacodynamic response. Upon review of the literature, two out of seven patients, including our own, treated concurrently with modafinil or armodafinil and an MAOI developed an adverse reaction. Physicians should exercise caution if using these classes of drugs together.

Case:

A 36-year-old woman with a history of bipolar disorder presented to our emergency department with acute onset of the “worst headache of (her) life”, less than one hour after ingesting armodafinil and the monoamine oxidase inhibitor (MAOI), tranylcypromine. The patient had been prescribed armodafinil, 250 mg daily, for daytime sleepiness, which she had been taking for approximately two months, and tranylcypromine as an antidepressant, which was gradually increased over the past two months. She was also prescribed brexpiprazole 0.5 mg daily, and alprazolam 0.5 mg as needed, which she did not take on the morning of presentation. There had been no recent changes in the dosing or scheduling of these medications. That morning, her provider had adjusted her tranylcypromine schedule

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from 20 mg twice daily to 40 mg in the morning. A holocephalic headache 3/10 in severity developed thirty minutes after ingestion and progressed to 10/10 over the next hour with associated nausea, blurry vision, and neck stiffness.

In the emergency department, she was found to be hypertensive (blood pressure 186/120) with blurry vision, neck stiffness, and altered alertness. Initial non-contrast head CT did not show acute hemorrhage. She was given intravenous morphine, which reduced the severity of her headache. Her blood pressure gradually decreased over the course of the day, along with her pain. Magnetic resonance imaging and venography were normal, and a bedside lumbar puncture was unsuccessful. The patient was admitted to the Neurology service for observation and her psychiatric medications were withheld. The following day, the patient's headache was present but reduced and her blood pressure returned to baseline. Her symptoms had subsided by the time of follow-up, three days later.

Discussion and Review:

The exact therapeutic mechanism of modafinil and its R-enantiomer, armodafinil, in vivo is unknown. However, both compounds are known to exhibit robust effects on levels of catecholamines and serotonin, among other systems, within the brain. Activation of these systems is mediated by extracellular catecholamine and serotonin release.[1] MAOIs inhibit the catabolism of catecholamines and serotonin, leading to increased concentration of these neurotransmitters within tissues, especially the brain.[2] Concurrent use of these two drug classes is therefore either recommended against[3] or contraindicated[4] due to pharmacodynamic synergism and a theoretical risk of cardiovascular/cerebrovascular events and acute hypertensive episodes. Compared with modafinil, armodafinil has a longer half-life[5] and is up to twice as potent.[6] To our knowledge, there are no reports of armodafinil being used concurrently with tranlycypromine. Upon review of the literature, we identified six patients who were treated with modafinil and an MAOI (Table).[7–10] Five of the patients had no adverse events. However, one patient, described by Vytopil et al., developed acute chorea, confusion, and hyperthermia three days after modafinil was added to tranlycypromine, which resolved two days after the drugs were discontinued. The authors hypothesized that the symptoms were due to the combined central serotonergic and dopaminergic effects of the two drugs.

The differential diagnosis for acute onset of “worst headache of life” includes subarachnoid hemorrhage, reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous thrombosis, carotid or vertebral artery dissection, cerebral infection (meningitis, encephalitis, abscess), pituitary apoplexy, hypertensive emergency with or without reversible posterior encephalopathy syndrome, complicated sinusitis, ischemic stroke, and acute closed-angle glaucoma, amongst others.[11] The majority of these structural causes were ruled out with imaging.

The onset and resolution of our patient's symptoms correlated temporally with her likely plasma drug concentrations, based on averages from pharmacokinetic studies (Figure).[5, 12] It is therefore most likely that the sympathomimetic effects of the two drugs, mediated by increased catecholamine release, were responsible for the hypertensive crisis, with

subsequent headache and blurry vision as a consequence. Pain caused by her headache may have also exacerbated the underlying hypertension. Alternatively, the combined serotonergic effects of the two drugs[1, 2] may have precipitated RCVS. RCVS is characterized by sudden onset of severe headache with or without neurological symptoms and can be caused by vasoactive substances that modulate serotonin activity in the brain.[13] Although the resolution of clinical signs and symptoms corresponded with the half-life of the drug, administration of morphine may have also contributed to the alleviation of symptoms through pain control and direct vasodilatory effects.[14] Both of these possible mechanisms that we propose are consistent with the theoretical contraindication and the case described by Vytopil et al.

