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Effects of a nicotinic agonist on the Brief Psychiatric Rating Scale five-factor subscale model in schizophrenia

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To the Editor:

The excitatory, ligand-gated α7 nicotinic acetylcholine receptor (nAChR) has been implicated in the pathophysiology of schizophrenia based on convergent genetic, post-mortem, and psychopharmacological studies (reviewed in (Freedman, 2014)). Preclinical animal studies (reviewed in (Lewis et al., 2017)), as well as early phase clinical studies of patients with schizophrenia (Olincy et al., 2006), suggest α7 nAChR agonists may be useful for treatment of cognitive dysfunction in schizophrenia. However, results of larger randomized placebo-controlled clinical trials of α7 nAChR agonists with a primary cognitive outcome have been mixed, despite these agents being well tolerated (Freedman et al., 2008; Keefe et al., 2015; Umbricht et al., 2014).

3-(2,4-dimethoxy-benzylidene) anabaseine (DMXB-A, also known as GTS-21) is an α7 nAChR partial agonist that improved auditory P50 suppression and cognitive performance in a placebo-controlled proof-of-concept study of non-smoking subjects with schizophrenia (Olincy et al., 2006). In a subsequent crossover study, DMXB-A also significantly improved the Scale for the Assessment of Negative Symptoms total score and anhedonia and alogia subscales, as well as demonstrated benefit in a subset of cognitive subdomains (Freedman et al., 2008). Interestingly, multiple other α7 nAChR agonists have shown benefit for negative symptoms, in some cases despite lack of cognitive benefit (Keefe et al., 2015; Umbricht et al., 2014), suggesting potential effects of α7 nAChR agonists on clinically significant, non-

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cognitive symptom clusters in schizophrenia. As current pharmacotherapies in schizophrenia inadequately address symptom domains such as negative or affective symptoms that result in substantial disability for patients, identification of novel treatment targets for these domains is of critical importance.

We further explored this question in a *post-hoc* analysis of a 31-subject placebo-controlled double blind crossover study of DMXB-A in subjects with schizophrenia (Freedman et al., 2008) to determine whether DMXB-A significantly improved Brief Psychiatric Rating Scale (BPRS) subscales of affect, positive symptoms, negative symptoms, resistance, and activation, identified from a meta-analysis of factor analyses (Shafer, 2005). This trial (www.clinicaltrials.gov NCT00100165) enrolled clinically stable male and female outpatients age 21-60 without drug abuse or nicotine use in the prior month meeting DSM-IV-TR criteria for schizophrenia. Twenty-five subjects were enrolled at the Denver VA Medical Center/University of Colorado and six subjects at the Maryland Psychiatric Research Center. All subjects gave informed consent, and the sites' institutional review board approved the study. Subjects were assigned to four weeks of twice daily (b.i.d.) DMXB-A (75 mg or 150 mg) or placebo, with one-week placebo washout periods between treatment arms. DMXB-A drug levels were obtained from plasma specimens drawn at the end of each treatment arm in the Colorado subjects. Baseline BPRS scores were obtained after a one-week placebo run-in period and treatment scores obtained at the end of each four-week treatment arm. From 29 subjects completing at least one treatment arm, scores for each BPRS subscale were ranked and analyzed using a mixed effects model (SPSS version 24, IBM, Armonk, NY), with treatment, encounter, site, treatment sequence, and treatment x encounter interaction as fixed effects, and baseline subscale score as a covariate.

We identified a significant effect of treatment on affect subscale scores, with DMXB-A 150 mg b.i.d. differing significantly from placebo (Cohen's $d = 0.34$; Table 1). The 75 mg dose did not differ significantly from placebo. There were no significant effects of encounter, site, treatment sequence, or treatment x encounter interaction on the affect subscale. In subjects with elevated baseline affect subscale scores, DMXB-A plasma levels during 150 mg b.i.d. treatment significantly correlated with improvement from baseline in affect subscale scores (Spearman's $r = 0.58$, $N = 13$, $p = 0.037$). A significant treatment x encounter interaction was identified in the resistance subscale, whereby DMXB-A 75 mg b.i.d. significantly worsened symptoms during the second encounter. Treatment effects did not reach significance in the remaining three BPRS subscales, though a trend toward improvement was observed in the negative symptom subscale.

