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ORIGINAL PAPER

A double-blind randomized clinical trial of different doses of transdermal nicotine patch for smoking reduction and cessation in long-term hospitalized schizophrenic patients

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Abstract There have been many studies of smoking cessation using nicotine replacement therapy (NRT) with schizophrenic patients, but none exploring the smoking-reduction effects of varying doses of NRT in long-stay patients with schizophrenia. This study aimed to examine the effect of different doses of the nicotine transdermal patch on smoking-reduction and cessation outcomes in long-term hospitalized schizophrenic patients. A total of 184 subjects participated in a randomized, controlled, double-blind 8-week clinical trial. Participants were randomized into two groups using two different doses of NRT: a high-dose NRT group (31.2 mg for the first 4 weeks, then 20.8 mg for 4 weeks, $n = 92$) or a low-dose NRT group (20.8 mg for 8 weeks, $n = 92$). The 7-day point prevalence of abstinence was 2.7 % (5/184). Participants in the low-dose NRT group reduced smoking by 3.1 more cigarettes on average than those in the high-dose group ($p = 0.005$). However, a repeated measures analysis of variance revealed that the main effect of changes in the number of cigarettes smoked, comparing the two types of treatment across periods, was not significant ($p = 0.35$, partial eta square $= 0.018$). In summary, among a cohort of chronic institutionalized schizophrenic patients, smoking cessation and reduction outcomes were not correlated with NRT dose, and the cessation rate was much lower than rates in similar studies. It indicates that long-term hospitalized schizophrenic patients have more difficulties with quitting smoking. More effective integrative smoking cessation programs should be addressed for these patients.

Keywords Schizophrenia · Nicotine replacement therapy · Smoking cessation · Smoking reduction · Long-term hospitalization

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Introduction

The smoking rate in patients with schizophrenia is higher than in the general public [9], ranging from 58 to 90 % [1–5]. Possible reasons for this high prevalence rate of nicotine addiction in schizophrenic patients include the decrease in negative symptoms with nicotine use [1, 2], the amelioration of cognitive deficits [6], the reduction in the risk of movement disorders, improved auditory gating impairments [7–9], and an increase in the release of dopamine in the nucleus accumbens and the prefrontal cortex [10–13].

For the treatment of schizophrenic patients, it is important to encourage them to quit smoking because of followings reasons: (1) tobacco consumption has well-known risks; (2) nicotine is a highly addictive substance, especially for patients with schizophrenia; (3) patients with psychiatric disorders often have more difficulties on

quitting smoking; (4) hospitals and institutions set a limit to smoking for reducing the exposure to second-hand smoke in nonsmokers [14, 15]. Several smoking cessation clinical trials have been conducted with schizophrenic patients. Nicotine replacement with behavioral group therapy was found to be effective in patients with schizophrenia [15–18]. In prior research, smoking cessation rates for schizophrenic patients at week 7–10 ranged from 42 to 26.9 %. Limitations of these clinical studies were, first, that they all focused on outpatients or those who were in day care centers. The smoking-reduction effects on long-term hospitalized patients have yet to be investigated. Second, there has been a lack of clinical trials comparing different doses of NRT in patients with schizophrenia. One study, the first part of a research series, enrolled healthy volunteers using 22 mg nicotine transdermal patches for 8 weeks and appeared to have a lower cessation rate in comparison with the second part of the study, which involved smokers using 44 mg nicotine patches for 4 weeks followed by 22 mg nicotine patches for 4 weeks (46.7 vs. 55 % at week 8) [19, 20]. A double-blind randomized controlled study in a general population ($n = 400$) revealed that subjects with high-dose NRT (a combination of a nicotine inhaler and patch) had significantly higher cessation rates than those on low-dose NRT (a nicotine inhaler alone), 60.5 vs. 47.5 % at week 6, respectively, and 42 vs. 31 % at week 12, respectively [21]. Accordingly, we were interested in conducting a study to test whether there is an association between NRT dose and smoking-reduction and cessation outcomes in long-term hospitalized schizophrenic patients.

