Brief Report

Gabapentin for smoking cessation

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Abstract

Introduction: We conducted a preliminary proof-of-concept study evaluating gabapentin for the treatment of tobacco dependence.

Methods: Subjects ($N = 80$) were randomized to gabapentin (600 mg three times per day or 900 mg three times per day) or placebo. After a 2-week dose titration, the target dose was maintained for 9 weeks and then tapered over 1 week. Follow-up was for 12 weeks after the medication phase.

Results: The study had high dropout rates with more than one half of participants in each arm discontinuing study. Gabapentin-treated participants exhibited lower abstinence rates than placebo-treated participants; however, this difference was not significant. Smoking reduction was observed across all treatment arms compared with baseline ($p < .01$) but did not differ across treatment groups.

Discussion: Although not definitive, our findings suggest that gabapentin administered at these doses with this dosing regimen holds little promise for the treatment of tobacco dependence in a population of smokers seeking treatment.

Introduction

Smoking is the leading preventable cause of morbidity and mortality in the United States, and smoking-related illnesses cost \$96 billion annually (Centers for Disease Control and Prevention [CDC], 2008b). In 2007, the adult smoking prevalence was 19.8% (CDC, 2008a). Currently available drugs for smoking cessation have limited long-term efficacy. Exploration of novel pharmacotherapies is needed to increase options for smokers, enhance long-term efficacy, and address the needs of smokers with comorbidities (e.g., seizure disorder, bulimia, anorexia nervosa) preventing the use of existing treatments (e.g., bupropion SR; Hays & Ebbert, 2003).

Gabapentin is an antiepileptic drug (Gilron et al., 2005; McLean & Gidal, 2003) that binds to the $\alpha_2\text{-}\delta$ subunit of voltage-dependent calcium channels (Gee et al., 1996) and inhibits neuronal glutamate release (Coderre, Kumar, Lefebvre, & Yu,

2005). Gabapentin activates presynaptic γ -aminobutyric acid type B (GABA_B) heteroreceptors (Parker, Ong, Marino, & Kerr, 2004) and elevates the concentration of GABA in the brain (Petroff, Hyder, Rothman, & Mattson, 2000). Activation of GABA_B receptors and inhibition of glutamatergic transmission have separately been observed to decrease nicotine self-administration in rodents (Markou, Paterson, & Semenova, 2004).

Gabapentin attenuates nicotine withdrawal symptoms and may increase short-term nicotine abstinence (Myrick, Malcolm, Henderson, & McCormick, 2001). In a randomized open-label pilot study including 36 subjects, bupropion SR was associated with higher abstinence rates than gabapentin when given for 6 weeks (prolonged abstinence 26.3% vs. 5.9%, $p = .1821$; White, Crockford, el-Guebaly, & Patten, 2005). We recently conducted a pilot study of gabapentin for smoking cessation (Sood et al., 2007). We initiated gabapentin at 300 mg twice daily gradually increasing the dose over 2 weeks to 600 mg three times daily. This dose was maintained for 5 weeks and then tapered over 1 week. After 8 weeks of treatment, the prolonged smoking abstinence rate among participants treated with gabapentin was 24% (95% CI = 13%–38%). Participants reporting smoking at the 6-month follow-up demonstrated a significant reduction in the number of cigarettes smoked per day compared with baseline (-10.0 ± 8.2 , $p < .001$).

In order to further explore gabapentin for smoking cessation, we conducted a proof-of-concept pilot study.

Methods

Subjects

The Mayo Clinic Institutional Review Board approved this study. Study procedures for the current study were identical to our previous pilot study (Sood et al., 2007). The present study consisted of a phone prescreen interview, two screen visits, nine clinic visits during treatment phase, and two posttreatment visits (one phone visit and one clinic visit).

Study treatment

All study participants were randomized to one of three study arms. One group received 1,800 mg of gabapentin per day; one

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received 2,700 mg of gabapentin per day; and one received matching placebo. Gabapentin was initiated at a dose of 300 mg by mouth in the morning and night. The dose was increased over the first 2 weeks to the target doses of 600 and 900 mg three times a day. This dose was continued for the next 9 weeks and tapered in the last week to minimize the risk of possible medication withdrawal-related seizures (Barrueto, Green, Howland, Hoffman, & Nelson, 2002; Pfizer, 2009). The medication was stopped at the end of 12 weeks. Identical-appearing placebo tablets were used and dispensed according to unique subject identification by assistants who had no subject contact. All participants received the same number of pills at corresponding times during the study.

