5-HT6 Receptor Antagonist as an Adjunct Treatment Targeting Residual Symptoms in Patients With Schizophrenia

Unexpected Sex-Related Effects (Double-Blind Placebo-Controlled Trial)

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Abstract:

Background: Treating patients who experience residual psychotic symptoms during remission of schizophrenia remains one of the most challenging problems. The mechanisms underlying these symptoms differ from those of acute hallucinations and delusions. 5-HT6 receptor antagonists have been considered promising agents in treatment of residual psychotic symptoms and cognitive dysfunction. The aim of the study was to assess the efficacy of a selective 5-HT6 inhibitor Avisetron in the reduction of residual psychotic symptoms in patients with schizophrenia on stable antipsychotic therapy.

Methods: Eighty clinically stable outpatient subjects with schizophrenia with residual psychotic symptoms were randomized in a double-blind manner to 6 weeks of Avisetron or placebo at 1:1 ratio. Subjects received 8 mg of Avisetron or placebo on top their stable antipsychotic treatment. Standard clinical scales and cognitive tests were used for endpoint assessment. The primary efficacy endpoint was the mean reduction of total Positive and Negative Syndrome Scale score after 6 weeks of treatment.

Results: No significant differences in the primary and secondary endpoints were found between the groups. However, based on the subgroup analysis, the significant improvement of total Positive and Negative Syndrome Scale score and residual psychotic symptoms was observed in female patients.

Conclusions: It was a negative study with unexpected benefits of the drug only in females. We hypothesized that the role of patients' sex can impact the treatment response to serotonergic drugs in general. We suggest a possible synergistic interaction between estrogen and Avisetron by means of modulating the effect of estrogens on the serotonergic system. Future studies targeting the sex-related effects of serotonergic drugs are warranted.

Key Words: schizophrenia, partial remission, 5-HT6 antagonist add-on treatment, sex, psychotic symptoms

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The choice of individual treatment strategy for patients with schizophrenia poses an intriguing problem. In acute phases of the disease, modern antipsychotics are usually highly effective, but treatment is much less effective for patients in remission who exhibit residual symptoms such as hallucinations and paranoia. Only about 33% of patients achieve complete reduction of psychotic symptoms despite adequate antipsychotic therapy.[1–6]

Partial but not complete remission is usually accompanied by severe impairment in other mental areas. These patients experience deficits in working memory and planning, whereas according to some researchers, patients in complete remission perform nearly as well as healthy controls.[7] The patients in partial remission also display a significant reduction in social functioning.[8]

There have been numerous attempts to develop treatment approaches for residual psychotic symptoms. The hypothesis that the insufficient blockade of dopamine receptors is responsible for such symptoms has been rejected because the significant increases in antipsychotic doses have no effect.[9–11] It has been suggested that the neurophysiological mechanisms underlying the residual psychotic symptoms differ from those involved in acute psychosis.[12] However, neither a medication nor a complex therapeutic approach for treatment of residual psychotic symptoms has been registered yet.

For many years, dysfunction of the serotonin system has been discussed as the basis for psychosis. Its hypothesized importance in schizophrenia precedes the dopamine one.[13] However, to date, the role of serotonergic dysfunction in specific clinical manifestations of schizophrenia remains unclear, and the significant impact of antipsychotics on serotonergic receptors indicates that further research in this direction is warranted. Moreover, there is a growing body of research regarding the interaction of serotonin receptors with other systems in the brain, especially the glutamatergic system, which has become a subject of keen interest to researchers of schizophrenia. Abraham et al[14] have demonstrated that the blockade of 5-HT6 receptors causes a considerable increase in the concentration of glutamate. Gasquet et al[15] have further demonstrated that treatment with olanzapine, an antipsychotic with high antagonistic affinity for 5-HT6 receptors, aids in achieving stable and complete remission in comparison to conventional or other atypical antipsychotics. Olanzapine enhances the effects of serotonin reuptake inhibitors through antagonistic GABAergic action on 5-HT6 receptors in the dorsal raphe nucleus.[16] Clozapine also has an influence on this area, demonstrating a unique combination of effects: the reduction of persistent psychotic symptoms (resistant to other antipsychotics) and improvement of cognitive function in patients with schizophrenia.[17,18] It has been observed that sertindole, another antipsychotic with an antagonistic effect on 5HT-6 receptors, improves cognitive dysfunction in animal models.[19]

5-HT6 receptor antagonists may improve the processes of forming new skills and knowledge assimilation.[20] In a model of scopolamine-induced memory deficit in mice, the use of 5-HT6 receptor antagonists significantly improves the working memory and learning, but not the episodic memory.[21] Tripathy et al[22]

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demonstrated the improvement in social cognition in rats after the administration of a 5-HT6 receptor antagonist.

