media's representation of these animals (i.e., cartoons of Looney Toons high-pitched Tweety Bird or Disney's low-pitched Jiminy Cricket). While it is possibly due to the opioids themselves, heroin is frequently adulterated with fillers which may contain hallucinogenic properties, any of which may have been the pathogenic factor. Autophobia, or the need for social contact, may be the nidus motivating such communicative anthropomorphism. Query as to the presence of such Doctor Dolittle hallucinations in those with heroin or other intoxicants may be revealing.
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Electroconvulsive Therapy in Thrombocytopenic Patients: A Case Report and Literature Review

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Abstract

Introduction. Electroconvulsive therapy (ECT) continues to be one of the most effective treatments for severe and treatment-resistant major depression. Although there are no absolute contraindications to performing ECT, the risks and benefits need to be assessed in all patients. We present a patient with a history of paroxysmal nocturnal hemoglobinuria (PNH) with significant thrombocytopenia, who completed an index course of six ECT sessions without complication. Currently, there are only two published case reports which describe the use of ECT in patients with thrombocytopenia.
Methods. AD is a 37-year-old female with a history significant for MDD, GAD, panic disorder, PNH, and Budd Chiari, who presented to ED for suicidal ideation. Initial labs showed pancytopenia (Hb 4.56 mg/dl, Absolute Neutrophil 0.7 x 10^3/mL). Given her history of multiple failed SSRIs, ECT was proposed to treat her depression. Anesthesia delayed her initial pre-operative assessment due to concerns regarding her platelet count and risk of bleeding. They recommended transfusion with a preprocedural platelet count goal of 50 x 10^3/mL. Psychiatry recommended a platelet goal of 20 x 10^3/mL given previous ECT literature. Patient underwent six ECT sessions without complications. Her platelets ranged from 24–40 x 10^3/mL and she did not require preprocedural platelet transfusion.
Results. Due to a lack of published literature, there are no formal guidelines for performing ECT in thrombocytopenic patients. The first case report details a 64-year-old female who underwent 12 ECT sessions without complication, while her platelet count ranged from 7–38 x 10^3/mL. The most recent case report describes a 74-year-old male who underwent nine ECT treatments without complications. The authors decided to transfuse prophylactically if pre-procedure platelet count was less than 20 x 10^3/mL. The patient underwent nine treatments, requiring eight transfusions. CT head did not show any signs of hemorrhage or structural changes. The authors remarked it is unclear whether the transfusions were necessary.
Conclusions. Even though ECT has been in use for over 80 years, there is still much that is unknown about this treatment modality. This case highlights the lack of absolute contraindications to performing ECT. However, the lack of literature and studies regarding platelet goals in thrombocytopenic patients for ECT delayed patient care in this specific case. We add a third case report in a thrombocytopenic patient who underwent ECT without complications with a pre-procedure transfusion criterion if platelet count was less than 20 x 10^3/mL. More research needs to be conducted to determine risk and cut-off limits for platelet transfusion prior to performing ECT in thrombocytopenic patients.
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Evaluating the Impact of Caffeine on the Incidence of Adverse Events During Treatment with Viloxazine Extended-Release (Qelbree®) in Adults with ADHD

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Abstract

Introduction. Viloxazine ER (viloxazine extended-release capsules (Qelbree®) is a novel, nonstimulant, FDA-approved treatment for attention-deficit/hyperactivity disorder (ADHD) in adults and children ≥6 years of age. Viloxazine ER inhibits cytochrome P450-1A2, the enzyme responsible for caffeine metabolism. In a Phase 1 study, the peak exposure (C_{max}) of caffeine was unchanged, while the systemic total exposure (AUC) was shown to increase ~5-fold following coadministration of caffeine (200mg) with viloxazine ER (900 mg/day x 4 days) compared to caffeine alone. Except for insomnia (44.4%), and possibly dizziness (8.3%), the incidence of adverse events (AEs) was not notably higher following coadministration vs. either caffeine or viloxazine ER alone. The objective of this analysis was to evaluate the impact of caffeine consumption on the incidence of AEs in adults with ADHD treated with viloxazine ER.
Methods. Data were analyzed from the Phase 3, double-blind (DB), placebo-controlled trial (NCT04016779) and ensuing (ongoing) open-label extension (OLE) safety trial (NCT04143217) supporting the viloxazine ER indication for adults with ADHD. Participants reported caffeine intake during the past week at each study visit.