Our findings extend previous rodent studies reporting antidepressant effects of α7 nAChR agonists (Marcus et al., 2016), as well as a role for α7 nAChR signaling to modulate depression-like behaviors induced by hypercholinergic states (Mineur et al., 2016). Relatedly, we recently reported that DMXB-A significantly reduces aggression in mouse models (Lewis et al., 2015), which may in part reflect regulation of affective or motivational states. Limitations of our study include its *post-hoc* nature and relatively small sample size, both of which urge caution in the interpretation of the identified effect size and estimation of clinical significance. The significant correlation between DMXB-A plasma level and affect subscale improvement suggests a biological relationship and argues against a false positive

treatment effect on the affect subscale. Taken together, these findings support prospective study of DMXB-A for the treatment of affective symptoms in schizophrenia, which confer a substantial burden on this large group of patients and for which novel treatment options with favorable safety profiles are critically needed.

Abbreviations:

nAChR	nicotinic acetylcholine receptor
BPRS	Brief Psychiatric Rating Scale
DMXB-A	3-(2,4-dimethoxy-benzylidene) anabaseine
b.i.d.	twice daily

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Table 1.

BPRS subscale scores for subjects with schizophrenia after each 4-week crossover treatment arm with placebo and two doses of DMXB-A.

BPRS subscale	Subscale composition (minimum score)	Baseline (N = 29)		Placebo (N = 29)		DMXB-A 75 mg b.i.d. (N = 29)		DMXB-A 150 mg b.i.d. (N = 28)		Treatment effect[a]		
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	*p*
Affect	anxiety, guilt, depression, somatic (4)	6.00	2.44	6.31	3.25	5.93	3.01	5.29	2.11	3.68	2, 25.8	0.039[b]
Positive symptoms	thought content, conceptual disorganization, hallucinatory behavior, grandiosity (4)	6.79	3.85	6.34	3.79	6.45	3.46	6.14	3.25	0.12	2, 27.1	0.89
Negative symptoms	blunted affect, emotional withdrawal, motor retardation (3)	5.17	2.51	5.52	2.96	4.72	2.59	5.11	2.44	2.08	2, 26.6	0.14
Resistance[c]	hostility, uncooperativeness, suspiciousness (3)	4.55	2.11	3.93	1.49	4.31	1.77	3.96	1.53	–	–	–
Activation	excitement, tension, mannerisms-posturing (3)	3.86	1.46	3.55	1.30	3.52	1.15	3.68	1.33	0.69	2, 26.3	0.51

[a] If treatment × encounter interaction $p > 0.10$, model was re-calculated without the interaction term, and the main effects are reported.

[b] Estimated marginal mean difference (EMMD) [75 mg dose - placebo] = −0.36, SE = 0.46, t = 0.78, df = 25.9, $p = 0.88$ (Bonferroni corrected). EMMD [150 mg dose - placebo] = −1.00, SE = 0.40, t = 2.48, df = 27.6, $p = 0.039$ (Bonferroni corrected). Cohen's $d = 0.34$.

[c] Resistance subscale treatment × encounter interaction was significant (F = 3.57, df = 4, 39.0, $p = 0.014$). Simple effects analysis revealed during the week 11 encounter DMXB-A 75 mg b.i.d. differs significantly from placebo (EMMD [75 mg b.i.d. - placebo] = 1.51, SE = 0.43, t = 3.49, df = 48.5, $p = 0.001$ (uncorrected)) and from 150 mg b.i.d. (EMMD [75 mg b.i.d. - 150 mg b.i.d.] = 0.94, SE = 0.44, t = 2.11, df = 36.2, $p = 0.042$ (uncorrected)). No significant differences were detected between the three treatment arms during the remaining encounters at week 6 or 16.