There is some evidence that the impact of antagonists on 5-HT6 receptors causes improvement in some cognitive functions in patients with schizophrenia, such as social intelligence, attention shifting, working memory, and other executive functions.[23,24] Mohler and colleagues[23] suggest that 5-HT6 receptor antagonists enhance synaptogenesis by increasing the number of polysialylated-neural cell adhesion molecule immunoreactive neurons in the dentate gyrus, affecting the function of the dopamine system through influencing dopamine-and cyclic adenosine monophosphate – regulated phosphoprotein-32, and reducing γ-aminobutyric acid release and excitability of γ-aminobutyric acid interneurons, leading to the disinhibition of release of glutamate and/or acetylcholine. This process results in an increase in synaptic plasticity, an important factor for healthy brain functioning.

In a review of clinical trials of the 5-HT6 receptor antagonist idalopirdine in patients with Alzheimer disease,[25] Da Silva Costa-Aze with colleagues[21] and Galimberti and Scarpini[26] suggest that such an effect on serotonergic structures may lead to restoration of function in a damaged cholinergic system. Several studies have investigated the effects of 5-HT6 receptor antagonists as adjuvant agents that modulate the effects of the base therapy. Abraham et al[27] showed that the 5-HT6 receptor antagonist PRX-07034, in combination with low doses of the alpha-1 receptor blocker prazosin, exerts an antipsychotic effect in animals. In addition, add-on therapy of a 5-HT6 receptor antagonist significantly enhances the antipsychotic effects of clozapine and risperidone, but not haloperidol, in rats.[28]

Lesem[29] demonstrated the positive effect of idalopirdine in combination with antipsychotic therapy (risperidone, olanzapine, aripiprazole, and quetiapine) on cognitive function in stable patients with schizophrenia. The author noted that the effect was dose dependent and increased with the dose escalation, which ranged from 60 to 240 mg.

The drug Avisetron (AVN-211 or CD-008-0173) is one of the most well-known selective inhibitors of 5-HT6 receptors, with a competitive binding assay of $K_i^b = 1.09$ nM and a functional assay of $K_i^f = 0.83$ to 1.97 nM.[30] In preclinical experiments, the drug was tested in the Alzheimer disease models with positive results.[31]

Previously, a clinical study of the efficacy and safety of Avisetron when given as an add-on treatment for stable patients with schizophrenia exhibiting severe impairment of attention was conducted.[32] The primary outcome of the study was negative, as Avisetron 4 mg once daily for 28 days did not differ from placebo in the primary efficacy endpoint—changes in the attention test battery scores. The only noted difference between Avisetron and placebo was the improvement of selectivity of attention. The secondary objective of the study was to prove that the add-on Avisetron did not cause the exacerbation of psychosis. There was no difference in exacerbation rates between the study groups; however, the improvement of residual psychotic symptoms was observed only in the Avisetron group. The latter finding was used as the basis for the study presented here.

We hypothesized that the add-on treatment with the 5-HT6 receptor antagonist could be effective in reducing residual psychotic symptoms in patients with or without cognitive disturbances both through a direct effect on the serotonergic system and via its indirect influence on the glutamatergic system.

MATERIALS AND METHODS

Eighty patients aged 18 to 65 years with a clinical diagnosis of schizophrenia (according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*) undergoing stable antipsychotic treatment were included in the study. The patients did not have the psychotic exacerbation for at least 3 months before screening. Therapeutic stability was defined as up to 2 antipsychotics with maximum total daily dose equivalent to chlorpromazine 600 mg for 3 months before screening (or 6 months for prolonged forms) and stable doses of anticholinergic drugs, antidepressants, and mood stabilizers (except for carbamazepine) for 3 months before screening.