Correlation was assessed between viloxazine ER dose (mg/day) and weekly total caffeine consumption (mg) and between ADHD Investigator Symptom Rating Scale (AISRS)

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Total score and caffeine consumption. Fifteen AE preferred terms, known to be associated with caffeine consumption, were evaluated. For viloxazine ER-treated subjects (200–600 mg/day) who experienced a potentially caffeine-associated AE, the probability the AE occurred as a function of viloxazine ER dose and caffeine consumption during the DB or OLE trials was estimated using a logistic regression model for AEs with an incidence ≥5%.
Results. Of 372 enrolled subjects ~85% reported caffeine use during the DB trial; mean caffeine use was 1034 mg/week for the placebo group and 859 mg/week for the viloxazine ER group. There was no correlation between viloxazine ER dose and caffeine consumption (p=0.73), nor between AISRS total score and caffeine consumption (p=0.908). Of subjects reporting caffeine use, 44 (DB placebo), 79 (DB viloxazine ER), and 33 (OLE viloxazine ER) reported any of the pre-identified caffeine- associated AEs and were included in the regression analysis. For these subjects, insomnia-related AEs, fatigue, nausea, headache-related AEs, decreased appetite, and somnolence-related AEs occurred in ≥5% of viloxazine ER-treated subjects. Based on the regression analysis, caffeine consumption significantly increased the probability of experiencing insomnia-related AEs only (p=0.02).
Conclusions. This analysis suggests using caffeine concomitantly with viloxazine ER does not increase the likelihood of experiencing caffeine-related AEs except for insomnia. Still patients should be aware of the potential for viloxazine ER to augment caffeine exposure.
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Characterization of Viloxazine Effects on Cortical Serotonin Neurotransmission at Doses Relevant for ADHD Treatment

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Abstract

Introduction. Most ADHD treatments are thought to be effective due to augmentation of dopamine (DA) and norepinephrine (NE). Our prior preclinical studies found that the ADHD treatment, viloxazine, may augment serotonin (5-HT) in addition to NE and DA; however, it was unclear if these effects occurred at clinically relevant concentrations. To further understand these potential 5-HT effects, we conducted a series of experiments with two objectives: 1) Can we confirm and better elucidate the previously observed serotonergic effects of viloxazine and determine if they occur at clinically relevant concentrations? 2) Are these effects observed in species with close physiology to humans?

Methods. Objective 1: The affinity of viloxazine for human isoforms of 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 receptors was assessed via cell-based binding assays. Viloxazine agonism of 5-HT_{2C} and antagonism at 5-HT_7 was elucidated with IP_1, Ca^{2+}, β-arrestin, internalization, and cAMP assays in cells expressing human receptor isoforms. A microdialysis study was conducted in rats to determine the relationship between viloxazine concentrations in the interstitial fluid (ISF) and changes in NE, DA, 5-HT, and their metabolite concentrations in the prefrontal cortex (PFC). Objective 2: A PET imaging study using a 5-$HT_{2A/2C}$ radioligand agonist, [^{11}C]CIMBI-36, is being conducted in non-human primates (NHPs) to evaluate if viloxazine binds these receptors and/or increases 5-HT release.

Animal research was approved by animal care and use committees. Animals were cared for according to international standards.
Results. Objective 1: Cell-based assays to measure viloxazine affinity for NET, 5-HT_{2B}, 5-HT_{2C}, and 5-HT_7 found K_i values of 0.14, 0.65, 0.84, 1.90 μM respectively. These values were lower than therapeutically relevant rat ISF concentrations (3.5 ± 1.6 μM) approximating pediatric ADHD patients unbound plasma concentrations (2.1-3.3 μM), indicating receptor recruitment. Binding affinity and functional activity assays found viloxazine had negligible activity for 5-HT_{2A} and SERT at therapeutic concentrations. Viloxazine 5-HT_{2C} agonism activated G_q-protein signaling (EC_{50}=1.6 μM, Ca^{2+} assay), but not β-arrestin or internalization pathways (EC_{50} values >150 μM). Viloxazine 5-HT_7 antagonism decreased G_s-protein signaling (IC_{50} =6.7 μM). The microdialysis study found that at therapeutically relevant ISF concentrations, 5-HT levels were significantly increased over baseline; no changes were seen in the 5-HIAA metabolite, indicating 5-HT increase is not due to 5-HT reuptake inhibition. Objective 2: PET imaging studies are ongoing.
Conclusions. To date, our experiments to further elucidate the potential 5-HT effects of viloxazine have shown that the previously observed effects of viloxazine on 5-HT receptors and its augmentation of 5-HT in rat PFC occur at clinically relevant concentrations. Further exploration is needed to ascertain if these effects occur in NHPs and are relevant to ADHD.
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Lumateperone 42 mg in an Open-Label Switch Study in Patients with Stable Schizophrenia: Results by Previous Antipsychotic

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