A Randomized Trial of Nortriptyline for Smoking Cessation

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**Background:** Smoking cessation rates with current therapy are suboptimal. One class of drugs that may improve cessation is the tricyclics.

**Objective:** To add nortriptyline hydrochloride to a behavioral smoking cessation program to enhance cessation rates and reduce withdrawal symptoms.

**Subjects and Methods:** We conducted a randomized, double-blind, placebo-controlled trial at an affiliated Department of Veterans Affairs Medical Center and an Army Medical Center. Subjects were aged 18 through 70 years, smoked 10 or more cigarettes per day, and were without current major depression. Nortriptyline hydrochloride or matched placebo was started at 25 mg before bed 10 days prior to quit day and titrated to 75 mg/d or to the maximal tolerated dose. The behavioral intervention consisted of 2 group sessions and 12 individual follow-up visits. Withdrawal symptoms were measured using a daily diary, and smoking cessation was defined as self-reported abstinence, expired carbon monoxide of 9 ppm or less, and a 6-month urine cotinine level of less than 50 ng/mL.

**Results:** A total of 214 patients were randomized (108 to nortriptyline and 106 to placebo). There was a significant reduction in several withdrawal symptoms including anxious/tense, anger/irritability, difficulty concentrating, restlessness, and impatience by day 8 after quit day in the nortriptyline group. The cessation rate at 6 months was 15 (14%) of 108 and 3 (3%) of 106, respectively ($P = .003$; absolute difference, 11%; 95% confidence interval, −18% to −4%). Nortriptyline caused frequent adverse effects, including dry mouth (64%) and dysgeusia (20%).

**Conclusions:** We conclude that nortriptyline led to an increased short-term cessation rate compared with placebo. In addition, there were significant, but relatively small, reductions in withdrawal symptoms. Nortriptyline may represent a new therapeutic approach to smoking cessation.

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drawal symptoms by 1 week after quit day including irritability/anger, difficulty concentrating, restlessness, impatience, and insomnia, but not for craving, excess hunger, drowsiness, and increased eating (Table 2).

The validated cessation rate over the follow-up period was higher in the nortriptyline group at every time point. The nortriptyline group had a 6-month sustained abstinence rate higher than the placebo group (absolute difference, 11%; 95% confidence interval, 4%-18%) (Figure 3).

There was no significant effect on the quit rate for history of depression, baseline pack-years smoked, sex, age, Fagerstrom score, or Beck Depression Inventory scores. Adverse effects were significantly higher in the nortriptyline group compared with the placebo group (Table 3). Nortriptyline therapy was discontinued due to adverse events in 10 of 108 subjects (4 with constipation and indigestion, 1 with rash, 1 with trouble uri-
bedtime, either nortriptyline hydrochloride (25 mg) or placebo, 10 days before quit day, then increased to 2 capsules per day (30 mg of nortriptyline hydrochloride) after 3 days, and finally after 3 more days increased to 3 capsules per day (75 mg of nortriptyline hydrochloride), if tolerated. They continued receiving the maximal tolerated dose for 8 weeks after their quit date.

All visits while subjects were receiving study drugs were individual sessions with the study nurse who reviewed problems quitting and helped develop strategies for abstinence from smoking. The study drug was dispensed in weekly increments and the returned pills were collected at each visit to reduce the possibility of overdose and to monitor compliance. If adverse effects developed, the dosage was reduced as necessary.

Blood samples were drawn 1 week after quit day, when subjects had been taking the maximal dose of study drug for at least 11 days. An unblinded research pharmacist recommended dosage reductions for those above the therapeutic range (≥150 ng/mL) and dosage increases for those who were subtherapeutic (<50 ng/mL). To maintain binding, dose reductions and increases on an equal number of randomly selected placebo-treated subjects were also recommended. The dosage of study drug was tapered to 50 mg/d beginning 8 weeks after quit day (day 56). All subjects stopped receiving study drug by week 10 (day 70).

Expired carbon monoxide was determined using a Bedfont expired carbon monoxide analyzer (Bedfont Technical Instruments Ltd, Sittingbourne, Kent, England). Urine cotinine levels were measured using a radioimmunoassay with gas chromatographic/mass spectroscopic confirmation by the Toxicology Laboratory, Colorado Department of Health, Denver.

Subjects completed a daily diary of the number of cigarettes smoked for the first week after quit day and selected nicotine withdrawal symptoms rated on a 0- to 5-point scale, with 5 representing severe symptoms. We used the Beck Depression Inventory to identify depressive symptoms at baseline, 1 week after cessation, and at the end of nortriptyline therapy.