Each patient had a caregiver and gave the informed consent. The study was conducted in accordance with good clinical practice.

The total Positive and Negative Syndrome Scale (PANSS) score ranged from 70 to 90 (inclusively). Scores of 4 or higher were required on at least 2 of the following items: P1, P3, P6, and G9. To exclude patients with the beginning of exacerbation, scores of 3 or lower were required for items P4, P5, and G14.

Eighty patients were randomized in a double-blind manner into 2 treatment groups at 1:1 ratio: Avisetron or placebo. Data on patients' sex, age, severity of the disease, basic treatment, and antipsychotic loading are presented in Table 1.

Study Design

This study is a double-blind placebo-controlled multicenter trial. Twelve Russian sites participated in this study (see Appendix 1); the study was approved by the Russian regulatory authorities (No. 406 dated July 1, 2013) and the local ethics committees of each site. All subjects were outpatients. The duration of the treatment period was 6 weeks. The starting dose of Avisetron or placebo was 4 mg (1 tablet) once daily. After 1 week, the dose was increased to the target dose of 8 mg (2 tablets) once daily.

Study Medication

The daily dose of Avisetron (CD-008-0173) 8 mg was chosen as a maximum dose studied in phase I for safety and tolerability. The dose proved to be safe in healthy volunteers and

TABLE 1. Demographics, Severity of Disease, and Chlorpromazine Equivalent of Basic Treatment in the Avisetron and Placebo Groups

	Avisetron Group (n = 40)	Placebo Group (n = 40)	*P*
Female/male ratio	18 women (45%), 22 men (55%)	10 women (25%), 30 men (75%)	0.062
Mean age, y	38.1 ± 13.9	36.1 ± 10.2	0.470
Basic treatment (antipsychotics)	17 (42.5%) typical 23 (57.5%) atypical	16 (40.0%) typical 24 (60.0%) atypical	0.821
Mean dose of antipsychotics (chlorpromazine equivalent), mg/d	280.8 ± 157.2	318.7 ± 147.0	0.269
Total PANSS score	79.8 ± 5.4	81.7 ± 5.9	0.142
CGI-S	3.8 ± 0.4	3.9 ± 0.3	0.245
Early withdrawal due to worsening of schizophrenia	2	5	0.24

TABLE 2. PANSS and CGI-S Scores at Baseline and End of Treatment (MITT-LOCF)

	Avisetron Group				Placebo Group			
Scales	**Baseline, Mean (SD)**	**End of Treatment**	**Mean Change**	***P***	**Baseline**	**End of Treatment**	**Mean Change**	***P***
PANSS positive	18.9 (±2.1)	16.7 ± 3.9	−2.2 ± 3.7	0.001	18.0 ± 2.6	16.6 ± 3.8	−1.5 ± 3.8	0.051
PANSS negative	22.7 ± 2.9	21.1 ± 3.5	−1.7 ± 2.7	0.029	24.5 ± 2.8	22.8 ± 3.0	−1.7 ± 2.6	0.010
PANSS general	38.3 ± 4.5	35.3 ± 6.1	−3.1 ± 5.5	0.017	39.2 ± 3.6	37.5 ± 5.7	−1.7 ± 4.8	0.107
PANSS total	79.8 ± 5.4	72.9 ± 10.6	−6.9 ± 9.2	0.0005	81.7 ± 5.9	76.8 ± 10.4	−4.9 ± 9.9	0.012
CGI-S	3.8 ± 0.4	3.6 ± 0.6	−0.21 ± 0.5	0.131	3.9 ± 0.3	3.8 ± 0.6	−0.1 ± 0.6	0.496

MITT-LOSF indicates modified intent-to treat-last observation carried forward.

is supposed to provide the sufficient clinical effect in the target patients' population. The daily dose was allowed to be reduced to 4 mg for any safety reason; however, no such cases were reported during the study. Avisetron and placebo were provided in tablets, containing 4 mg of active substance or placebo. The drug was packed in plastic bottles. It was manufactured by MiraxBioPharma Ltd by the order of Avineuro LLC.

