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Letter to the Editors

Effects of galantamine on cognitive deficits in smokers and non-smokers with schizophrenia

Dear Editors,

Numerous studies have documented neurocognitive impairment in patients with schizophrenia (Green, 1996). Cigarette smoking is highly co-morbid with schizophrenia (Kalman et al., 2005). Studies of nicotine's effects on neurocognition in schizophrenia have suggested that it may ameliorate certain cognitive deficits associated with this illness (Depatie et al., 2002; George et al., 2002; Smith et al., 2006). We have found that cigarette smoking abstinence impairs and smoking reinstatement enhances spatial working memory and sustained attention and that such smoking-related cognitive enhancement may be mediated by central nicotinic acetylcholine receptors (nAChR) stimulation (Sacco et al., 2005).

Galantamine is a cholinesterase inhibitor which appears to be a potent allosteric modulator of central nAChRs (Coyle and Kershaw, 2001). It is >90% bioavailable within 1 h of acute administration (Farlow, 2003). Preliminary results from several clinical trials using GAL (up to 24 mg/day) of patients with schizophrenia suggest some degree of efficacy in targeting cognitive impairments (Schubert et al., 2006; Buchanan et al., 2007).

In this double-blind, placebo-controlled, mixed-factorial study, we examined the effects of acute doses of the galantamine (0, 4 and 8 mg) on neurocognitive measures in satiated and abstinent smokers and non-smokers with schizophrenia. We predicted that GAL would dose-dependently improve cognitive deficits, with the greatest effects in nonsmokers.

Patients were determined to have schizophrenia by SCID for DSM-IV interview and were screened for a deficit in visuospatial working memory (Sacco et al., 2005). Twenty-one patients were enrolled. Each patient underwent a pre-study (training) neuropsychological battery, followed by testing on three separate testing days, preceded by an acute dose GAL. Smokers were instructed to smoke ad lib and were provided with smoking breaks during the sessions. Abstinent smokers refrained from smoking overnight prior to and during each of the testing sessions. The neurocognitive battery, which commenced 30 min after administration of GAL, included tests of attentional functioning, cognitive switching, verbal fluency, fine motor dexterity, working memory, learning and memory, and visuospatial working memory. The duration of the neurocognitive battery was 90 min.

Of $N=21$ participants randomized, nine were non-smokers, six were satiated smokers, and six were abstinent smokers. Groups were comparable on baseline demographic and clinical characteristics (Table 1) and performed similarly on baseline cognitive tasks (all $ps>0.05$). We found no main effects of GAL on cognitive outcomes. However, nonsmoking status was associated with enhanced attentional discrimination (CPT Attentiveness d'; $p<0.01$ versus satiated smokers), simple auditory attention (Digit Span Forward; $p<0.05$ versus abstinent and satiated smokers), and response inhibition (Stroop Color Word Test Interference; $p<0.05$ versus abstinent and satiated smokers). Satiated smoker performance was improved in visuospatial working memory (VSWM 30 s delay; $p<0.05$ versus nonsmokers), cognitive switching (Trail Making Test Part B; $p<0.01$ versus nonsmokers and abstinent smokers), and attentional consistency (CPT Variability Index; $p<0.05$) versus abstinent smokers. Smoking status x GAL interactions were non-significant for all neurocognitive outcomes (all $ps>0.05$). ANCOVA analyses to account for potential baseline group differences in IQ and education (Table 1) did not change the pattern of neurocognitive outcomes. There were no effects of GAL on positive or negative psychiatric symptoms, and no effects of smoking status on psychiatric or mood symptoms. No significant adverse events were associated with GAL at either active dose.

Accordingly, this exploratory study did not demonstrate that GAL, at acute doses up to 8 mg, improved neurocognitive deficits in schizophrenia. Nonsmokers demonstrated the best performance on several measures of attention, even after co-varying for baseline differences in IQ and education. Satiated smoking status was associated

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Table 1
Demographics and baseline clinical characteristics