Methods

Participants

A total of 264 patients were assessed at first. Forty-six patients declined to participate, 24 patients did not meet the criteria, and 10 patients were excluded due to other reasons. Finally, 184 subjects participated in a randomized, controlled, double-blind clinical trial from June 2005 to December 2006. Patients with schizophrenia or schizoaffective disorders were recruited from the chronic wards of two public psychiatric hospitals in Hualien County, Taiwan. All participants gave informed consent. These studies were approved by the institutional review board of these two hospitals. We recruited only those patients who met the diagnostic criteria for schizophrenia or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and were regular daily smokers at the time of recruitment. Patients were excluded if they had the following conditions: (1) acute exacerbation of psychosis that was in need of transfer to acute wards for treatment or (2) severe respiratory and heart disease (Fig. 1).

Procedure

We adopted the method of a study designed for smokers using high-dose NRT in which high-dose nicotine patches were administered for 4 weeks followed by low-dose patches for 4 weeks [19]. This study's intent was to use 44- and 22-mg transdermal nicotine patches as Fredrickson and his colleagues did. However, the same products were not available in Taiwan, so instead 31.2- and 20.8-mg transdermal nicotine patches were used for comparison. Participants were randomized into one of two types of medication groups: a high-dose NRT group (31.2 mg for the first 4 weeks, then 20.8 mg for week 5 to week 8, $n = 92$) and a low-dose NRT group (20.8 mg for 8 weeks, $n = 92$). Six sessions of smoking cessation psycho-education (each session lasting 20 min, two sessions per week) were provided after clinical trial initiation. In each session, about 25 participants were gathered to watch videotapes. Medical staff oriented participants to the material used in the sessions. Topics included an introduction to the physical harm caused by smoking, benefits of smoking cessation, therapeutic effects and possible side effects of NRT, coping skills needed in smoking cessation, and laws stipulating the prohibition of smoking. During the entire course of the program, we gave priority to smoking cessation over reduction and tried to persuade patients to stop smoking if they could. We also conveyed the message that if they felt it was too hard to stop smoking they could at least try to reduce the number of cigarettes smoked. There were no significant differences in the regulation of smoking behavior between the participants and other uninvolved patients (e.g., the time periods allowed for the patients to smoke or the purchase of cigarettes). Because of patient reluctance to take part in the smoking cessation program, we did not set a quit date as other studies did. Medical staff monitored and supervised adherence to NRT.

Measures

We collected data on demographic features (age, sex, and educational level), tobacco smoking factors (lifetime tobacco use, age of onset of smoking, and number of cigarettes smoked on average per day), clinical features regarding schizophrenia (age of onset, duration of current hospitalization, and number of hospitalizations), and treatment history (type of antipsychotics and antipsychotic dosage). We converted daily doses of antipsychotics to approximate daily mean chlorpromazine milligram equivalents [22]. Readiness to quit smoking was assessed based