Behavioral intervention

Participants received a 10-min behavioral intervention at each study visit guided by the Mayo Clinic "Smoke Free and Living It" manual. Target quit date was Day 15 of treatment.

Assessments

The Contemplation Ladder was used to evaluate participant readiness to make a quit attempt (Biener & Abrams, 1991). The Fagerström Test for Nicotine Dependence (FTND) was used to assess nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

Daily diaries were used to track study drug administration and tobacco use. Self-reported tobacco use status was recorded at each study visit during the medication phase and verified by expired-air carbon monoxide (CO) measurements.

Abstinence outcome definitions

The primary endpoint was 7-day point-prevalence smoking abstinence at the end of 12 weeks of treatment. The secondary endpoint was 7-day point-prevalence tobacco abstinence at 6 months.

Point prevalence tobacco abstinence was adjudicated if the following conditions were met: (a) self-reported tobacco abstinence for the previous 7 days with a negative response to the question "Have you used any type of tobacco, even a puff, in the past 7 days?" and (b) CO $\leq$ 8 ppm (Hughes et al., 2003).

Statistical analysis

Data were compared between treatment groups using analysis of variance for continuous variables and Fisher's exact test for binary outcomes. Pair-wise comparisons of each active gabapentin group versus placebo were performed as appropriate. For the primary outcome, a one-tailed p value $<.05$ was considered statistically significant. For all other comparisons, two-tailed p values are reported.

Results

The original intent was to enroll a total of 120 subjects in this double-blind Phase II trial. However, due to an unexpectedly high study dropout rate, a review of the primary endpoint was performed after 80 subjects were enrolled. Based on that review, the decision was made to discontinue further enrollment.

Baseline characteristics

Subjects were similar at baseline as depicted in Table 1.

Abstinence and smoking reduction outcomes

Abstinence outcomes are presented in Table 2. Although the active treatment groups had lower abstinence rates than the control group, no significant differences in the biochemically confirmed abstinence rates were observed between groups at Week 12 (end-of-medication) or Week 24. Assuming baseline smoking rates for subjects who discontinued study participation, the average number of cigarettes smoked per day at Week 12 was significantly lower compared with baseline ($p < .001$) for all treatment groups (-4.8 ± 7.8 cigarettes per day [cpd] for placebo; -7.7 ± 10.7 cpd for 1,800 mg/day; and -4.6 ± 6.7 cpd for 2,700 mg/day). Smoking reduction rates for 1,800 and 2,700 mg/day groups did not differ significantly from placebo ($p = .23$ and $p = .93$, respectively).

Study dropout rates

Over one half of the participants in each study arm discontinued the study prior to Week 12. Of these, 34 withdrew consent, 7 were lost to follow-up, 2 reported scheduling difficulties, and 1 subject (assigned to 2,700 mg/day) discontinued because of an adverse effect (diarrhea). Dropout rates did not differ significantly by treatment group ($p = .91$). Of the 44 participants discontinuing during the medication phase, 6 (1, 1, and 4 receiving placebo; 1,800; and 2,700 mg/day, respectively) did not attend any study visits after starting medication. Among the remaining participants, there were 4 (2, 2, 0), 7 (4, 2, 1), 6 (2, 3, 1), 8 (2, 5, 1), 5 (1, 0, 4), 3 (1, 0, 2), 4 (2, 0, 2), and 1 (0, 1, 0) whose last attended visit was after 1, 2, 3, 4, 5, 6, 8, and 10 weeks of medication, respectively. Of those who discontinued during the medication phase, 91% (40/44) reported smoking at the last study visit they attended (15/15 vs. 12/14 vs. 13/15 for placebo; 1,800; and 2,700 mg/day, respectively; Fisher's exact test $p = .44$).