STATISTICAL ANALYSIS

The primary outcome was sustained smoking abstinence, defined as self-reported cessation within 1 week of the quit day, expired carbon monoxide of 9 ppm or less at each visit, and verified by urine cotinine level of less than 50 ng/mL at the final visit (6 months). The sample size for the study (100 per group) was estimated based on assumptions of an 80% power, α of .05, and a 10% absolute difference in the 6-month validated quit rates between the groups. Data were analyzed using SPSSPC software (SPSS Inc, Chicago, III) and Stat-Exact 3 (Cytel Software Corporation, Cambridge, Mass). We compared the groups for continuous variables using t tests and Mann-Whitney U tests, as appropriate, and for categorical variables using χ² tests. We used the Bonferroni adjustment for the analysis of the 8 daily withdrawal symptom scores, leading to critical value for statistical significance of P<.006. We compared the 6-month cessation rates in the 2 groups using Fisher exact tests based on an intention-to-treat analysis.

This study demonstrates that the addition of nortriptyline to a smoking cessation program results in improved smoking cessation rates. These results are similar to the preliminary data presented by Humfleet et al, who found a short-term cessation rate of 50% with nortriptyline at 12 weeks compared with 35% with placebo. We also observed an improvement in withdrawal symptoms and an increase in anticholinergic adverse ef-

Table 2. Tobacco Withdrawal Symptoms*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Nortriptyline Hydrochloride, Day 8</th>
<th>Placebo, Day 8</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craving</td>
<td>2.1 (1.6)</td>
<td>2.8 (1.6)</td>
<td>.009</td>
</tr>
<tr>
<td>Irritable/angry</td>
<td>1.2 (1.3)</td>
<td>1.8 (1.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Anxious/tense</td>
<td>1.2 (1.4)</td>
<td>2.1 (1.7)</td>
<td>.003</td>
</tr>
<tr>
<td>Concentration</td>
<td>0.8 (1.1)</td>
<td>1.5 (1.4)</td>
<td>.001</td>
</tr>
<tr>
<td>Restless</td>
<td>1.0 (1.3)</td>
<td>1.9 (1.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Impatient</td>
<td>1.0 (1.3)</td>
<td>1.9 (1.6)</td>
<td>.001</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.6 (1.1)</td>
<td>1.1 (1.4)</td>
<td>.002</td>
</tr>
<tr>
<td>Increased eating</td>
<td>1.5 (1.4)</td>
<td>1.4 (1.5)</td>
<td>.66</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0.8 (1.1)</td>
<td>1.1 (1.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Headaches</td>
<td>0.4 (0.9)</td>
<td>0.8 (1.3)</td>
<td>.01</td>
</tr>
<tr>
<td>Excess hunger</td>
<td>1.4 (1.4)</td>
<td>1.5 (1.6)</td>
<td>.66</td>
</tr>
</tbody>
</table>

*Values are mean (SD).
†P value comparing the nortriptyline and placebo groups at day 8, Mann-Whitney U test.

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It is also possible that antidepressants suppress the symptoms of nicotine withdrawal with central noradrenergic receptor systems. Nortriptyline affects a number of neurotransmitter systems, predominantly acting to block reuptake of norepinephrine with a lesser effect on serotonin.\textsuperscript{23,24} Other drugs that are effective in smoking cessation, including bupropion and clonidine, also have effects on the central noradrenergic systems.\textsuperscript{27}

The cessation effect of nortriptyline may be due to anticholinergic actions,\textsuperscript{25} especially the dry mouth and taste changes. Subjects in this study frequently reported that cigarettes “did not taste good” when they were receiving the study drug, reminiscent of the frequent complaint of patients with hepatitis. Rose\textsuperscript{29} and Westman et al\textsuperscript{26} have demonstrated the importance of upper airway sensory stimulation in smoking and cessation. Most likely, the beneficial effects of nortriptyline use are due to a combination of these, and perhaps other mechanisms, with different mechanisms being more or less important in different individuals.

There are several limitations that must be kept in mind when interpreting the results of this study. First, we required subjects to be smoking 10 cigarettes per day at the time of study entry, and many were trying to quit and had already reduced the number of cigarettes smoked before their formal quit date. If they were already past the peak of their withdrawal symptoms, the apparent benefits of nortriptyline use would have been minimized. Second, our blinding was only partially effective. Because of the high frequency of dry mouth, the nurse and subjects were often able to identify the active drug. Third, the relatively small sample size limits our analysis of the effect of potential predictors of cessation such as sex, prior depression, level of nicotine dependence, and number of prior quit attempts. Since we enrolled fewer subjects with symptoms of depression than anticipated, we cannot determine whether nortriptyline would be more effective in depressed smokers.

We have demonstrated the efficacy of nortriptyline in smoking cessation; however, the ideal dosage and duration of treatment remain to be determined. The optimal effect of nortriptyline use may also require a longer precessation period of drug therapy. The relapse in the nortriptyline group after the drug was discontinued suggests that a longer duration of treatment may be more effective. The role of nortriptyline compared with or in combination with other agents is not yet known. Nortriptyline may prove to be most useful in those smokers who have failed standard smoking cessation therapy.

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REFERENCES


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