Assessment

Efficacy

The change of the total PANSS[32] score after 6 weeks of treatment was used as a primary efficacy endpoint. The PANSS subscales, Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I),[33] Negative Symptom Assessment,[34] Personal and Social Performance Scale,[35] and A Scale for Rating Functioning Related to Cognitive Impairment in Schizophrenia (CogFu)[36] were used as the secondary endpoint scales during 6 weeks of treatment. Cognitive function was assessed using Brief Assessment of Cognition in Schizophrenia[37] and Continuous Performance Test.[38]

For the secondary efficacy measurement, we developed the study-specific response criteria. Because the main objective of the study was the changes in the severity of the residual psychotic symptoms, we considered that the reduction of P1 (delusions) and P3 (hallucinatory behavior) as the criterion of response was more important than the reduction of the total PANSS score. Therefore, a patient was assessed as responder if at least 1 item relating to P1 and/or P3 was scored as absent (score 1) or borderline to normal (score 2) at the end of the study.

Safety

Safety assessments included the evaluation of treatment emergent adverse events (AEs), clinical laboratory parameters, electrocardiogram, physical examination, and vital signs.

Statistical Methods

The primary efficacy endpoint was the mean reduction of the total PANSS score from baseline at week 0 to the final assessment at week 6. The main purpose was to demonstrate the significant reduction in PANSS total score in the Avisetron group compared with the placebo group with the minimal expected difference of −7 points. The null hypothesis (H_0), that Avisetron was no different from placebo, was tested against the alternative hypothesis (H_a), that Avisetron was superior to placebo, using a 2-tailed *t* test with α value of .05, power of 80%, and SD of 10. The hypothesis H_0 can be rejected if the upper limit of the 95% confidence interval was below 0.

For the secondary endpoints, we used the descriptive statistics, the Wilcoxon *t* test for assessing the intragroup changes, and the Mann-Whitney *U* test for assessing differences between Avisetron and placebo.

RESULTS

The baseline characteristics of the main clinical scales were as follows: the total PANSS score of 79.8 ± 5.4 and 81.7 ± 5.9 and CGI-S score of 3.8 ± 0.4 and 3.9 ± 0.3 in Avisetron and placebo groups, respectively (no statistical difference).

The changes of PANSS and CGI-S scores in each study group over the 6 weeks of treatment are presented in Table 2. The PANSS total score and subscores (positive, negative, and general) decreased significantly in the Avisetron group, whereas in the placebo group, the statistically significant change was noted only for the total PANSS score and negative subscore. The CGI-S changed significantly in neither of the study groups.

The difference of −2.1 points in the mean change of the total PANSS score between the groups was not significant ($P = 0.341$). There was also no difference between the groups in the change of the PANSS subscores and CGI-S.

A comparison of the rate of reduction in symptoms severity revealed improvement for the Avisetron group during the first 2 weeks of treatment, whereas improvement in the placebo group was not observed until week 4 (Fig. 1).

The between-group differences were insignificant in every week of the treatment.

Rates of reduction in patients with different CGI-I scores at the end of Avisetron/placebo titration (1 week after randomization), week 4, and week 6 of treatment (study completion) are presented in Table 3.

We observed that only 18% (13 of 71) of the patients might be considered responders according to our criteria of treatment response. Three of these patients (8.6%) were in the placebo group, whereas 10 were (27.7%) in the Avisetron group.

No between-group differences were observed in the Negative Symptom Assessment, Personal and Social Performance Scale,

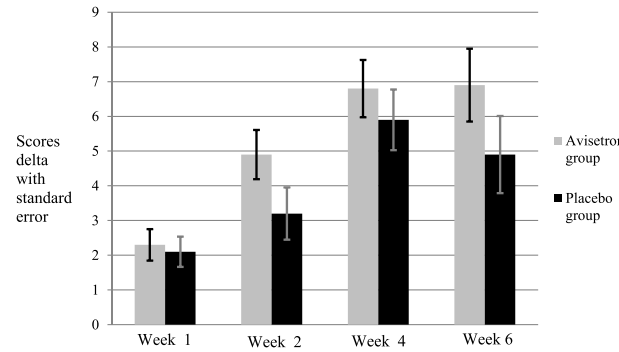

FIGURE 1. The reduction of total PANSS score.