Adverse effects

Adverse events considered possibly, probably, or definitely related to study drug did not differ significantly across groups. The specific adverse events and number of subjects reporting these events in each dose group (placebo; 1,800; and 2,700 mg/day) included dizziness (1, 4, 4), decreased concentration (0, 3, 0), edema (1, 2, 0), sleep disturbance (3, 0, 0), ataxia (0, 1, 1), dry mouth (0, 2, 0), fatigue (0, 2, 0), headache (1, 1, 0), nausea (1, 1, 0), rash (0, 1, 1), hand tremors (0, 0, 1), increased energy (0, 1, 0), and polyuria (0, 0, 1).

Adequacy of blinding and perceived efficacy

Of the 36 subjects who completed the medication phase, 34 completed an exit survey. The percentage of subjects who correctly guessed their treatment assignment on this survey was similar across groups (5/11 for placebo; 6/12 for 1,800 mg/day; and 7/11 for 2,700 mg/day; $p = .91$). The mean perceived helpfulness of medication did not differ significantly across groups (4.3 ± 2.8 vs. 4.2 ± 3.4 vs. 2.8 ± 2.1 for placebo; 1,800; and 2,700 mg/day, respectively; $p = .41$).

Discussion

No meaningful differences in smoking abstinence outcomes between treatment groups were detected. Compared with baseline, all treatment groups significantly reduced the number of

Table 1. Baseline characteristics of patients enrolled in a study of gabapentin for smoking cessation

Characteristic	Placebo, <i>N</i> = 27	1,800 mg/day; <i>N</i> = 27	2,700 mg/day; <i>N</i> = 26
Age			
Mean $\pm$ SD	41.0 $\pm$ 11.1	41.1 $\pm$ 9.5	40.7 $\pm$ 13.5
Median (range)	39 (21–61)	40 (25–65)	40 (21–64)
Gender, <i>n</i> (%)			
Male	16 (59)	16 (59)	18 (69)
Female	11 (41)	11 (41)	8 (31)
Race, <i>n</i> (%)			
White, non-Hispanic	26 (96)	27 (100)	25 (96)
Other ^a	1 (4)	0 (0)	1 (4)
Marital status, <i>n</i> (%)			
Never married	7 (26)	8 (30)	10 (38)
Separated/divorced	6 (22)	12 (44)	6 (23)
Married/living as married	14 (52)	7 (26)	10 (38)
Level of education, <i>n</i> (%)			
High school graduate or less	13 (48)	8 (30)	10 (38)
Some college or technical school	11 (41)	15 (56)	6 (23)
4-year college degree or more	3 (11)	4 (15)	10 (38)
Cigarettes per day			
Mean $\pm$ SD	20.0 $\pm$ 6.6	23.7 $\pm$ 6.9	20.9 $\pm$ 7.9
Median (range)	20 (10–35)	20 (12–40)	20 (10–45)
Number of years smoked			
Mean $\pm$ SD	21.7 $\pm$ 11.2	20.0 $\pm$ 9.5	21.0 $\pm$ 12.7
Median (range)	20 (5–44)	18 (2–45)	20 (3–50)
FTND			
Mean $\pm$ SD	5.8 $\pm$ 1.8	6.2 $\pm$ 2.1	5.2 $\pm$ 2.1
Median (range)	6 (2–10)	6 (2–10)	6 (0–9)
Contemplation Ladder			
Mean $\pm$ SD	9.0 $\pm$ 1.1	8.7 $\pm$ 1.4	9.2 $\pm$ 1.2
Median (range)	9 (7–10)	9 (6–10)	10 (6–10)
Previous stop attempts, <i>n</i> (%)			
None	5 (19)	3 (11)	6 (23)
1–2	6 (22)	10 (37)	7 (27)
3–5	11 (41)	8 (30)	8 (31)
6 or more	5 (19)	6 (22)	5 (19)
Other tobacco users in the household, <i>n</i> (%)			
No	19 (70)	15 (56)	16 (62)
Yes	8 (30)	12 (44)	10 (38)

Note. ^aThese include American Indian/Alaska native (*n* = 1) and White Hispanic (*n* = 1). FTND = Fagerström Test for Nicotine Dependence.

cigarettes smoked per day, but smoking reduction did not differ between treatment groups. Participant dropout rates were notably high with more than one half of subjects in each study arm discontinuing prior to the end of the medication phase.

