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Pharmacokinetics and pharmacodynamics of immediate release vs. extended release guanfacine in adult daily smokers

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Abstract

Background: Guanfacine is FDA-approved for hypertension and ADHD and has been used off-label for migraine prophylaxis, heroin withdrawal, and more recently, smoking cessation. Prior studies have shown positive effects of 3mg/day immediate-release (IR) guanfacine on smoking outcomes but the dose equivalency of the IR and extended-release (ER) formulations is unknown.

Procedures: A within-subject design was used to compare the pharmacokinetics and pharmacodynamics of 3mg/day IR, 4mg/day ER, and 6mg/day ER guanfacine in adult daily smokers (n=5). Plasma medication levels, vital signs, cigarettes per day, tobacco craving, and adverse events were assessed. Medication was titrated to stable dosing after each laboratory day (3mg/day IR, then 4mg/day ER, then 6mg/day ER).

Results: Plasma medication levels did not differ between the 3mg/day IR and 4mg/day ER doses following 24 hours from last dose, and were highest at the 6mg/day ER dose (3mg/day IR: M=3.40 ng/ml, SE=0.34 vs. 4mg/day ER: M=3.46 ng/ml, SE=0.67 vs. 6mg/day ER: M=5.92 ng/ml, SE=1.02). All doses of guanfacine decreased heart rate and blood pressure from baseline. Absolute values of cigarettes per day (6mg/day ER) and tobacco craving (4 and 6mg/day ER) were lowest with the ER formulations. Treatment-emergent adverse events were subject-rated as minimal to mild, except dry mouth.

Conclusions: We demonstrated similar pharmacokinetic profiles between 3mg/day IR guanfacine and 4mg/day ER guanfacine, as hypothesized. All doses of guanfacine were well-tolerated.

Keywords

guanfacine; pharmacokinetics; extended-release; smoking; pharmacodynamics

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Compliance with Ethical Standards: This study was approved by the Yale Human Investigations Committee. Informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

Introduction

Guanfacine, a selective alpha2a-adrenergic agonist, is approved by the Food and Drug Administration (FDA) for the treatment of hypertension [1]. Within the last decade, guanfacine extended-release (ER) tablets were approved as a monotherapy and as an adjunctive therapy to stimulant medications for attention deficit hyperactivity disorder (ADHD) in children and adolescents [2]. Off-label, guanfacine has commonly been used for Gilles de la Tourette's syndrome, migraine prophylaxis, heroin withdrawal, and opioid withdrawal. More recently, guanfacine has been used off-label for smoking cessation. In a well-validated human laboratory model of smoking-lapse behavior, guanfacine increased the time to initiate smoking and decreased smoking self-administration and tobacco craving in adult daily smokers compared to placebo [3]. In a subsequent brief 4-week treatment period, guanfacine reduced smoking and improved treatment retention, with a trend towards increased days abstinent [3]. In previous studies [3], guanfacine was administered at 3mg/day (2 times/day [bid]; immediate-release [IR]) only. However, the dose equivalency of the ER formulation is unknown. Use of ER guanfacine would extend the opportunity to dose once per day and may be of benefit to future studies in smokers if there are pharmacokinetic similarities between the IR and ER formulations.

In healthy adults and in children and adolescents with ADHD, single-dose ER guanfacine (up to 4mg tablets) demonstrates linear pharmacokinetic properties [4,5].However, the prescribing guidelines for ER guanfacine for ADHD indicate that the IR and ER guanfacine formulations are not equivalent regarding pharmacokinetics [2]. The ER formulation has reduced C_{max}, delayed T_{max}, and lower bioavailability compared to the same dose of IR guanfacine [2]. Peak concentration of ER guanfacine is reached within 5 hours following dosing, whereas peak concentration of the IR formulation is reached within 1–4 hours following dosing [1,2]. For ADHD, dosing guidelines recommend 1 to 4mg/day ER guanfacine, with doses ranging up to 7mg/day based on weight. The pharmacokinetics and pharmacodynamics of IR vs. ER guanfacine have yet to be compared in smokers. In vitro studies demonstrate that ER guanfacine is primarily metabolized by the CYP3A4 isoenzyme and does not inhibit the activity of the major cytochrome P450 isoenzymes [2]. Whether smoking affects CYP3A4 is not well-understood, but findings suggest that smoking does not alter CYP3A4 [6]. The primary aim of this small, open-label pharmacokinetic study was to evaluate the pharmacokinetics of IR guanfacine (3mg/day) vs. ER guanfacine (4 and 6mg/day) in adult daily smokers. We also aimed to assess the safety and tolerability of IR and ER guanfacine, and to evaluate indications of IR and ER guanfacine for smoking cessation. We hypothesized that 4mg/day ER guanfacine would demonstrate comparable plasma medication levels compared to 3mg/day IR guanfacine, and that 6mg/day ER guanfacine would demonstrate higher plasma medication levels overall. Based on prior findings [3], we also hypothesized that IR and ER guanfacine would reduce self-reported cigarettes per day and tobacco craving. We hypothesized that guanfacine would be well-tolerated across doses.

