Case Report

Eric L. Singman*, Brian Hocum, Jithin Yohannan and Virginia Pearson

Fluvoxamine-associated oscillopsia and a role for personalized medication dosing

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Abstract: A 60-year-old woman reported horizontal "shimmering" movement while reading crossword puzzles when using fluvoxamine, bupropion, quetiapine, lithium, and levothyroxine. This visual disturbance, likely oscillopsia, started after the fluvoxamine was added and waned as the fluvoxamine was tapered, disappearing after the drug was discontinued. Genetic testing to explore how the patient metabolizes these medications combined with YouScript® interaction analysis suggest that she may have had abnormally high plasma concentrations of fluvoxamine during this time. Oscillopsia may be a novel dose-dependent side effect of fluvoxamine. Genetic testing combined with YouScript has the potential to discover novel drug side effects, elucidate drug interactions and guide future prescribing decisions.

Keywords: adverse drug event; adverse drug reaction; bupropion; case report; CYP450; drug interaction; drug metabolism; drug side effect; fluvoxamine; genetic testing; nystagmus; oscillopsia; pharmacogenetics; quetiapine; shimmering; visual disturbance.

Case presentation

A 60-year-old women with a long history of depression underwent 18 treatments of electroconvulsive therapy (ECT) for refractory depression from March 24 until May 9, 2014. On the day prior to starting a second round of 13 ECT treatments (May 30 until July 7), the patient was prescribed fluvoxamine 50 mg PO qD. This was increased so that the total daily dose was 100 mg qD on June 2, 150 mg on June 24, 200 mg on June 25, 250 mg on June 30, and 300 mg on July 1. This total daily dose was maintained until August 13 when it was lowered to 250 mg. The dosage was lowered because the patient had reported to her psychiatrist that she was experiencing visual disturbances, as well as a hand tremor. The fluvoxamine dose was then tapered so that the total daily dose was 200 mg on August 14, 100 mg on August 15, 50 mg on August 18, and discontinued on August 19.

Prior to and during the period where the patient was suffering the visual disturbances, she was being treated with bupropion (200 mg PO AM, 100 mg PO PM), levothyroxine sodium (50 μg PO qD), lithium carbonate (450 mg PO BiD with serum levels monitored regularly), and quetiapine (100 mg PO qHS, increased to 200 mg on August 12). Because the patient reported her memory to be suboptimal, the timing and dosing of her concurrent medications was confirmed through her medical records.

The non-smoking, non-caffeine drinking woman visited the Neuro-ophthalmology Clinic in September 2014 with the chief complaint of abnormal visual occurrences during the previous 5 weeks. Specifically, she mentioned that as she worked on crossword puzzles, the vertical columns moved back and forth rhythmically and horizontally. She described the movement as "shimmering, like watching a ping-pong ball go back and forth". The patient indicated that the episodes lasted at least a few seconds. Initially the visual episodes occurred throughout the day, as often as every 30 min. The patient added that the visual problem and hand tremor eased as her dosage of fluvoxamine was lowered and had completely stopped by the time of her neuro-ophthalmology clinic visit.

The patient's review of systems was significant for a long history of depression, memory impairment since the electroconvulsive therapy (ECT) for refractory depression, hypothyroidism, migraines, and degenerative disc

***Corresponding author: Eric L. Singman,** Wilmer General Eye Services, Wilmer Eye Institute, Johns Hopkins Hospital, Wilmer B-29, 600 N. Wolfe St., Baltimore, MD 21287, USA, Phone: 410-955-9976, E-mail: esingma1@jhmi.edu
Brian Hocum: Genelex Corporation, Seattle, WA, USA
Jithin Yohannan: Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD, USA
Virginia Pearson: Department of Psychiatry, Johns Hopkins Hospital, Wilmer Eye Institute, Baltimore, MD, USA

disease secondary to scoliosis. Her ophthalmic and oculomotor examinations were entirely normal; the patient demonstrated 20/20 vision OU with correction, normal and symmetric pupillary function, normal color vision, normal visual fields by confrontation, normal fundus examination, and normal extra-ocular movement (orthophoric in all cardinal directions of gaze and no evidence of nystagmus).