TABLE 3. The Rates of Patients With Different CGI-I Courses

	Avisetron Group			Placebo Group		
	End of Titration, %	4 Weeks of Treatment	6 Weeks of Treatment	End of Titration	4 Weeks of Treatment	6 Weeks of Treatment
Improvement	30	61.1	60	16.2	51.4	52.5
No changes	62	33.3	32.5	81.1	42.9	32.5
Deterioration	7.5	5.6	7.5	2.7	5.7	15

and CogFu scales, nor in the Brief Assessment of Cognition in Schizophrenia or Continuous Performance Test performance at any stage of the study.

Analysis of the results accounting for patient sex revealed an interesting fact. The largest positive change in clinical symptoms (in terms of total PANSS score reduction) was observed in females in the Avisetron group (18 cases). Females in the placebo group showed a slight worsening of symptoms.

For males, a moderate improvement was observed in both the Avisetron and placebo groups. Interestingly, there was a significant diversity in the response of males in the Avisetron group. Some male patients showed substantial improvement in symptoms, whereas some exhibited worsening of symptoms. Males in the placebo group revealed less of a difference between the largest and smallest changes in severity of symptoms (Fig. 2).

In general, the factor of patient sex had a profound effect on therapeutic response ($F = 8.2$, $P = 0.005$).

Females in the Avisetron group displayed the most prominent decrease in residual psychotic symptoms (PANSS positive subscale score, $P < 0.001$; Marder factor of positive symptoms, $P < 0.005$), general psychopathological symptoms ($P < 0.01$), and disorganization (Marder factor of disorganization, $P < 0.05$). There were no sex-related effects in the response to Avisetron on negative symptoms. Changes of key indices from the baseline visit to the endpoint visit are presented in Table 4.

Avisetron demonstrated favorable safety profile similar to placebo. There were no serious AEs or severe AEs in the study. Twenty-seven AEs were registered in 16 (40.0%) patients on Avisetron, and 33 AEs were registered in 19 (47.5%) patients on placebo. The following events were registered in 5% or more of the patients: acute respiratory infection in 4 (10.0%), increased alanine aminotransferase in 2 (5.0%), and worsening of symptoms of schizophrenia in 2 (5.0%) patients on Avisetron; tachycardia in 2 (5.0%), headache in 2 (5.0%), orthostatic dizziness in 2 (5.0%), anxiety in 2 (5.0%), and deterioration of the mental status in 3 (7.5%) patients on placebo. In the Avisetron group 2 (5.0%) patients were withdrawn from the study due to AE (ischemic heart diseases and worsening of schizophrenia), whereas in the placebo group, 5 (12.5%) patients were discontinued early due to AE (worsening of schizophrenia).

DISCUSSION

The primary objective of the study was to prove that the adjunct treatment with a 5-HT6 receptor antagonist is effective in reducing residual psychotic symptoms in patients with schizophrenia. The results of this study failed to confirm this hypothesis. Therefore, it is a negative study. However, some unexpected findings were considered to be of interest.

We found a significant role of patient sex in the response to Avisetron. Its efficacy was reliably confirmed only in female patients. Significant improvement in extremely sluggish and resistant symptoms and low variability in response in female but not in male patients demonstrated that there were some important, but not obvious, factors, which influenced the efficacy of Avisetron in the treatment of this population. One of the explanations for this phenomenon could be the synergistic action of estrogen and Avisetron due to estrogen modulation of the sensitivity of serotonin receptors to ligands. Yokomaku et al[38] demonstrated facilitating effects of estrogen on glutamate transmission