Materials and Methods

Participants.

Eligible participants were 18–65 years of age, smoked ≥ 10 cigarettes/day for the past year, and were normotensive (sitting BP > 90/60 and < 160/100 mmHg). Participants were excluded if they met criteria for current (past 6-months) Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR Axis I psychiatric disorders (excluding nicotine dependence), if they met criteria for current (past 6-months) DSM-IV-TR ADHD, were using illicit drugs (assessed by urine toxicology), had any significant current medical conditions or used concurrent medication that would contraindicate guanfacine or smoking, and were currently taking medications known to be effective for smoking cessation. Women who were pregnant or nursing were also excluded. This study was approved by the Yale Human Investigations Committee and is in accordance with the Declaration of Helsinki. Participants were recruited from the community for a smoking laboratory study. All participants provided written informed consent after procedures and possible side effects were explained to them. Seven individuals were screened for the study. Two participants did not show to the first laboratory session. A total of 5 participants completed the study.

Procedures.

A within-subject design was used to compare the pharmacokinetics and pharmacodynamics of 3mg/day IR guanfacine, 4mg/day ER guanfacine, and 6mg/day ER guanfacine. Guanfacine was titrated up to 3mg/day (1.5mg bid) IR over 16 days. Participants received a constant dose of 3mg/day for an additional 6 days (see Table 1 for complete dosing schedule). Assessments for 3mg/day IR were evaluated on Day 22 (Laboratory 1). On Days 23–27, guanfacine was titrated up to 4mg/day ER (qd). Participants received a constant dose of 4mg/day ER for an additional 5 days. Assessments for 4mg/day ER were evaluated on Day 32 (Laboratory 2). On Days 33–36, guanfacine was titrated up to 6mg/day ER (qd). Participants received a constant dose of 6mg/day ER for an additional 5 days. Assessments for 6mg/day ER were evaluated on Day 41 (Laboratory 3). On laboratory days (Days 22, 32, and 41), medication was administered at +15 minutes after the start of the laboratory session for all doses and again at +6 hours for the 3mg/day IR dose only (administered at 1.5mg IR for each timepoint). Standardized meals were provided on each of the three laboratory days to control for time since last food and amount of food consumed. Medication was tapered over a 5-day period following completion of the third laboratory session. Medication compliance assessments were conducted and are described below.

Smoke breaks.

Participants were given smoking breaks every 3 hours during each laboratory session (Days 22, 32, and 41) and had an opportunity to smoke up to 2 cigarettes per break. Breaks were scheduled at 11am, 2pm, 5pm, and 8pm. At the 2pm smoke break, tobacco craving was assessed (pre-smoking; after 3 hours of deprivation).

Plasma medication levels.

Five milliliters of blood were collected every hour over a 10-hour period during each laboratory session and again at +24 hours following the beginning of each laboratory session. Plasma medication levels (ng/ml) were measured using tandem liquid chromatography – mass spectrometry (LC-MS/MS). Guanfacine standards (1–20 ng/ml) were prepared in plasma and determined with r^2 values of > 0.99. All study samples were determined with intra- and inter-assay coefficients of variance (CV). For intra-assay, guanfacine was determined in low (3.57 ng/ml) and high (13.0 ng/ml) quality assessment samples with CVs of 5.2% and 3.8%, respectively. For inter-assay, guanfacine was determined in low (3.57 ng/ml) and high (13.0 ng/ml) quality assessment samples with CVs of 3.4% and 10.2%, respectively.

Assessments.

