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Cognitive and antismoking effects of varenicline in patients with schizophrenia or schizoaffective disorder☆

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ABSTRACT

Objective: Varenicline has been shown to be an effective anti-smoking treatment in smokers without identified psychiatric illness, and the drug's pharmacology suggests possibilities of pro-cognitive effects. However, recent reports suggest varenicline may have the potential for important psychiatric side-effects in some people. We present the first prospective quantitative data on the effects of varenicline on cognitive function, cigarette smoking, and psychopathology in a small sample of schizophrenic patients.
Method: Fourteen schizophrenic smokers were enrolled in an open-label study of varenicline with a pre-post design. Measures of cognitive function (RBANS, Virtual Water-Maze Task), cigarette smoking (cotinine levels, CO levels, self-reported smoking and smoking urges), and psychopathology (PANSS) were evaluated prior to and during treatment with varenicline. Data on psychopathology changes among schizophrenic smokers in another drug study, in which patients were not receiving varenicline, were used for comparison.
Results: 12 patients completed the study, and 2 patients terminated in the first two weeks of active varenicline because of complaints of nausea or shaking. Varenicline produced significant improvements in some cognitive test scores, primarily associated with verbal learning and memory, but not in scores on visual-spatial learning or memory, or attention. Varenicline significantly decreased all indices of smoking, but did not produce complete smoking abstinence in most patients. During treatment with varenicline there were no significant increases in psychopathology scores and no patient developed signs of clinical depression or suicidal ideation.
Conclusions: Our small prospective study suggests that treatment with varenicline appears to have some beneficial cognitive effects which need to be confirmed in larger studies with additional neuropsychological tests. Varenicline appears to have some anti-smoking efficacy in schizophrenia but longer studies are needed to determine whether it will produce rates of smoking abstinence similar to those found in control smokers. Treatment with varenicline may not increase psychopathology or depression in most patients with schizophrenia, but we cannot accurately estimate the absolute risk of a potentially rare side-effect from this small sample.

1. Introduction

Varenicline is a nicotinic partial agonist–antagonist which has shown to be efficacious in smoking cessation trials in normal smokers, with efficacy greater than bupropion (Gonzales et al., 2006; Oncken et al., 2006; Tonstad et al., 2006). Schizophrenics have among the highest rates of cigarette smoking of any group

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(Glassman, 1993; Lohr and Flynn, 1992), and biochemical and psychophysiological studies show that schizophrenics may have deficits related to the number or functioning of nicotinic receptors in their brain (Breese et al., 2000; Freedman et al., 1995). Furthermore, biochemical studies suggest that varenicline may be a full agonist at the α_7 nicotinic receptor (Mihakak et al., 2006), and this is the receptor which has been implicated in the nicotinic deficits in the brains of schizophrenic patients and the potential ameliorative effects of smoking and nicotine on psychophysiological cognitive function in this group of patients (Adler et al., 1993, 1998; Freedman et al., 1997). This provides a rationale for trials of varenicline for smoking cessation and cognitive enhancement in schizophrenia. However, there have been case reports, and an FDA advisory, about possible psychiatric side-effects of varenicline including depression, suicidal ideation or attempts, and activation of psychotic or manic symptoms (Freedman, 2007; Kohen and Kremen, 2007; Morstad and Kutscher, 2008; FDA, 2008). If these occurred at a substantial rate in schizophrenic patients, it could limit the drug's usefulness in this population. However, these safety concerns are not based on prospective trials with quantitative data. Because of is potential for cognition enhancement and the drug's anti-smoking effects in normal subjects, we are reporting preliminary data from a prospective study, of a small sample of patients with schizophrenia or schizoaffective disorder, which evaluated the effects of varenicline on cognition, cigarette smoking, psychopathology, depression, suicidal ideation, and other side-effects.

