Metadoxine – A Novel Synthetic Transmitter Modulator With Low Abuse Potential in Development for Attention-Deficit/Hyperactivity Disorder (ADHD)

**Background**
- Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is an ion-pair salt of pyridoxal phosphate and pyrrolidone carboxylic acid. It has been used for more than 30 years to treat acute alcohol intoxication and chronic alcoholic liver disease in selected conditions.
- Metadoxine extended-release (XDR) is currently in clinical development for the treatment of attention-deficit/hyperactivity disorder (ADHD) and Fragile X syndrome (FXS).

**Methods**
- This Phase 2 clinical trial evaluated the safety, tolerability, and self-administration reinforcement effects of metadoxine in 82 adolescent patients with Fragile X syndrome (FXS). The trial was conducted in two phases: (1) a pharmacologically active dose determination phase and (2) a self-administration reinforcement effects phase.
- In the pharmacologically active dose determination phase, metadoxine (0.3, 1.0, 3.0, and 10 mg/kg/infusion, IV) was substituted for vehicle (1.0 mL/kg/infusion, IV) to determine the abuse liability of metadoxine.
- In the self-administration reinforcement effects phase, metadoxine (0.3, 1.0, 3.0, and 10 mg/kg/infusion, IV) was substituted for saline (1.0 mL/kg/infusion, IV) to assess the reinforcing effects of metadoxine.

**Results**
- Metadoxine did not induce any statistically significant effects on passive membrane properties, including resting membrane potential, conductance, and input resistance in the striatal medium spiny neurons.
- Metadoxine did not exhibit any statistically significant changes in DA and 5-HT release in the striatum.
- Metadoxine did not induce any statistically significant changes in the electrophysiology data.
- Statistical analysis showed no significant differences between metadoxine and control groups.

**Conclusions**
- Overall, these findings suggest a novel, monoamine-independent mechanism of action of metadoxine with a low abuse potential as a potential procognitive agent.
- These findings support the development of metadoxine as a potential treatment for ADHD and FXS, highlighting its potential for use in patients with comorbid conditions.

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**References**

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