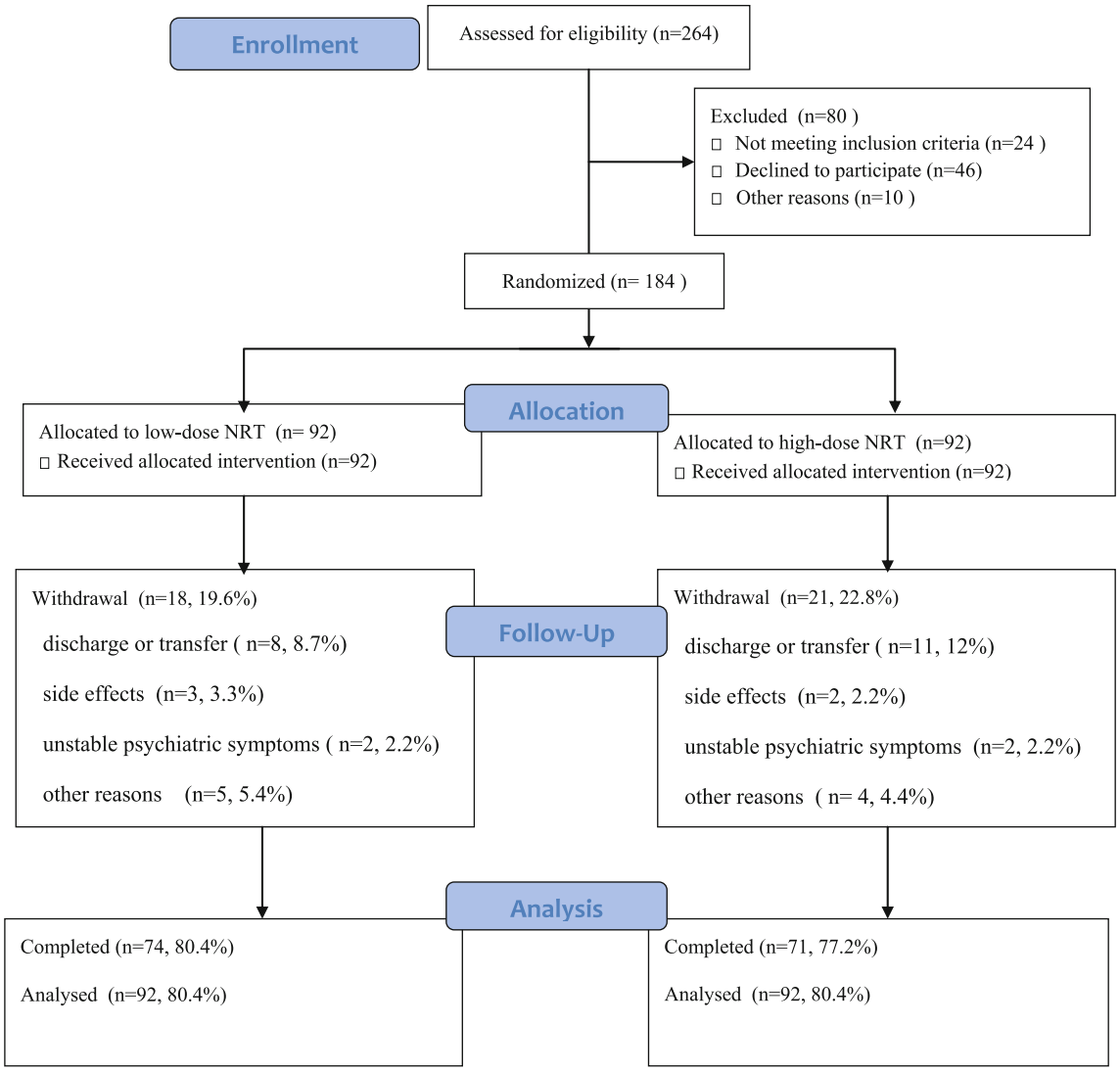

Fig. 1 Recruitment and attrition profiles

on the transtheoretical theory, which postulates three stages representing the level of readiness to quit, in ascending order: precontemplation, contemplation, and preparation [23]. A Chinese-language version of the Fagerstrom test for nicotine dependence (FTND) [24] that was found to have good reliability and validity against saliva cotinine levels was used [25]. The number of cigarettes was assessed at three points: before the trial, at the midpoint (week 5), and at the endpoint of the trial. Patients' clinical symptoms were rated using a Chinese-language version [26] of the PANSS [27], which includes scales on positive symptoms, negative symptoms, and general psychopathology. Neuroleptic-induced Parkinsonism was assessed using the Simpson-Angus Rating Scale (SARS) [28]. The end-tidal breath carbon monoxide (CO) level was measured by EC50 Micro III Smokerlyzer (Bedfont Scientific Ltd, Rochester, UK). FTND, PANSS, SARS, and CO were evaluated before and at the endpoint of the trial.