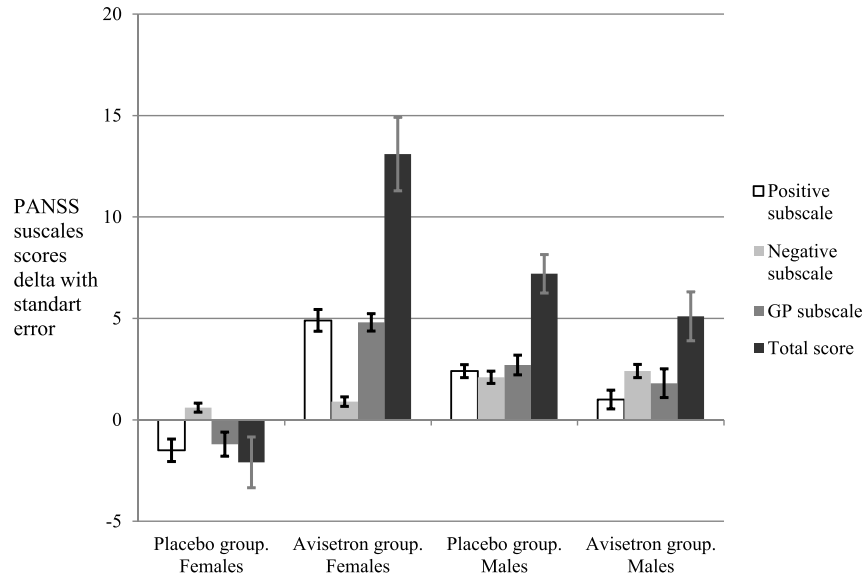

FIGURE 2. The dynamics of PANSS total and subscales' scores in the Avisetron and placebo groups with regard to the sex factor.

TABLE 4. The Dynamics of PANSS Factors in the Avisetron and Placebo Groups With Regard to the Sex Factor

	Females		Males	
	Avisetron Group	**Placebo Group**	**Avisetron Group**	**Placebo Group**
PANSS total score	13.1 (±16.1)	−2.1 (±11.1)*	5.1 (±10.7)	7.2 (±8.4)
PANSS positive subscale	4.9 (±4.8)	−1.5 (±4.9)*	1 (±4.1)	2.4 (±2.8)
PANSS negative subscale	0.88 (±2.1)	0.60 (±2.0)	2.41 (±2.9)	2.07 (±2.7)
PANSS general psychopathology subscale				
Marder factor of positive symptoms	3.35 (±2.3)	−0.2 (±2.57)*	0.7 (±2.4)	2.3 (±1.8)*
Marder factor of disorganization	1.7 (±1.9)	−0.8 (±3.1)*		

*The difference between the Avisetron and placebo groups is significant.

in the experiment. Estrogen promotes an increase in N-methyl-D-aspartate receptor subunit expression,[39] a neuronal sensitivity to synaptic input, mediated by N-methyl-D-aspartate glutamate receptors.[40] It modulates serotonergic system through several levels, regulating tryptophan hydrolase density[41] and influencing binding of 5HT receptors.[42]

There are data on increased efficacy of antipsychotic treatment after adding the estrogens. The effectiveness of add-on therapy with estrogen in women with persistent psychotic symptoms of schizophrenia was reported by Chakos et al.[43] Kulkarni et al[44] also demonstrated a significantly greater reduction of psychotic symptoms in women who took 100 mg of estradiol in addition to an antipsychotic, as compared with those undergoing antipsychotic therapy alone.

It was shown in experiments that testosterone in contrast to estrogen could not increase the density of serotonergic receptors[45] and reduces the activity of serotonergic system[46] and the sensitivity of serotonin receptors.[47,48]

These facts can be indirect explanations of the found sex-related difference of the efficacy of Avisetron. We hypothesize that much higher doses of Avisetron are required to achieve positive effects in males.

We were unable to find any studies of drug efficacy in which male and female patients were analyzed separately. Thus, it is difficult to conclude if the sex differences discovered are universal or specific to our study drug only.

Complete reduction in at least one of the residual psychotic symptoms was observed to be 3 times more frequent in the Avisetron group than in the placebo group. This also indicates the positive effects of Avisetron, at least in some groups of patients.

The lack of improvement in cognitive functioning in response to Avisetron was an unexpected result, in contrast with the experimental data and the results of previous studies. This may be due to insufficient doses Avisetron given.

It is also interesting that a decrease in some clinical symptoms was observed in stable patients without the administration of any new active agent. In the placebo group, reductions were observed for residual symptoms of delusion but not for hallucinations. We hypothesize that the pathogenesis of the latter is more greatly influenced by biological components, reducing the placebo effect.

