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Adjunctive varenicline treatment for smoking reduction in patients with schizophrenia: A randomized double-blind placebo-controlled trial

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ABSTRACT

Objectives: Smoking is more common among patients with schizophrenia than it is in the general population. Varenicline, a partial and full agonist at the α4β2 and α7 nicotine acetylcholine receptors, respectively, has been shown to be an effective anti-smoking treatment. This study examined the effects of varenicline treatment on smoking reduction in patients with schizophrenia.
Methods: Sixty smokers with schizophrenia were recruited and randomized to receive either varenicline or placebo. Smoking behavior was assessed with the Minnesota Nicotine Withdrawal Scale (mNWS), Brief Questionnaire of Smoking Urge (QSU-brief), and Modified Cigarette Evaluation Questionnaire (mCEQ). Exhaled carbon monoxide was also measured to assess smoking dependency and status. Data were analyzed with the two-tailed Student's *t*-test, χ^2 test, and repeated measures ANOVA.
Results: During the 8-week study, there was a significant time × group interaction, which showed that smoking decreased over time in the varenicline group. Expired CO levels also decreased in the varenicline group, showing a significant time effect, group effect, and time × group interaction. Total mCEQ scores decreased in the varenicline group, demonstrating a significant time × group interaction. Among the five domains of the mCEQ, the smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensation domains showed significant time × group interactions in the varenicline group. The QSU-brief and mNWS demonstrated a significant time effect, but not significant time × group interactions. Adjunctive varenicline treatment with antipsychotics was generally well-tolerated and safe.
Conclusions: Varenicline showed significant efficacy in reducing smoking in people with schizophrenia.

1. Introduction

Smoking is more common in patients with schizophrenia than in the general population and in patients with other severe mental illnesses. Their estimated smoking prevalence is 60–90% (odds ratio, 5.3) (de Leon and Diaz, 2005). A 13-year follow-up study showed that fatal tobacco-associated diseases occurred significantly more often in them than in the general population. Life expectancy was 20% lower, and smoking was identified as one of the most important risk factors (Ruther et al., 2014).

Smoking is perhaps the most significant and challenging modifiable lifestyle factor among people with schizophrenia. Media campaigns and tobacco price increases appear less effective at curbing smoking among people with mental illness (Stubbs et al., 2015). While it is not clear why patients with schizophrenia are more vulnerable to smoking, smoking may reduce symptoms and adverse effects of antipsychotic medications (Goff et al., 1992) and/or enhance cognitive performance (Adler et al., 1998; Kumari and Postma, 2005; Kumari et al., 2001). Kelly et al. (2012) showed that people with schizophrenia reported greater stimulation/state enhancement and social facilitation from smoking, showed less appreciation of smoking-associated health risks, and were less motivated to quit smoking than were healthy individuals.

The US Department of Health and Human Services's current clinical practice guidelines list the following drugs, in combination with counseling, as first-line treatments for smoking cessation: short- or long-acting nicotine replacement therapy, sustained-release bupropion, and varenicline (Fiore et al., 2008). Despite robust data on their safety

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and efficacy, few studies have examined their use in mentally ill patients (Ruther et al., 2014). Stubbs et al. (2015) performed a systematic clinical review showing that varenicline may help achieve smoking cessation in people with schizophrenia, but longer-term randomized controlled trials are required. Additionally, trials should carefully consider patients' psychiatric symptoms, particularly in those at risk of self-harm and suicide. In addition to adverse psychiatric effects, some studies have reported adverse cardiovascular effects, although a Cochrane review reported that their incidence related to varenicline was inconclusive (Ruther et al., 2014).

It is critical to identify reliable predictors of positive responses to varenicline in smokers with schizophrenia to optimize treatment risk-to-benefit ratios. Dutra et al. (2012) estimated negative symptoms as predictors of a response to varenicline. Symptoms of affective flattening were proposed as reliable behavioral markers. DRD4 variation was proposed as an informative biological predictor of subjective responses to nicotine (Harrell et al., 2015). There is an increasing interest in determining behavioral and biological markers that predict responses to smoking-focused therapies.

This study examined the effects of varenicline used concomitantly with antipsychotic medications on smoking cessation in patients with schizophrenia. We used various scales to determine which smoking behaviors might benefit from varenicline treatment.

2. Methods

2.1. Subjects

This study used a secondary analysis of data from our previous randomized, double-blind, parallel-group, placebo-controlled, 8-week trial examining the effects of varenicline on smoking behavior (Shim et al., 2012). Sixty clinically stable, smoking outpatients with schizophrenia were recruited from over 2 years. This study included patients diagnosed with schizophrenia based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (APA, 1994) who satisfied the following: 1) aged 18–60 years, 2) less than moderate severity (Positive and Negative Syndrome Scale (PANSS) total score ≤ 75; (Leucht et al., 2005)) for the previous 3 months; and 3) no changes in medications for the past 3 months. Exclusion criteria were: 1) any serious or unstable medical disorder within the preceding 6-month period, 2) substance abuse or dependence (other than nicotine) in the preceding 12 months, 3) high suicide risk, 4) pregnant or breastfeeding, or 5) currently using non-cigarette tobacco products or other forms of nicotine replacement therapy.