Outcomes

According to unpublished results of our pilot study on smoking cessation with NRT, a very low percentage of subjects achieved smoking cessation (1/50, 2 %); thus, we chose smoking reduction as the primary outcome and smoking cessation as the secondary outcome. At the 8-week endpoint, we examined smoking reduction, defined as the change in self-reported number of cigarettes smoked (post-trial number minus pre-trial number), or smoking cessation outcome (i.e., 7-day smoking abstinence, defined

as a self-reported 0 cigarettes smoked in the preceding 7 days plus an expired CO level of less than 10 ppm) [29].

Statistical analysis

Group comparisons were conducted before the clinical trial using the independent *t* test for continuous variables and the chi-squared test for categorical variables. At the endpoint, the change in cigarettes smoked, FTND, PANSS, SARS, and CO were compared using the independent *t* test. The 7-day point prevalence rate of abstinence was compared using a chi-squared test between groups. The intent-to-treat approach was adopted for the analysis. Those who withdrew from the study were treated as failing to achieve cessation. Their endpoint number of cigarettes smoked was coded to be the same as before the initiation of the trial. Clinical characteristics of those who withdrew from the trial and those who remained were compared. A repeated measures analysis of variance (ANOVA) was conducted to assess the impact of the two different interventions (high-dose NRT and low-dose NRT) on participants' number of cigarettes smoked per day at three time periods (pre-intervention, week 5, and endpoint). SPSS version 11.5 was used for statistical analysis. The value of the significance level was set at 0.05.

Results

Characteristics of subjects before treatment and discontinuation of participation in trials

Table 1 shows participant characteristics. The majority of subjects were male patients (171/184, 92.9 %). A total of 141 subjects (76.7 %) were diagnosed with schizophrenia. There were no baseline differences between the two groups regarding key demographic clinical variables. Thirty-nine subjects (21.2 %) had ceased participation in the trial by the end: 2 due to voluntary withdrawal from the trial without stating reasons; 5 due to side effects; 4 due to unstable psychiatric symptoms; 19 due to discharge or transfer to other wards; and 9 were lost to follow-up. Aside

Table 1 Characteristics of participants in the two different NRT groups before the clinical trial

Variables	Total participants ($n = 184$) Mean (SD)	Low-dose NRT ($n = 92$) Mean (SD)	High-dose NRT ($n = 92$) Mean (SD)
Sex, male, *n* (%)	171 (92.9)	85 (92.4)	86 (93.5)
Age (years)	45.2 (9.3)	45.4 (11.0)	46.6 (9.8)
Education (years)	9.7 (3.4)	9.3 (3.5)	10.1 (3.3)
Years of current hospitalization	8.8 (6.6)	8.6 (5.7)	9.0 (7.4)
Number of hospitalizations	4.4 (3.9)	4.5 (4.5)	4.3 (3.1)
Age of onset of psychosis (years)	25.3 (7.9)	24.3 (7.3)	26.3 (8.4)
Age of onset of smoking (years)	20.4 (9.5)	20.0 (8.4)	21.6 (8.3)
Years of smoking	21.6 (9.8)	20.7 (4.2)	22.5 (10.4)
Typical antipsychotics, *n* (%)	68.0 (38.2)	39.0 (43.3)	29.0 (33.0)
Schizophrenia, *n* (%)	141.0 (76.6)	69.0 (75.0)	72.0 (78.3)
Stage of change			
Preparation, *n* (%)	63.0 (36.2)	33.0 (37.9)	34.0 (39.1)
Contemplation, *n* (%)	44.0 (25.3)	22.0 (25.3)	22.0 (25.3)
Chlorpromazine equivalents (mg)	561.0 (434.2)	554.0 (359.0)	568.2 (502.9)
Daily cigarettes, number	13.1 (7.8)	13.6 (8.0)	12.6 (7.6)
FTND	5.3 (2.2)	5.2 (2.1)	5.3 (2.3)
Carbon monoxide	10.1 (8.9)	13.6 (8.0)	11.0 (9.8)
PANSS score	60.4 (15.0)	61.6 (16.0)	59.2 (13.8)
Positive subscale	12.0 (4.4)	12.3 (4.5)	11.7 (4.3)
Negative subscale	19.4 (7.7)	19.7 (8.0)	19.2 (7.4)
General subscale	29.2 (8.2)	28.4 (6.3)	28.4 (5.8)
Simpson-Angus rating scale score	0.33 (0.26)	0.31 (0.24)	0.34 (0.27)