Despite the traditional point of view that subjects with schizophrenia are resistant to the placebo effect,[49] the results of a large number of multicenter clinical trials in recent years refute this judgment, with the present study supporting this conclusion.[50] The problem is most evident in situations in which the effects of well-known antipsychotic agents are indistinguishable from those of a placebo.[51] Difficulties with signal detection arise due to the placebo effect, reducing effect size even in studies of monotherapy.[52] It is reasonable that the role of the placebo effect increases in add-on studies due to the difficulty involved in detecting and quantifying cognitive and behavioral changes. Possible reasons for high values of the placebo response in schizophrenia trials include some characteristics of patients, specificities of sites, and differences in the designs of the study protocol.[50] Presumably, binary outcomes decrease or prevent placebo response.[53]

Another paradigm described in research on the placebo effect refers to attributes of the patient's personality, which contribute to the biological response to an inactive substance, focusing on the importance of the patient's beliefs in the formation of this biological response.[49] We surmise that unconscious expectations of researchers can also indirectly influence the observed efficacy of the studied drug. In contrast to the typical dynamics observed in the placebo response, which displays maximum intensity at the beginning of the study and subsequently achieves a plateau, the most prominent placebo effects in this study were deferred, which may point to an additional mediating component.

Despite the ambiguous results of this study, the cumulative experimental and clinical data regarding the importance of 5-HT6 receptor dysfunction suggest further studies of Avisetron are required, though challenging. The significance of appropriate dosages of the drug, especially relating to the factor of patient sex, should be taken into account during the creation of subsequent protocols.

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AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

REFERENCES

1. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry.* 1994;151:1409–1416.
2. Menezes NM, Arenovich T, Zipursky RB. A systematic review of longitudinal outcome studies of first-episode psychosis. *Psychol Med.* 2006;36:1349–1362.
3. Novick D, Haro JM, Suarez D, et al. Symptomatic remission in previously untreated patients with schizophrenia: 2-year results from the SOHO study. *Psychopharmacology (Berl).* 2007;191:1015–1022.