Genetic testing was ordered to characterize the patient's metabolic phenotypes. The rationale therein was to determine whether her ability to metabolize medications might have permitted abnormal or unexpected plasma concentrations of fluvoxamine or other prescribed medication resulting in the visual disturbance. Genetic polymorphisms of metabolic enzymes cytochrome P450 (CYP) 2D6, 2C19, and 3A4 were detected using a laboratory-developed, polymerase chain reaction based assays. The results were as follows:

CYP2D6 intermediate metabolizer genotype *4/*35
CYP2C19 ultra rapid metabolizer genotype *17/*17
CYP3A4 normal metabolizer genotype *1/*1

Discussion

Visual disturbances associated with medications in general and neuro-active drugs in particular are not uncommon [1–3]. Indeed, all of the patient's neuro-active medications have been associated with visual and/or ocular side effects. Lithium has been reported to cause downbeat nystagmus [4–8] and photophobia [9], and quetiapine has been associated with photopsias (flashing lights) [10]. There is a case report associating bupropion with diplopia [11], and quetiapine has been reported to aggravate glaucoma and cause sustained upward gaze (ocular dystonia) [12]. The patient presented in this report described shimmering in her vision that seems most likely to be oscillopsia. Oscillopsia is the sense of the visual world vibrating and is the subjective correlate of nystagmus. Importantly, there is no one who witnessed nystagmus, so it would be presumptive to suggest that there was nystagmus. None of the medications that the patient used have been associated with horizontal shimmering or oscillopsia.

Utilizing the YouScript® (Genelex, Seattle, WA, USA) drug interaction database, the patient's predicted metabolism of her prescribed medications was examined and potential interactions assessed. Fluvoxamine is a selective serotonin reuptake inhibitor antidepressant. It is primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 [13, 14]. It has been described as a potent inhibitor of CYP1A2 [15] and CYP2C19 [16], and a mild to moderate inhibitor of CYP2B6 [17] and CYP3A4 [18]. It has also been shown to inhibit numerous other pathways and the efflux transport protein P-glycoprotein (P-gp), although data on the latter are conflicting [19, 20].

Bupropion is a norepinephrine and dopamine reuptake inhibitor antidepressant. It is primarily metabolized by CYP2B6 (not tested in this patient) to the active metabolite, hydroxybupropion. It is metabolized to a lesser extent by CYP2C19 to other hydroxy-metabolites [21]. Bupropion is a potent CYP2D6 inhibitor [22, 23]. Hydroxybupropion is primarily metabolized by CYP2D6 and is also an inhibitor of this pathway [22, 24].

Quetiapine is an atypical antipsychotic. It is primarily metabolized by CYP3A4 and to a lesser extent by CYP2D6 [25]. It is a substrate for the P-gp transporter [26]. The primary active metabolite, norquetiapine, is a major substrate of CYP2D6 and CYP3A4 [27].

Lithium is a mood stabilizer that undergoes renal excretion (lithium product insert).

Levothyroxine is not metabolized by the cytochromes, although it is a weak inducer of CYP1A2 [28] and P-gp [29].

Table 1 summarizes the interactions of the medications used by the patient.

Table 1: Summary of interactions of medications used by the patient in this case report.

Interaction table						
	CYP2D6	**CYP2C19**	**CYP1A2**	**CYP3A4**	**CYP2B6**	**P-gp**
Fluvoxamine	Sub	Inh	Sub, Inh	Inh	Inh	Inh
Bupropion	Inh	Sub			Sub	
Hydroxybupropion	Sub, Inh					
Quetiapine	Sub			Sub		Sub
Norquetiapine	Sub			Sub		
Levothyroxine			Ind			Ind
Lithium						

Sub, substrate; Inh, inhibitor; Ind, inducer.

Fluvoxamine exposure has been reported to increase in individuals with the CYP2D6 intermediate metabolizer phenotype compared to normal metabolizers [30]. Interestingly, there have been no studies about fluvoxamine pharmacokinetics conducted when co-administered with potent CYP2D6 inhibitors (e.g. bupropion, fluoxetine, quinidine, paroxetine), but there have been studies showing increased plasma concentration and half-life of fluvoxamine from 10 to 31 h in CYP2D6 poor metabolizers [30, 31]. We suspect that CYP2D6 activity is comparable in CYP2D6 poor metabolizers and individuals receiving potent CYP2D6 inhibitors, because in both groups there is inability of the CYP2D6 substrate to be metabolized by the CYP2D6 enzyme. Based on this assumption, it is reasonable to predict that giving a CYP2D6-potent inhibitor (i.e. bupropion) to a patient who is a CYP2D6 intermediate metabolizer may have resulted in increased fluvoxamine exposure relative to an individual with normal and unimpaired CYP2D6 activity.