Our ability to interpret the negative study findings is compromised by the high dropout rate. Two possible reasons for the high dropout rate are difficulty with the three times daily dosing regimen and lack of efficacy. In support of the former hypothesis, five participants (14% of those who completed exit surveys) noted that they had difficulty adhering to the three times daily dosing regimen. The more likely explanation for high dropout in the present study is lack of treatment efficacy. In support of this hypothesis, perceived drug efficacy did not differ by treatment assignment and neither did dropout rates. In the literature, dropout rates in placebo arms of randomized controlled clinical trials are consistently reported to be higher than those

observed in active treatment arms when the treatment is efficacious, suggesting that lack of efficacy plays a role in influencing dropout (Gonzales et al., 2006; Jorenby et al., 2006; Jorenby et al., 1999; Oncken et al., 2006).

In a pilot study of gabapentin for smoking cessation, 35% (*N* = 6) of subjects receiving gabapentin failed to complete the 6-week study and 12% (*N* = 2) dropped out due to adverse events (White et al., 2005). In another pilot study of cigarette smokers (*N* = 50) receiving gabapentin for 8 weeks, 22% (*N* = 11) of subjects dropped out prior to the end of the medication phase (Sood et al., 2007). Dropout rates in both of these studies were lower than in the current study; however, both studies were open-label and had a shorter duration of therapy.

The finding that a difference in dropout was not observed between the active and control arms of this study is consistent

Table 2. Abstinence outcomes among patients enrolled in a study of gabapentin for smoking cessation^a

Week/group	N	Discontinued study No. (%)	Reported smoking No. (%)	Failed biochemical confirmation No. (%)	Biochemically confirmed abstinent No. (%)	p value ^b
Week 12						
Placebo	27	15 (56)	7 (26)	0 (0)	5 (19)	
1,800 mg/day	27	14 (52)	9 (33)	0 (0)	4 (15)	0.77
2,700 mg/day	26	15 (58)	11 (42)	0 (0)	0 (0)	1.00
Week 24						
Placebo	27	15 (56)	8 (30)	0 (0)	4 (15)	
1,800 mg/day	27	15 (56)	9 (33)	1 (4)	2 (7)	0.90
2,700 mg/day	26	15 (58)	9 (35)	1 (4)	1 (4)	0.97

Note. ^a7-day point prevalence.

^bOne-tailed Fisher's exact test comparing the biochemically confirmed abstinence rate for the given group versus placebo.

with the hypothesis that gabapentin is no more efficacious than placebo for smoking cessation. However, we cannot rule out the possibility that gabapentin may be deleterious to smoking cessation. Several drugs have been explored for the treatment of tobacco dependence based upon theoretical constructs. Methylphenidate has been proposed as a possible treatment option because of similar neurobiological effects as nicotine and early suggestive data (Robinson et al., 1995). However, methylphenidate was subsequently observed to enhance the abuse-related behavioral effects of nicotine in animal models (Wooters, Neugebauer, Rush, & Bardo, 2008), and human laboratory studies observed that methylphenidate increased tobacco smoking (Rush et al., 2005). One interpretation of this data is that methylphenidate attenuates the reinforcing effect of nicotine leading to increased nicotine intake to overcome decreased reinforcement. Given the design of the current trial, we could not evaluate this hypothesis.

The small sample size coupled with the high dropout rate in this study limits our ability to draw any definitive conclusions about gabapentin for the treatment of tobacco dependence. Our original intent was to enroll a total of 120 subjects, which was based on a hypothesized end-of-treatment abstinence rate of 15% for placebo and determined to provide statistical power (one-tailed, $\alpha = .05$) of 82% to detect an abstinence rate of 40% or greater for gabapentin compared with placebo. Due to the high dropout, a review of the primary endpoint was performed after 80 subjects were enrolled. For the hypothesized abstinence rates, this effective sample size provided statistical power of 90% for a one-tailed $\alpha = .20$ level test, which has been suggested to be appropriate for randomized Phase II studies assessing whether future studies of a given therapy are warranted (Rubinstein et al., 2005). Therefore, even though our study was stopped early and not definitive, our findings suggest that with the doses explored, the dosing regimen provided and in the smoking population studied, gabapentin has little clinical utility for the treatment of tobacco dependence.

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Declaration of Interests

None to declare.

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