

Abuse Liability Assessment of Atomoxetine in a Drug-abusing Population

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ABSTRACT

Atomoxetine is a nonamphetamine approved to treat attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. Abuse of methylphenidate and other amphetamines used to treat ADHD is common and is a recognized public health problem. This study examines the liability of atomoxetine to produce subjective effects that lead to abuse.

Following consent and screening, 46 experienced, stimulant-preferring drug abusers on an inpatient unit were randomized and received double-blind, single doses of 8 treatments using a balanced Latin square design. Treatments were placebo, 90 mg methylphenidate, 60 mg phentermine, 100 and 200 mg desipramine, and 45, 90, and 180 mg atomoxetine. Forty subjects received all 8 doses. The Drug Rating Questionnaire-Subject (DRQS), and subscales of the Addiction Research Center Inventory (ARCI) were collected for 24 hours after each dose. Six-hour areas under the curve (AUC) were compared using analysis of variance (ANOVA) with Dunnett's correction.

Methylphenidate and phentermine produced amphetamine-like effects and euphoria, with significant scores on the DRQS liking scale, the Morphine-Benzidine Group Scale (euphoria), and the Amphetamine and Benzedrine Group Scales (amphetamine-like effects). In contrast, no dose of desipramine or atomoxetine produced amphetamine-like subjective effects or euphoria as evidenced by lack of effect on these same scales.

Atomoxetine is not a euphoriant and does not produce amphetamine-like subjective effects. Therefore, atomoxetine has significantly less abuse liability than methylphenidate (Schedule II, US Controlled Substances Act) or phentermine (Schedule IV, US Controlled Substances Act), and no greater abuse liability than desipramine or placebo. Overall, atomoxetine is judged to be a psychotropic, not liable to abuse like that of methylphenidate and other amphetamines.

INTRODUCTION

- Atomoxetine is a nonamphetamine approved to treat attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults.
- Abuse of methylphenidate and other amphetamines used to treat ADHD is common and is a recognized public health problem.
- This study examines the liability of atomoxetine to produce subjective effects that lead to abuse.

METHODS

- Validated procedures for assessing amphetamine-like drugs for abuse potential
- Cross-over study
- 46 subjects total, 40 subjects completed
 - 8 females
 - 32 males

- 8 treatments at 48-hour intervals
- 18 days on residential unit

Inclusion Criteria

- Males and females
- 21-55 years old
- Currently abusing stimulants
- Extensive metabolizers

Exclusion Criteria

- Physically dependent on benzodiazepines, opiates, or alcohol
- Presence or history of any medically diagnosed, clinically significant psychiatric disorder (including mental retardation)
- Has significant prior or current medical conditions
- Unsuitable in any way, in the opinion of the investigator

Study Design

- 5 double-blind, balanced Latin squares with 8 treatment groups
- Treatments
 - Placebo (PLA)
 - Methylphenidate 90 mg (M90)
 - Phentermine 60 mg (PH60)
 - Desipramine 100 and 200 mg (D100, D200)
 - Atomoxetine 45, 90, and 180 mg (A45, A90, A180)

Controls

- Negative control – placebo
- Positive control – methylphenidate as Schedule II amphetamine
- Positive control – phentermine as Schedule IV amphetamine
- Negative control and comparator drug – desipramine

Measures

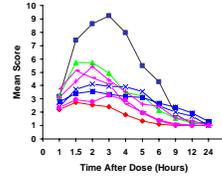
- Euphoria for reinforcing effects
 - Liking Scale and Morphine Benzidine Group
- Amphetamine-like subjective effects
 - Amphetamine and Benzedrine Group scales
- Relative Reinforcing value
 - Treatment Enjoyment Assessment Questionnaire
 - Street Value Assessment

Statistical Methods

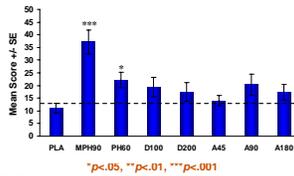
- 6-hour areas under the curve (AUC). Note that the time courses for all drugs were similar.
- 6-hour maximum scores are not presented, but yielded similar results.
- Treatments compared with placebo using analysis of variance (ANOVA) with Dunnett's correction.