Notably, this does not necessarily prove that the fluvoxamine alone caused oscillopsia in the patient presented. Although no studies of bupropion use in individuals deficient for CYP2D6 enzyme metabolism or taking CYP2D6 inhibitors have observed changes in bupropion exposure, an increase in the plasma level/dose ratio of hydroxybupropion has been observed in CYP2D6 poor metabolizers [24, 32]. In this patient, it is reasonable to predict increased hydroxybupropion exposure due to a combination of her being a CYP2D6 intermediate metabolizer and possible auto-inhibition of CYP2D6 by buproprion/hydroxybupropion. Increased hydroxybupropion has been associated with increased adverse drug reactions, although oscillopsia has not been reported to be one of them [24]. One could speculate that the bupropion plasma concentration was increased via fluvoxamine-induced inhibition of CYP2C19 and CYP2B6. That being said, one could suggest that the increased bupropion exposure (parent drug and metabolite) may have directly caused the oscillopsia. The discontinuation of fluvoxamine and the fact that the patient is a CYP2C19 ultra rapid metabolizer (i.e. rapid decrease in bupropion exposure) may help explain why the visual disturbance dissipated rapidly with downward titration and discontinuation of fluvoxamine, if indeed increased bupropion plasma concentrations can be implicated. Conversely, because these postulated elevated concentrations of bupropion/hydroxybupropion could super-inhibit CYP2D6-metabolism of fluvoxamine, the concern for fluvoxamine toxicity causing oscillopsia remains.

It is important to consider these types of interactions for all the patient's medications. Although no pharmacokinetic interaction between quetiapine and bupropion have been reported, this combination may hypothetically result in increased norquetiapine. This might occur because the norquetiapine produced by the CYP3A4 pathway would accumulate in a patient who is a CYP2D6 intermediate metabolizer receiving a drug (bupropion) that further inhibits CYP2D6. Furthermore, there is a possibility that quetiapine itself might rise to supranormal concentrations in this patient, because fluvoxamine inhibits both CYP3A4 (the main metabolizer of quetiapine) and P-gp, the efflux pump that removes this drug from the central nervous system (CNS) to the bloodstream. One could, therefore, postulate that either elevated plasma or CNS concentrations of quetiapine could increase the potential for ocular adverse drug reactions. However, it must be noted that the quetiapine dose was doubled on August 12; despite this change in drug regimen, the patient's visual disturbance continued to abate.

Lithium and quetiapine have been co-administered without changes to the pharmacokinetics of either drug, although an increase in mild adverse drug reactions including somnolence, dry mouth, asthenia, nausea, dizziness, tremor, and insomnia has been reported with this combination [33]. Finally, although it is possible that combined use of lithium and fluvoxamine might result in additive pro-serotonergic effects, the authors found no reports in the literature suggesting serotonin toxicity leads to either nystagmus or oscillopsia.

In summary, it would seem that the patient's described oscillopsia may be a novel dose-dependent side effect of fluvoxamine. The fact that it started when the patient began using fluvoxamine, decreased as the fluvoxamine dose was lowered, and ceased when the fluvoxamine was discontinued scores a 5 on the Naranjo scale of adverse drug reactions, suggesting a probable correlation [34]. Although not directly measured, the predicted increase in fluvoxamine plasma concentrations due to diminished CYP2D6 activity resulting from the cumulative impact of being a CYP2D6 intermediate metabolizer and receiving a potent CYP2D6 inhibitor strengthens the causal association between this drug and the adverse drug reaction, oscillopsia. As demonstrated, genetic testing of metabolic pathways combined with YouScript interaction analysis revealed a plethora of possible interactions and possible discovery of a novel side effect. In patients taking complicated drug regimens that have numerous potential interactions, genetic testing of metabolic pathways and YouScript interaction analysis may aid in the detection of current problematic interaction and also guide future prescribing and dosing decisions when the information is used prospectively before medications are prescribed. As an example in this case, a review article recommends

that fluvoxamine plasma concentrations be monitored and that the dose is slightly decreased in CYP2D6 intermediate metabolizers [32]. The same review recommends that CYP2D6 poor metabolizers receive a 25%–50% dose decrease [32]. Due to potential phenoconversion from a CYP2D6 intermediate metabolizer to a CYP2D6 poor metabolizer by the potent CYP2D6 inhibitor, bupropion for this patient would likely have been a candidate for the 25%–50% dose reduction, which corresponds with the clinical course of this case.

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