A pulse sensor was attached to participants' forefinger to obtain a measure of pulse rate throughout each laboratory session. Systolic and diastolic blood pressure were measured using a Critikon Dynamap throughout each laboratory session. Self-reported cigarettes per day were collected at baseline, on both days prior to each laboratory session, and on each laboratory session day. A self-report assessment of tobacco craving (Questionnaire of Smoking Urges [QSU]-brief, Factor 1 [smoking for positive reinforcement] [7]) was collected immediately prior to smoking during each laboratory session. As we have done in prior human laboratory studies [3,8–10], medication compliance was assessed by pill counts and a riboflavin marker [11].

Adverse events.

Adverse events were assessed twice weekly during each titration period and once during each of the three laboratory sessions (SAFTEE) [12]. Participants were queried regarding common adverse events associated with guanfacine (e.g., dry mouth, dizziness, fatigue).

Statistical analyses.

Repeated measures analysis of variance (ANOVA) was used to compare within-subject effects of plasma medication levels (+24 hours following the beginning of each laboratory session), vital signs (at steady-state medication levels [2pm on each laboratory session day], cigarettes per day (3-day average using the 2 days prior to each laboratory session day and each laboratory session day), and tobacco craving by medication dose.

Results

Baseline characteristics.

Two females and 3 males completed the study (n=5 participants). On average, participants were 45.80 (SD=2.49; range 42–48) years of age and smoked 17 cigarettes per day (SD=5.70) at study intake.

Plasma medication levels.

Figure 1 presents plasma medication levels of guanfacine collected over a 10-hour period during each laboratory day and again at +24 hours following the beginning of each laboratory session (Days 22, 32, and 41). Plasma trough medication levels were comparable between the 3mg/day IR and 4mg/day ER doses, and were highest at the 6mg/day ER dose (3mg/day IR: M=3.40, SE=0.34 vs. 4mg/day ER: M=3.46, SE=0.67 vs. 6mg/day ER: M=5.92, SE=1.02 at the +24-hour timepoint; $F(1,4)=7.94$, $p=0.048$, Cohen's d=2.82).

Vital signs.

Heart rate ($F(1,4)=31.00$, $p=0.005$, Cohen's d=5.57), systolic blood pressure ($F(1,4)=24.38$, $p=0.008$, Cohen's d=4.94), and diastolic blood pressure ($F(1,4)=34.17$, $p=0.004$, Cohen's d=5.85) decreased from baseline (i.e., before medication administration), with comparable decreases across doses at steady-state (at the 2pm timepoint on each laboratory day; see Figure 2).

Cigarettes per day & tobacco craving.

Self-reported cigarettes per day did not differ between baseline (i.e., before medication administration) and across doses at steady-state ($F(1,4)=4.56$, $p=0.10$, Cohen's d=2.14; see Figure 3). Tobacco craving did not differ across doses at steady-state ($F(1,4)=0.31$, $p=0.74$, Cohen's d=0.56; see Figure 4). Absolute values of cigarettes per day (6mg/day ER) and tobacco craving (4 and 6mg/day ER) were lowest with the ER formulations.

Adverse events.

All treatment-emergent subject-rated adverse events were rated as minimal to mild, except dry mouth (dry mouth was rated as moderate by 1 participant at the 6mg/day ER dose). No subject discontinued treatment or required a dose adjustment due to adverse events (see Table 2). Chi-square comparisons across medication conditions revealed no significant differences in rates of reported adverse events (all ps > 0.05).

Discussion

To our knowledge, this is the first investigation to evaluate the pharmacokinetics and pharmacodynamics of 3mg/day IR guanfacine vs. 4mg/day and 6mg/day ER guanfacine in adult daily smokers. The prescribing guidelines for ADHD indicate that the IR and ER formulations have different pharmacokinetic characteristics [2]. We demonstrated that plasma trough medication levels were comparable between 3mg/day IR guanfacine and 4mg/day ER guanfacine. As expected, plasma trough medication levels were highest at 6mg/day ER guanfacine, with plasma concentrations increasing approximately 75% from the IR formulation. All doses of guanfacine reduced vital signs (e.g., heart rate, blood pressure) to a similar degree, consistent with its clinical indication. We did not demonstrate a significant effect of IR or ER guanfacine on self-reported cigarettes per day or tobacco craving; however, there was some evidence suggesting a dose-related decrease for both outcomes. This contrasts with a human laboratory study that found decreases in smoking self-administration at the 3mg/day IR dose [3]. The discrepancy is likely due to our small sample

size; though, the effect size for self-reported cigarettes per day in the present study was large (Cohen's d=2.14).