RESULTS

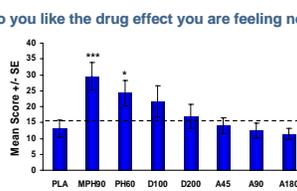
Time Course of Psycho-activity Do you feel a drug effect now?



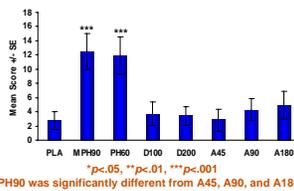
Do you feel a drug effect now?



Euphoria Measures: Reinforcing Effects Do you like the drug effect you are feeling now?



Morphine-Benzidine Group Scale

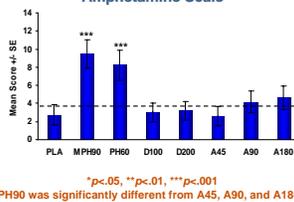


Euphoria Scales

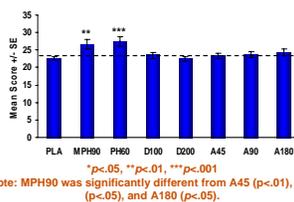
- Methylphenidate and phentermine produce euphoria.
- Atomoxetine and desipramine do not produce euphoria.

Amphetamine-like Subjective Effects

Amphetamine Scale



Benzedrine Group Scale

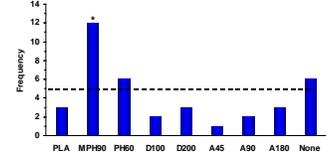


Amphetamine-like Subjective Effects

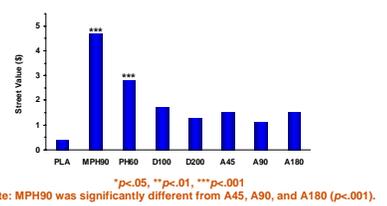
- Methylphenidate and phentermine produce amphetamine-like subjective effects.
- Desipramine and atomoxetine do not produce amphetamine-like subjective effects.

Relative Reinforcing Value

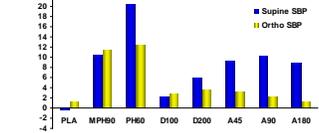
TEAQ: Which of the 8 treatments would you enjoy taking again?



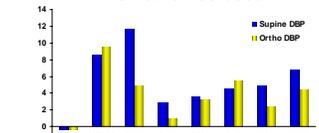
Street Value Assessment



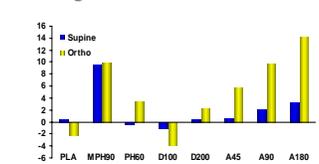
Change in Systolic Blood Pressure (SBP) 1.5 hours Postdose



Change in Diastolic Blood Pressure (DBP) 1.5 hours Postdose



Change in Pulse 1.5 hours Postdose



Blood Pressure and Pulse

- Measured ½ hour before drug administration and 1 ½ hours after drug administration
- Supine after 2 minutes standing
- Effect determined as difference from baseline
- Methylphenidate, phentermine, desipramine, and atomoxetine increase blood pressure and pulse
- Probably related to noradrenergic activity

CONCLUSIONS

- Atomoxetine does not have amphetamine-like properties.
- Atomoxetine has significantly less abuse liability than either methylphenidate (Schedule II) or phentermine (Schedule IV).
- Atomoxetine has no greater abuse liability than desipramine.

REFERENCES

- Griffiths RR, Bigelow GE, & Aton NA. Principles of initial experimental drug abuse liability assessment in humans. *Drug and Alcohol Dependence* 2003, 70: S41-54.
- Klein-Schwartz, W, McGrath J. Poison centers' experience with methylphenidate abuse in pre-teens and adolescents. *Journal of the American Academy Child and Adolescent Psychiatry* 2003, 42:288-294.