2. Method

2.1. Subjects

Subjects were male patients in a tertiary care psychiatric hospital or its associated outpatient clinic, with a diagnosis of schizophrenia or schizoaffective disorder, who had a long history of smoking cigarettes. (Although recruitment for the study was not limited to male patients, only male patients qualified and consented to the study in this initial sample). The hospital administration had a strong desire to reduce or eliminate cigarette smoking and encouraged the use of varenicline as well as other anti-smoking medications. Since varenicline was a new drug used in this institution we were asked to conduct an evaluation of its effects and enlisted the cooperation of physicians who were going to try to prescribe the drug for their patients to see if it would reduce or eliminate their cigarette smoking. We added additional biochemical and cognitive measures to this evaluation study. Inpatient subjects were patients who continually violated hospital non-smoking rules in spite of consequences such as losing off-ward privileges for each offense. Outpatient subjects were those who self-reported smoking at east 10 cigarettes a day on baseline screening. Patients verbally reported that they had smoked cigarettes for a long time, but we did not initially collect quantitative data on years or pack-years of smoking. We were later able to recontact some, but not all, of the participants and obtain self reported data on years of prior cigarette smoking. Subjects signed informed consent to participate in a protocol approved by the Nathan Kline Institute's IRB. Subjects agreed to the trial of an antismoking drug for their cigarette smoking habit although most did not have a strong personal desire to definitely stop smoking. Fourteen patients entered the study and 12 completed.

Table 1
Background characteristics, smoking behavior related variables, and psychopathology scores of patients in study.

Background characteristics					Number of cigarettes smoked/week (self- report)		CO level		Plasma cotinine level		PANSS total score		PANSS depression factor score	
Pt. no.	Inpatient or outpatient	Age	Ethnicity	AP, AD, and MS drug treatment	Pre-drug baseline	End of varenicline treatment	Pre-drug baseline	End of varenicline treatment	Pre-drug baseline	End of varenicline treatment	Pre-drug baseline	End of varenicline treatment	Pre-drug baseline	End of varenicline treatment
1	Inpatient	27	AA	Risperidone	4.00	1.75	3.17	1.25	97	49	60	44	5	5
2	Inpatient	34	AA	Fluphenazine, Quetiapine, Lithium	3.00	2.25	3.17	3.50	224	121	69	66	7	10
3	Inpatient	49	AA	Quetiapine, Risperidone, Lithium	1.67	2.50	1.83	1.38	55	0	51	72	6	8
4	Inpatient	49	AA	Quetiapine, Risperidone	4.33	3.00	11.33	5.50	304	187	40	42	6	3
5	Inpatient	34	AA	Risperidone, Lithium	0	0	7.33	2.25	143	0	73	61	7	3
7	Inpatient	37	Hispanic	Quetiapine, Clozapine, Lithium	3.67	4.50	9.33	6.13	422	360	39	45	6	11
8	Inpatient	30	AA	Clozapine	0.83	1.75	3.00	1.25	59	16	68	53	10	3
10	Outpatient	43	White	Risperidone, Quetiapine, Lithium	140	62.5	18.00	16.38	263	98	48	53	6	7
11	Outpatient	43	AA	Risperidone, Quetiapine, Lithium	19.00	8.00	18.00	3.50	441	92	73	64	6	6
12	Inpatient	28	AA	Aripiprazole	0.0	0.25	4.00	1.88	110	23	47	50	3	6
13	Outpatient	49	Hispanic	Clozapine, Fluphenazine	183.33	20.0	17.33	9.38	490	384	47	57	7	5
14	Outpatient	52	AA	Fluphenazine	77.67	43.75	11.17	5.83	255	227	65	60	9	5

Numbers represent either single value obtained a baseline (before starting varenicline) or at 8–9 weeks of varenicline treatment (Cotinine, PANSS), or mean value based on 3–4 weeks of baseline assessments or based on assessment during each of weeks 6–9 during treatment with varenicline (variables: cigarettes smoked, CO Level). AA = African American or non-Hispanic Black; AP = antipsychotic medication, AD = antidepressant medication, MS = mood stabilizer medication. All patients were male and had a chart diagnosis of schizophrenia ($N = 9$) or schizoaffective disorder ($N = 3$). Two patients terminated the study within a few weeks of starting varenicline because of nausea related side-effects.