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LETTER TO THE EDITOR

Galantamine may improve attention and speech in schizophrenia

Dear Editor

Negative symptoms of schizophrenia that are correlated with cognitive deficits are sometimes refractory to second generation antipsychotics (SGAs) (O'Leary *et al*., 2000). Neuronal nicotinic acetylcholine receptors (nAChRs) participate in normal cognitive processing (Levin *et al*., 2005) and there is preliminary evidence that galantamine (a positive allosteric modulator of nAChRs (Maelicke and Albuquerque, 2000)) can improve negative symptoms in Schizophrenia (Allen and McEvoy, 2002; Rosse and Deutsch, 2002). It is thus reasonable to assume that nAChRs may improve cognitive deficits related to negative symptoms as well.

In this letter we describe 2 out of 13 patients diagnosed using DSM-IV-TR criteria for schizophrenia and exhibiting prominent negative symptoms at the time of admission. The Scale for the Assessment of Negative Symptoms (SANS) was used to define severity of negative symptoms (i.e., a rating ≥ 4 in at least two of the five items of the SANS). Both patients had a negative urine test for metamphetamines and cocaine. One patient was non-adherent to his medication regime, whereas the other was already stable on a SGA and a mood stabilizer.

Patient #1 was a 54-year-old caucasian male admitted in June of 2003. He smoked 20 cigarettes a day and he had both disorganized behavior and thinking plus marked paucity of speech. He had been non-adherent to his medication regime (olanzapine) for the last 4 months. This person (as well as the other 11 patients co-treated with galantamine) gave informed consent according to current protocols followed at the Sacramento County Mental Health Treatment Center.

Olanzapine was re-started (10 mg/d) and galantamine was added 2 days later (8 mg/d). After the first 7–10 days, the patient exhibited a decrease in total SANS scores (from 86 on admission to 63). At the time of his discharge, 20 days after admission, his thought processes were more organized and he was able to maintain a coherent conversation. Speech and attention showed marked improvements with less gains in anhedonia, affective flattening, avolition or apathy.

Patient #2 was a 47-year-old African–American male symptomatically stable on olanzapine (20 mg/d) and divalproex (1500 mg/d). He smoked 5–6 cigarettes a day and was briefly admitted to the hospital in September of 2003 because of behavioral discontrol at his Care home. He had prominent alogia, was unable to perform serial 7's, and had a SANS score of 96.

Galantamine (10 mg/d) was added to his current medications. After 12 days of treatment, a marked improvement in his SANS score (22) was observed. In addition, he was able to verbalize his feelings, was more communicative, and was able to perform serial 7's. He returned to his Board and Care home.

Two years later, patient #2 was re-examined in the outpatient setting. In the intervening period, the galantamine had been discontinued but his earlier medication regimen was maintained. The Screen for Cognitive Impairment in Psychosis (SCIP) (Purdon, 2005) revealed impairment of working memory, new learning, verbal fluency, visuomotor tracking, and delayed recall. Galantamine was again initiated at 8 mg/d. After 34 days the patient showed a remarkable improvement in working memory and delayed recall, though he continued to show impairment in the other examined domains. Negative symptom ratings on the SANS also revealed improvement of attention and speech.

Galantamine, used to treat dementia of the Alzheimer's type (Tariot *et al*., 2000; Wilcock *et al*., 2000b), inhibits acetylcholinesterase (AChE), and is a positive allosteric modulator of nAChRs (Maelicke and Albuquerque, 2000). The latter differentiates galantamine from other pure AChE inhibitors (Maelicke and Albuquerque, 2000) such as donepezil which does not have an effect on neither positive nor negative symptoms of schizophrenia (Buchanan *et al*., 2003).

nAchRs, particularly the α_7 and the $\alpha_4\beta_2$ subtypes, appear relevant to cognitive processing (Levin *et al*., 2005). The $\alpha_4\beta_2$ nAchR is the most abundant in the

mammalian brain (Flores *et al*., 1992) and the one that is preferentially up-regulated (Flores *et al*., 1992), activated, and desensitized by nicotine (Vibat *et al*., 1995). Positive allosteric modulation of nAChRs (Maelicke and Albuquerque, 2000) makes galantamine particularly useful for adjuvant treatment of negative symptoms of schizophrenia.

Allen and McEvoy combined risperidone and galantamine in two treatment-resistant patients with schizophrenia previously exposed to clozapine (Allen and McEvoy, 2002). Both positive and negative symptoms decreased after 2 months of treatment (Allen and McEvoy, 2002).

Rosse and Deutsch (2002) reported the case of a 42-year-old man with diagnosis of schizophrenia treated with galantamine initiated at 8 mg/d and increased to 24 mg/d over 2 months. There was an improvement in SANS negative but not positive symptoms, and the negative symptoms returned dramatically after discontinuation of the galantamine.

Finally, Arnold *et al*. (Arnold *et al*., 2004), reported an adjuvant therapeutic effect of galantamine on apathy in one patient with schizophrenia, supporting the notion of galantamine-induced cognitive enhancement in this condition.

In agreement with the prior reports (Allen and McEvoy, 2002; Rosse and Deutsch, 2002, Arnold *et al*., 2004), we also observed a rapid (15–20 days) improvement in negative symptoms of schizophrenia in 13 in-patients treated with adjuvant galantamine. Clinical ratings of alogia and attention were specifically improved in most cases. One patient also showed a marked improvement of working memory and delayed recall on a psychometric measure of cognitive impairment in schizophrenia (Purdon, 2005).

Galantamine has a reasonable safety profile when combined with SGAs (Wilcock *et al*., 2000a), and it would be useful to undertake controlled clinical trials to assess its potential as a cognitive enhancer in schizophrenia.

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