Guanfacine was safe and well-tolerated across IR and ER doses. Mean participant-rated severity ratings for treatment-emergent adverse events were reported as minimal to mild, except for dry mouth. Dry mouth was reported as moderate by one subject at the 6mg/day ER dose. Rates of adverse events were greatest for dry mouth, drowsiness, fatigue, dizziness, and constipation, with up to 4 out of 5 participants reporting symptoms. No subject discontinued medication or required a dose adjustment because of adverse events.

This study is not without limitations. Although our sample size was well-suited to examine pharmacokinetics and pharmacodynamics of different doses and formulations of guanfacine, we were likely underpowered to detect differences in smoking outcomes. Thus, sample size is a limitation of the study. Second, our dose effects could be confounded by the length of time on treatment. However, this study allowed us to confirm the pharmacokinetics and pharmacodynamics of guanfacine across IR and ER formulations. Based on findings that 3mg/day IR guanfacine is efficacious in reducing smoking-related outcomes in a human laboratory study of smoking-lapse behavior [3] and the comparable pharmacokinetic profiles across doses in our sample of adult daily smokers, future work should examine the potential therapeutic benefit of the 4 and 6mg/day ER guanfacine formulations for smoking cessation.

Acknowledgments

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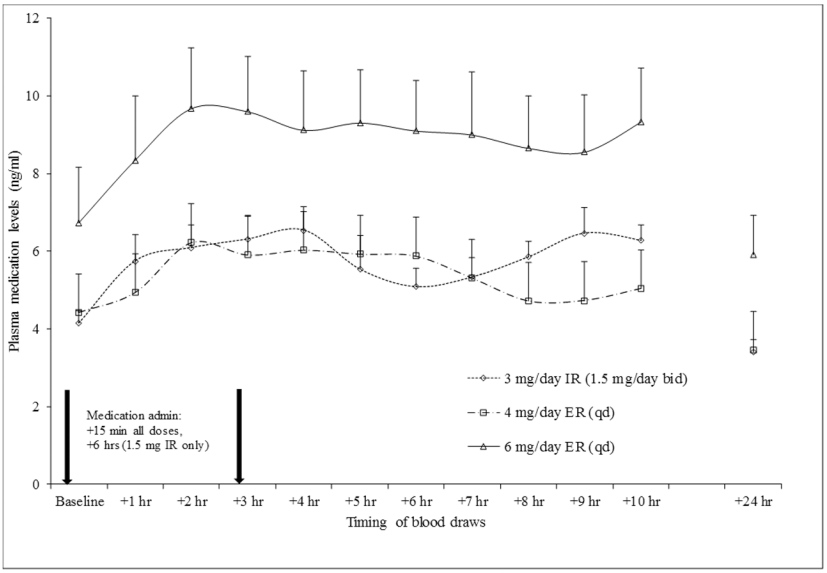

Figure 1.

Plasma medication levels of guanfacine collected over a 10-hour period during each laboratory day and again at +24 hours following the beginning of each laboratory session (Days 22, 32, and 41). Arrows indicate medication administration.