There was no significant difference in these variables between the two groups using an independent *t* test or chi-squared test

Low-dose NRT: nicotine patches 20.8 mg for the 1–8th weeks

High-dose NRT: nicotine patches 31.2 mg for the 1–4th weeks, then 20.8 mg for the 5–8th weeks

NRT nicotine replacement therapy, *FTND* Fagerstrom test for nicotine dependence, *PANSS* positive and negative syndrome scale

from the participants who withdrew from the trial having a younger age of onset of smoking (18.4 vs. 22.4, $p = 0.003$), there were no significant differences in variables between these two groups.

Overall changes in smoking

The 7-day point prevalence of abstinence was 2.7 % (5/184): four in the low-dose group (4.3 %, 4/92) and one in the high-dose group (1.1 %, 1/92). There were no significant differences in abstinence between groups ($\chi^2 = 1.85$, $df = 1$, $p = 0.174$), and there were no significant differences in nicotine dependence, CO level, psychopathology and antipsychotics-induced extrapyramidal symptoms between groups. As Table 2 shows, participants in the low-dose NRT group reduced smoking by 3.1 more cigarettes on average than those in the high-dose group ($t = -2.8$, $df = 182$, $p = 0.005$). A repeated measures ANOVA revealed that there was a substantial main effect for time (Wilks' lambda = 0.29, $p = 0.001$, partial eta square = 0.27) with both groups showing a reduction in the number of cigarettes smoked at three time periods. The main effect of changes in the number of cigarettes smoked, comparing the two types of treatment, was not significant ($p = 0.35$, partial eta square = 0.018).

Discussion

We failed to draw meaningful inferences on abstinence because only a small number of patients ($n = 5$) stopped smoking. Regarding smoking reduction, subjects in the low-dose NRT group seemed to be able to reduce smoking more than those who were in the high-dose NRT group. However, despite the dosage difference of NRT in this trial, the finding has questionable clinical significance for treating patients with tobacco addiction, even with the magnitude of the changes in number of cigarettes smoked per day. First, the repeated measures ANOVA examined 2 × 2 factors (time × treatment), which suggested no differences in the reduced number of cigarettes across three time periods between groups with an extremely small effect size (partial eta square = 0.018). It indicates that the proportion of variance of smoking reduction explained by the treatment effect (high-dose NRT vs. low-dose NRT) is very low. Second, changes in the number of cigarettes smoked were not reflected in changes in FTND scores and CO levels before and after the trial.