Our patient was also taking brexpiprazole, an atypical antipsychotic, at the time of presentation. Brexpiprazole is a serotonin-dopamine activity modulator, with partial agonism at the 5-HT_{1A}, D2, and D3 receptors.[15] It is hypothetically possible that the patient's symptoms were due to serotonergic/dopaminergic activity mediated by the combination of brexpiprazole with tranylcypromine or armodafinil. The U.S. Food and Drug Administration recently approved brexpiprazole as an adjunctive therapy for treatment-resistant depression. [16, 17] However, the studies were carried out using brexpiprazole with selective serotonin or serotonin-norepinephrine reuptake inhibitors, and brexpiprazole's safety with MAOIs has not been extensively studied. A recent review concluded that the combination of atypical antipsychotics with MAOIs is safe and unlikely to cause serotonin syndrome, except in the case of ziprasidone, which has stronger affinity for the serotonin receptor.[18] We found no contraindication involving the use of brexpiprazole with MAOIs.[3, 4] Regarding the use of atypical antipsychotics with armodafinil, a randomized, double-blind, placebo-controlled clinical trial with 72 patients found the combination to be safe.[19] We, therefore, find it unlikely that the patient's symptoms were due solely to the combination of brexpiprazole with tranylcypromine or armodafinil. It is possible, however, that brexpiprazole exacerbated or contributed to the underlying symptoms. It should be noted that none of the cases reviewed by us in which modafinil/armodafinil was combined with a MAOI involved the use of an atypical antipsychotic.

Several case studies have suggested that the combination of modafinil/armodafinil with MAOIs may be safe. Upon review of all published cases, two out of seven patients developed an adverse event. We, therefore, advocate that physicians exercise caution if using these classes of drugs together.

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Figure - Timing of signs and symptoms in relation to theoretical plasma drug concentration*
 Plasma drug concentrations of armodafinil and tranylcypromine are represented on the left y-axis. Systolic blood pressure and severity of pain were assessed during serial examinations and are represented on the right y-axes. Medication was ingested at time $t=0$. C_{max} = maximum plasma drug concentration. *Theoretical plasma drug concentrations in this figure are adapted from Darwish et al.[5] and Mallinger et al.[12] Armodafinil was administered after multiple (daily) doses to achieve steady state.[5] Tranylcypromine was administered as a one-time single dose.[12]

Table -
Review of patients treated with modafinil/armodafinil and concomitant monoamine oxidase inhibitor

Patient	Age	Sex	Diagnosis	Stimulant (dose)	MAOI(dose)	Other Medications (dose)	Reaction	Study
1	54	Female	Dysthymia	Modafinil (100 mg qD)	Phenelzine (30 mg TID)	Lamotrigine (200 mg BID)	None	Ashton, 2004
2	49	Female	MDD	Modafinil (200 mg qD)	Tranylcypromine (25 mg BID)	Thioridazine (50 mg HS)	None	Clemons et al., 2004
3	34	Female	MDD	Modafinil, (200 mg qD)	Tranylcypromine (80 mg qD, schedule not specified)	NA	Acute chorea and hyperthermia	Vytopil et al., 2007
4	58	Male	MDD w/ atypical features	Modafinil, (400 mg qD)	Selegiline (STS 24 mg qD)	Carbamazepine (200 mg BID)	None	Tobe, 2015
5	55	Male	MDD	Modafinil (400 mg qD)	Selegiline (STS 24 mg qD)	NA	None	Tobe, 2015
6	60	Female	MDD w/ atypical features	Modafinil (400 mg qD)	Tranylcypromine (120 mg qD)	Tianeptine (37.5 qD)	None	Tobe, 2015
7	36	Female	Bipolar Disorder	Armodafinil (250 mg qD)	Tranylcypromine (40 mg qAM)	Bexiprazole (0.5 mg qD)	Acute hypertensive episode with worst headache of life	Current case

MDD- Major depressive disorder. STS- Selegiline transdermal system. MAOI- Monoamine oxidase inhibitor. qD- Daily. qAM- Every morning. TID- Three times per day. BID- Two times per day. HS- Nightly. NA- Not applicable.