	Smokers satiated (N=6)	Smokers abstinent (N=6)	Nonsmokers (N=9)	p-value
Age	44.7±4.6	47.0±7.1	48.6±7.3	p=0.55
Gender	3 M/3 F	0 M/6 F	4 M/5 F	p=0.12
Race	3 C/3 AA	2 C/4 AA	6 C/3 AA	p=0.44
Education (yrs)	12.3±1.6	11.3±1.9	14.1±3.3	p=0.14
IQ	90.2±11.2	77.0±6.1	91.8±17.2	p=0.12
BDI	9.0±7.7	9.0±10.7	9.8±7.5	p=0.98
PANSS Total	64.8±7.0	60.0±8.5	62.3±6.5	p=0.53
FTND Score	6.7.±1.8	6.2±1.3	n/a	p=0.47
Cigarettes/Day	17.7±9.9	14.9±4.0	n/a	p=0.39

Abbreviations: M=Male; F=Female; C=Caucasian; AA=African American; IQ=Intelligence Quotient; BDI=Beck Depression Inventory; PANSS=Positive and Negative Symptoms Scales for Schizophrenia; FTND=Fagerstrom Test for Nicotine Dependence.

with better performances in the areas of VSWM, cognitive flexibility, and attentional consistency.

Strengths of our study were the pre-study neuropsychological training session, the within-subjects design for drug dosing, the conduct of the testing battery during the period of anticipated peak plasma levels of galantamine after acute dosing, and the between-subjects comparison as a function of smoking status. Limitations in this study included the acute dosing schedule, the low doses of GAL, and the small study sample. The study of nAChRs in mediating cognitive enhancement in schizophrenia may require alternative agents to galantamine.

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References

Buchanan, R.W., Conley, R.R., Dickinson, D., Ball, M.P., Feldman, S., Gold, J.M., McMahon, R.P., 2007. Galantamine for the treatment of cognitive impairments in people with schizophrenia. Am. J. Psychiatry 165, 82–89.

Coyle, J., Kershaw, P., 2001. Galanthamine, a cholinesterase inhibitor that allosterically modulates nicotinic receptors: effects on the course of Alzheimer's disease. Biol. Psychiatry 49, 289–299.

Depatie, L., Driscoll, G.A., Holahan, A.-L.V., Atkinson, V., Thavundayil, J.X., Ying Kin, N.N., Samarthji, L., 2002. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. Neuropsychopharmacology 27, 1056–1070.

Farlow, M.R., 2003. Clinical pharmacokinetics of galantamine. Clin. Pharmacokinet. 42, 1383–1392.

George, T.P., Vessicchio, J.C., Termine, A., Sahady, D.M., Head, C.A., Pepper, W.T., Kosten, T.R., Wexler, B.E., 2002. Effects of smoking abstinence on visuospatial working memory function in schizophrenia. Neuropsychopharmacology 26, 75–85.

Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? Am. J. Psychiatry 153 (3), 321–330.

Kalman, D., Morrisette, S.B., George, T.P., 2005. Co-morbidity of smoking with psychiatric and substance use disorders. Am. J. Addict. 14, 106–123.

Sacco, K.A., Termine, A., Seyal, A.A., Dudas, M.M., Vessicchio, J.C., Krishnan-Sarin, S., Jatlow, P.I., Wexler, B.E., George, T.P., 2005. Effects of cigarette smoking function on spatial working memory and attentional function in schizophrenia: involvement of nicotinic receptor mechanisms. Arch. Gen. Psychiatry 62, 649–659.

Schubert, M.H., Young, K.A., Hicks, P.B., 2006. Galantamine improves cognition in schizophrenic patients stabilized on risperidone. Biol. Psychiatry 60, 530–533.

Smith, R.C., Warner-Cohen, J., Matute, M., Butler, E., Kelly, E., Vaidhyanathaswamy, S., Khan, A., 2006. Effects of nicotine nasal spray on cognitive function in schizophrenia. Neuropsychopharmacology 31, 637–643.

Kristi A. Sacco*
Cerissa Creeden
Erin L. Reutenauer
Tony P. George
Program for Research in Smokers with Mental Illness (PRISM), Division of Substance Abuse, Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut 06519, USA
*Corresponding author. Research Affiliate, Yale School of Medicine, 191 Post Road West, Westport, CT 06880, USA.
Tel.: +1 203 767 0366.
E-mail address: kristi.sacco@yale.edu (K.A. Sacco).

Tony P. George
Department of Psychiatry, University of Toronto and The Centre for Addiction and Mental Health, Toronto, Ontario Canada M5S 2S1

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