Regarding the dose effect of NRT on smoking cessation, our findings were different from those of some studies in which high-dose NRT helped subjects without schizophrenia enhance smoking abstinence, compared with low-dose NRT [19–21, 30]. The current study demonstrated that there were no significant differences in smoking cessation and reduction between groups. Possible reasons are that patients with schizophrenia are strongly addicted to tobacco smoking, and cessation rates are apparently lower than those of the general population; therefore, the differences in smoking reduction accounted for by various doses of NRT might not be apparent. In addition, the difference in patch dose is smaller, and the high-dose NRT was tapered midway through the trial; both circumstances could have reduced the efficacy of the group in our study. We adopted the design where subjects in the intervention group were given high-dose nicotine patches followed by low-dose patches [19]. The original study arranged for 44 mg of NRT for 4 weeks followed by 22 mg of NRT for 4 weeks. However, the same product was unavailable in Taiwan, so we chose 31.2 mg as the high-dose treatment and 20.8 mg as the low-dose treatment. A lack of a significant difference in smoking reduction in patients receiving different treatments might in part be explained by a too-little difference of NRT dose between groups. Concerning cessation and 50 % smoking-reduction rates in schizophrenic patients receiving NRT, our rates were much lower compared with those in prior smoking cessation studies. For example, Baker and collaborators [31] arranged a program similar to the aforementioned guideline, with 8 weekly sessions of cognitive behavioral therapy and NRT doses (21 mg/day for week 3 to week 8, 14 mg/day week 9 to 10, and 7 mg/day for week 11 and 12) for psychotic patients. Comparing their data to ours, the point prevalence abstinence was 15 vs. 2.8 %, respectively, and the 50 % smoking-reduction rate at week 12 was 43 vs. 22.5 % (32/184) at week 8 in our study.

In comparison with other studies, the cessation rate of 2.8 % in our study was much lower. In a study for schizophrenic patients participating in 10 weeks of treatment with 21 mg/day of NRT and 10 weekly group therapy sessions, the cessation rate was 35 % [18]. Addington et al. [16] studied schizophrenic patients receiving 7 weekly sessions of group therapy and nicotine patches (21 mg/day for 6 weeks, then 14 mg/day and 7 mg/day for 2 weeks). The cessation rates were 42 % at week 8 and 16 % at week 12. A study for schizophrenic patients treated with NRT for 8 weeks (14 mg per day during weeks 1–6 and 7 mg per day during weeks 7–8) revealed that the point prevalence rate of abstinence was 26.9 % at week 8 [17]. A 10-week, double-blind, placebo-controlled trial of bupropion (300 mg/day) in combination with NRT (21 mg/24 h) for smokers with schizophrenia showed continuous smoking abstinence was 27.6 % (8/29) at weeks 6–10 [32]. A possible explanation for the relatively low cessation rate in our study is that subjects in prior studies were all in outpatient departments, communities, or day centers—our participants were all chronically institutionalized schizophrenic patients. They seemed to have a higher degree of general

Table 2 Comparison of smoking-reduction measures and psychopathological scores at baseline and at the endpoint between the two groups with either low-dose ($n = 92$) or high-dose ($n = 92$) nicotine replacement therapy

Variables	Baseline[§]/midpoint[$]		Endpoint		Change	
	Low dose Mean (SD)	High dose Mean (SD)	Low dose Mean (SD)	High dose Mean (SD)	Low dose Mean (SD)	High dose Mean (SD)
Daily number of cigarettes smoked	13.7 (8.0) 9.7 (5.7)[$]	12.7 (7.6) 11.0 (7.7)[$]	10.1 (7.7)	12.0 (9.2)	−3.2 (7.1)[ab] 0.04[c]	−0.15 (7.4)
Carbon monoxide level	9.2 (8.0)	11.0 (9.7)	9.2 (8.3)	9.2 (8.4)	−0.1 (6.4)	−0.6 (6.5)
Fagerstrom test for nicotine dependence	5.2 (2.1)	5.3 (2.3)	3.9 (2.3)	4.5 (2.5)	−1.2 (2.3)[a]	−0.6 (2.4)[a]
Positive and negative syndrome scale	61.6 (16.0)	59.2 (13.8)	59.2 (14.8)	57.9 (15.4)	−2.5 (11.0)	−2.5 (11.0)
Positive subscale	12.3 (4.5)	11.7 (4.3)	11.4 (3.8)	11.1 (3.7)	−0.8 (3.9)	−0.8 (3.2)[a]
Negative subscale	19.7 (8.0)	19.2 (7.4)	19.0 (7.5)	18.8 (7.7)	−0.3 (4.6)	−0.4 (4.9)
General subscale	30.1 (7.9)	28.4 (6.7)	28.8 (6.8)	28.1 (7.8)	−1.2 (5.6)[a]	−1.2 (5.9)
Simpson-Angus rating scale score	0.31 (0.24)	0.34 (0.26)	0.26 (0.22)	0.32 (0.37)	−0.02 (0.2)	−0.02 (0.3)