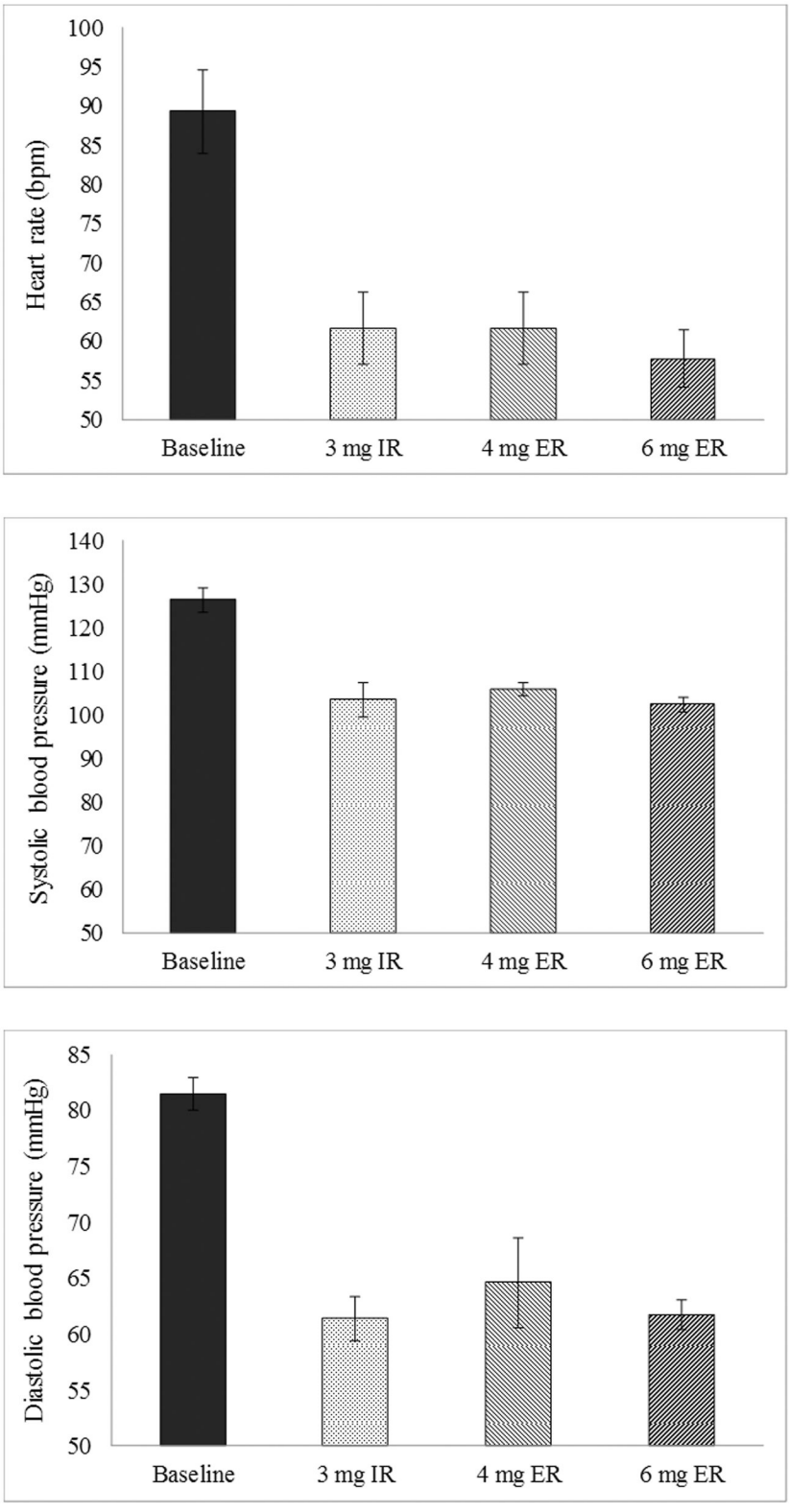

Figure 2.

(a) Mean (±SE) heart rate, (b) mean (±SE) systolic blood pressure, and (c) mean (±SE) diastolic blood pressure at baseline (i.e., before medication administration) and at steady-state medication levels (2pm on laboratory days [Days 22, 32, and 41]).

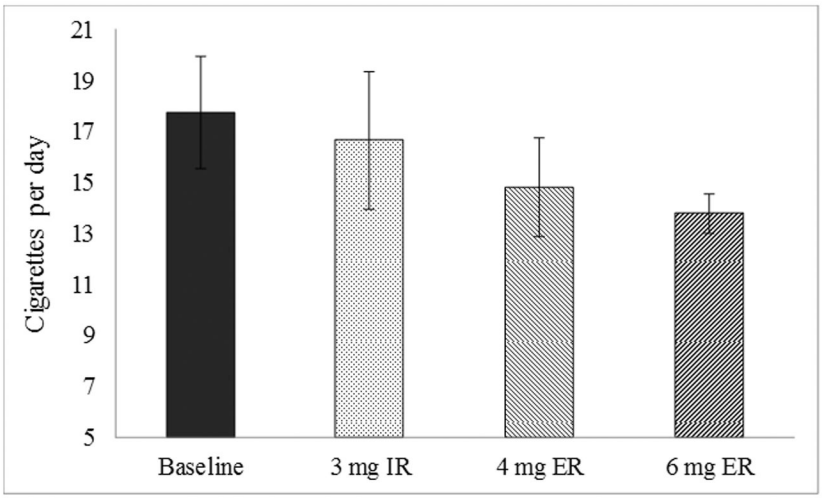

Figure 3.

Mean (±SE) self-reported cigarettes per day at baseline (i.e., before medication administration) and at steady-state medication levels (2pm on laboratory days [Days 22, 32, and 41]).