The smoking group was defined as those smoking > 10 cigarettes daily for ≥1 year with an expired carbon monoxide (CO) level ≥ 10 ppm. CO level was measured by the PiCO+ Smokerlyzer® (Bedfont Scientific Company).

Participants were assigned in a 1:1 ratio to receive varenicline or placebo. Varenicline was titrated up to 1 mg twice daily for weeks 2–8. Clinical, smoking, and safety assessments were administered at baseline and weeks 1, 2, 4, and 8. Participants received a self-help booklet for smoking cessation. Telephone visits were conducted every week. Participants could smoke freely for the entire period of study; smoking cessation was their choice.

We obtained signed written consent forms from all patients who agreed to participate, and the study was approved by our Institutional Review Board.

2.2. Demographic data

We used patient interviews and medical records to determine patients' sex, age, education level, illness duration, number of hospitalizations, smoking status, and medication type/dose. Antipsychotic medication dosages were converted into chlorpromazine-equivalent doses (Gardner et al., 2010; Rey et al., 1989).

2.3. Medications

Participants were receiving antipsychotic medication at the time of study inclusion. Antipsychotic and concomitant medication doses remained fixed throughout the study. Medication allocation was concealed from patients and research staff with identically appearing varenicline and sucrose placebo capsules. Doses of varenicline or matching placebo were titrated upward as follows: varenicline, 0.5 mg for days 1–3, 0.5 mg twice per day for days 4–7, and 1 mg twice daily for weeks 2–8. Lorazepam (1–4 mg/day) was permitted for anxiety and insomnia, but was not administered for 12 h before each visit. Anticholinergic medications were also permitted; however, doses were to remain fixed throughout the study.

2.4. Clinical assessments

Clinical symptoms were assessed with the PANSS (Kay et al., 1987), modified Scales for the Assessment for Negative Symptoms (SANS) (Andreasen, 1982), Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and Clinical Global Impression severity (CGI-S) (Guy, 1970) at baseline and weeks 1, 2, 4, and 8. Safety assessments, including the Simpson-Angus Rating Scale (Simpson and Angus, 1970), Barnes Akathisia Rating Scale (Barnes, 2003), and Side Effect Checklist (Kelly et al., 2009) were performed at baseline and weeks 1, 2, 4, and 8. To ensure inter-rater reliability, all raters successfully completed rater training before study participation, achieving an interclass correlation coefficient of >0.75.

2.5. Efficacy measures

Smoking assessment was administered at baseline and weeks 1, 2, 4, and 8. Numbers of cigarettes smoked daily and exhaled CO levels indicated smoking intensity. Items were summed and divided by total item numbers to yield a total average score.

2.5.1. The Minnesota Nicotine Withdrawal Scale (MNWS)

The Minnesota Nicotine Withdrawal Scale (MNWS) (Hughes and Hatsukami, 1986) is frequently used. With the exception of urge to smoke, items on the MNWS generally reflect symptoms listed for nicotine withdrawal syndrome in the DSM-IV (Cappelleri et al., 2005). The MNWS had acceptable reliability in a study investigating internal consistency and test-retest reliability between smokers with schizophrenia and control smokers (Weinberger et al., 2007). The MNWS version used here consists of nine items rated on a 5-point ordinal scale: 0, not at all; 1, slight; 2, moderate; 3, quite a bit; and 4, extreme.

2.5.2. The Brief Questionnaire of Smoking Urge (QSU-brief)

Nicotine craving is important in the relapse process. The 32-item Questionnaire on Smoking Urges (QSU) and its 10 items forming the QSU-brief have become widely used to assess craving (West and Ussher, 2010). The 10-item QSU-brief, used in this study, has good internal consistency and was identified as reliable for estimating smoking urges (Toll et al., 2006). Each statement is scored on a Likert scale from 1 (strongly disagree) to 7 (strongly agree), where higher scores indicate stronger smoking urges.

2.5.3. The Modified Cigarette Evaluation Questionnaire (mCEQ)

The Cigarette Evaluation Questionnaire (CEQ) contains 11 items covering both the reinforcing and aversive effects of smoking. The modified Cigarette Evaluation Questionnaire (mCEQ) has one extra item (on enjoying smoking) in addition to the 11 original items (Cappelleri et al., 2007). These items are rated on a 7-point scale ranging from 1 (not at all) to 7 (extremely). A previous study showed that the questionnaire is suitable for use in clinical and research settings (Cappelleri et al., 2007). The above scales have all been found to be valid and reliable

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