[a] $p < 0.05$ for the intra-group comparison (paired t test, two-tailed)

[b] $p < 0.05$ for the comparison between the high-dose group and low-dose group (independent t test, two-tailed)

[c] Effect size presented by partial eta square for the comparison between the high-dose group and low-dose group

[§] There was no significant difference in baseline variables between the two groups

[$] Number of cigarettes smoked per day at midpoint (week 5)

psychopathology and tended to smoke to relieve affective symptoms [33] and therefore had lower cessation rates. Second, compared with other studies in which subjects either expressed a strong desire to stop smoking [16] or had high motivation for quitting smoking [31], only one-third of our patients at the start were in the stage of preparation to quit smoking. This suggested that a relatively large proportion of our hospitalized chronic schizophrenic patients lacked incentive to stop smoking, which was also reflected in the fact that we had difficulties asking our participants to set a quit date, as some clinical trials have demanded their subjects do [18, 34]. Additionally, although our protocol supplied a simple psycho-education program for the participants, it was different from the cognitive behavioral therapy or group treatment of the other studies that focused deeply on the patient's psychological factors and behavioral changes [15, 17, 18, 34, 35]. This also sheds light on the importance of enhancing psychological factors to increase readiness to quit in patients with schizophrenia during smoking cessation programs.

The strength of this study is that it is the first to use a large sample size to explore the smoking-reduction effects of different doses of NRT in chronic institutionalized schizophrenic patients. Nonetheless, the collection of data for the study analysis did have some limitations. The first question is that of generalizability. The study population could not be representative of all schizophrenic patients. Our participants were all chronic schizophrenic patients whose mean length of current hospitalization was 8.7 years. Besides, very few female patients were recruited in this study. According to our informal survey, the prevalence rates of tobacco smoking among schizophrenic patients in these two hospitals were 66 % for male patients and 15 % for female patients. The low prevalence of smoking in female population was compatible with the fact that few female subjects participated in this study. It would be beneficial to replicate this study in different populations, for example, those who are female, live in the community, reside in rehabilitation centers, or participate in supportive occupational programs, rather than long-term hospitalized patients. Moreover, the observation period of this trial was only 8 weeks. Longer trial durations of 6 and 12 months are warranted to examine the feasibility of smoking reduction in these patients.

Conclusions

In summary, among a cohort of chronic institutionalized schizophrenic patients who took part in smoking cessation programs, smoking cessation and reduction outcomes were not correlated with NRT dose, and the cessation rate was much lower than those in similar studies. However, it would be wrong to conclude that it is useless to use high-dose NRT to achieve higher cessation rates in chronic hospitalized patients or that it is of no value to use NRT to treat similar patients with nicotine dependence. It may be the case that long-term hospitalized schizophrenic patients

are a unique population for whom smoking-reduction outcomes are much different from those who are in the communities. Low quit rates in this trial could indeed be due to lack of motivation in these patients, which could have been addressed in a psychosocial program before the trial in future studies. In addition to NRT and bupropion, using other medications for smoking cessation [36, 37] is worth trying in patients with schizophrenia. How to design further research and smoking cessation programs with corrections of the aforementioned protocol flaws and limitations and how to enhance patients' readiness to quit with cognitive behavioral therapy are important issues to consider. Much remains to be done. We hope that this work will allow further studies to develop more alternatives for smoking reduction and cessation in schizophrenic patients.

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Conflict of interest None.

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