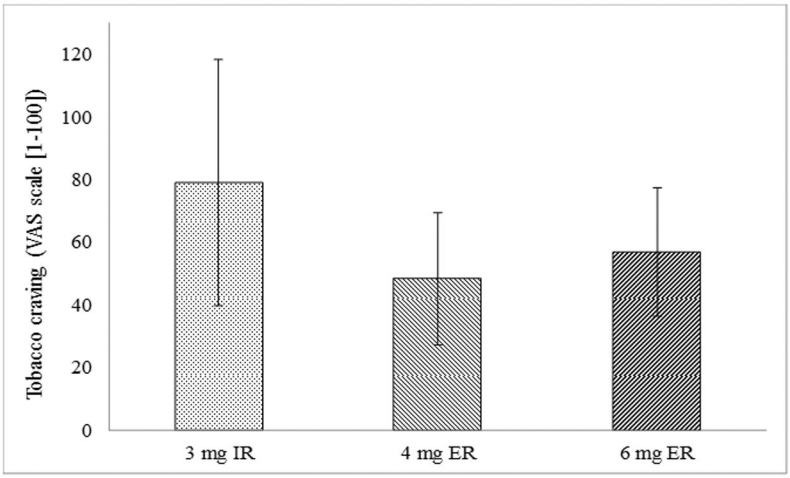

Figure 4.

Mean (±SE) tobacco craving at steady-state medication levels prior to smoking after 3 hours of nicotine deprivation (2pm on laboratory days [Days 22, 32, and 41]).

Table 1.

Dosing schedule for within-subject dosing of 3 mg/day IR guanfacine, 4 mg/day ER guanfacine, and 6 mg/day ER guanfacine.

Day	3 mg/day IR
1-3	8:00 AM: 0 mg IR
	8:00 PM: 0.5 mg IR
4-7	8:00 AM: 0.5 mg IR
	8:00 PM: 1.0 mg IR
8-12	8:00 AM: 1.0 mg IR
	8:00 PM: 1.0 mg IR
13-15	8:00 AM: 1.0 mg IR
	8:00 PM: 1.5 mg IR
16-21	8:00 AM: 1.5 mg IR
	8:00 PM: 1.5 mg IR
22 (Lab 1)	9:00 AM: 1.5 mg IR
	3:00 PM: 1.5 mg IR
	4 mg/day ER
23-26	8:00 PM: 3 mg ER
27-30	8:00 PM: 4 mg ER
31	3:00 PM: 4 mg ER
32 (Lab 2)	12:00 PM: 4 mg ER
	6 mg/day ER
33-35	8:00 PM: 5 mg ER
36-40	8:00 PM: 6 mg ER
41 (Lab 3)	12:00 PM: 6 mg ER
	Taper
42	8:00 PM: 5 mg ER
43	8:00 PM: 4 mg ER
44	8:00 PM: 3 mg ER
45	8:00 PM: 2 mg ER
46	8:00 PM: 1 mg ER

Table 2.

Frequency counts of treatment-emergent adverse events commonly associated with guanfacine (≥5% and at least twice placebo rate [1,2]). *Note*: Participants were prompted with a list of common and rare adverse events associated with guanfacine. All subject-rated events were rated as minimal to mild on a 4-point scale (1=minimal, 2=mild, 3=moderate, 4=severe), except dry mouth (1 subject rated dry mouth as moderate at the 6 mg/day ER dose). Chi-square comparisons across medication conditions revealed no significant differences in rates of reported adverse events (all *p*s > 0.05).

Symptom [n (%)]	3 mg/day IR	4 mg/day ER	6 mg/day ER
Dry mouth	2 (40%)	4 (80%)	4 (80%)
Drowsiness	3 (60%)	3 (60%)	3 (60%)
Dizziness	2 (40%)	2 (40%)	2 (40%)
Constipation	2 (40%)	2 (40%)	2 (40%)
Fatigue	3 (60%)	3 (60%)	3 (60%)
Headache	2 (40%)	1 (20%)	0 (0%)
Insomnia	0 (0%)	1 (20%)	0 (0%)
Weakness	1 (20%)	0 (0%)	2 (40%)
Nausea or vomiting	0 (0%)	0 (0%)	0 (0%)
Impotence	2 (40%)	0 (0%)	1 (20%)
Abdominal pain	1 (20%)	0 (0%)	0 (0%)