4. Novick D, Haro JM, Suarez D, et al. Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study. *Schizophr Res*. 2009;108:223–230.
5. Robinson DG, Woerner MG, McMeniman M, et al. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161:473–479.
6. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009;374:635–645.
7. Braw Y, Benozio A, Levkovitz Y. Executive functioning during full and partial remission (positive and negative symptomatic remission) of schizophrenia. *Schizophr Res*. 2012;142:122–128.
8. Karow A, Moritz S, Lambert M, et al. Remitted but still impaired? Symptomatic versus functional remission in patients with schizophrenia. *Eur Psychiatry*. 2012;27:401–405.
9. Kinon BJ, Volavka J, Stauffer V, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. *J Clin Psychopharmacol*. 2008;28:392–400.
10. Ganguli R, Brar JS, Mahmoud R, et al. Assessment of strategies for switching patients from olanzapine to risperidone: a randomized, open-label, rater-blinded study. *BMC Med*. 2008;6:17.
11. Lindenmayer JP, Czobor P, Volavka J, et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: an open-label switch study. *J Clin Psychiatry*. 2002;63: 931–935.
12. de Bartolomeis A, Sarappa C, Magara S, et al. Targeting glutamate system for novel antipsychotic approaches: relevance for residual psychotic symptoms and treatment resistant schizophrenia. *Eur J Pharmacol*. 2012; 682:1–11.
13. Baumeister AA, Hawkins MF. The serotonin hypothesis of schizophrenia: a historical case study on the heuristic value of theory in clinical neuroscience. *J Hist Neurosci*. 2004;13:277–291.
14. Abraham R, Nirogi R, Shinde A. Role of glutamate and advantages of combining memantine with a 5HT 6 ligand in a model of depression. *Pharmacol Rep*. 2014;66:394–398.
15. Gasquet I, Haro JM, Tcherny-Lessenot S, et al. Remission in the outpatient care of schizophrenia: 3-year results from the Schizophrenia Outpatients Health Outcomes (SOHO) study in France. *Eur Psychiatry*. 2008;23: 491–496.
16. Asaoka N, Nagayasu K, Nishitani N, et al. Olanzapine augments the effect of selective serotonin reuptake inhibitors by suppressing GABAergic inhibition via antagonism of 5-HT_6 receptors in the dorsal raphe nucleus. *Neuropharmacology*. 2015;95:261–268.
17. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. *Schizophr Res*. 2002;56:1–10.
18. Micoulaud-Franchi JA, Aramaki M, Geoffroy PA, et al. Effects of clozapine on perceptual abnormalities and sensory gating: a preliminary cross-sectional study in schizophrenia. *J Clin Psychopharmacol*. 2015;35: 184–187.
19. Idris N, Neill J, Grayson B, et al. Sertindole improves sub-chronic PCP-induced reversal learning and episodic memory deficits in rodents: involvement of 5-HT(6) and 5-HT (2A) receptor mechanisms. *Psychopharmacology (Berl)*. 2010;208:23–36.
20. Huerta-Rivas A, Pérez-García G, González-Espinosa C, et al. Time-course of 5-HT(6) receptor mRNA expression during memory consolidation and amnesia. *Neurobiol Learn Mem*. 2010;93:99–110.
21. Da Silva Costa-Aze V, Quiedeville A, Boulouard M, et al. 5-HT6 receptor blockade differentially affects scopolamine-induced deficits of working memory, recognition memory and aversive learning in mice. *Psychopharmacology (Berl)*. 2012;222:99–115.
22. Tripathy R, McHugh RJ, Bacon ER, et al. Discovery of 7-arylsulfonyl-1,2,3,4, 4a,9a-hexahydro-benzo[4,5]furo[2,3-c] pyridines: identification of a potent and selective 5-HT_6 receptor antagonist showing activity in rat social recognition test. *Bioorg Med Chem Lett*. 2012;22:1421–1426.
23. Mohler EG, Baker PM, Gannon KS, et al. The effects of PRX-07034, a novel 5-HT6 antagonist, on cognitive flexibility and working memory in rats. *Psychopharmacology (Berl)*. 2012;220:687–696.
24. de Bruin NM, Kruse CG. 5-HT6 receptor antagonists: potential efficacy for the treatment of cognitive impairment in schizophrenia. *Curr Pharm Des*. 2015;21:3739–3759.
25. Wilkinson D, Windfeld K, Colding-Jørgensen E. Safety and efficacy of idalopirdine, a 5-HT6 receptor antagonist, in patients with moderate Alzheimer's disease (LADDER): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet Neurol*. 2014;13:1092–1099.
26. Galimberti D, Scarpini E. Idalopirdine as a treatment for Alzheimer's disease. *Expert Opin Investig Drugs*. 2015;24:981–987.
27. Abraham R, Nirogi R, Shinde A, et al. Low-dose prazosin in combination with 5-HT6 antagonist PRX-07034 has antipsychotic effects. *Can J Physiol Pharmacol*. 2014;93:13–21.
28. Fijał K, Popik P, Nikiforuk A. Co-administration of 5-HT6 receptor antagonists with clozapine, risperidone, and a 5-HT2A receptor antagonist: effects on prepulse inhibition in rats. *Psychopharmacology (Berl)*. 2014; 231:269–281.
29. Lesem M. A randomized, placebo-controlled phase IIa trial of SGS518 for treating cognitive impairment associated with schizophrenia. *Schizophr Bull*. 2007;33:441–441.
30. Ivachtchenko A, Golovina E, Kadieva M, et al. Synthesis of substituted diphenyl sulfones and their structure-activity relationship with the antagonism of 5-HT6 receptors. *Bioorg Med Chem*. 2013;21: 4614–4627.
31. Ivachtchenko AV, Lavrovsky Y, Ivanenkov YA. AVN-211, novel and highly selective 5-HT6 receptor small molecule antagonist, for the treatment of Alzheimer's disease. *Mol Pharm*. 2016;13:945–63.
32. Morozova MA, Lepilkina TA, Rupchev GE, et al. Add-on clinical effects of selective antagonist of 5HT6 receptors AVN-211 (CD-008-0173) in patients with schizophrenia stabilized on antipsychotic treatment: pilot study. *CNS Spectr*. 2014;19:316–323.
33. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.
34. Axelrod BN, Goldman RS, Alphs LD. Validation of 16-item negative symptom assessment. *J Psychiatr Res*. 1993;27:253–58.
35. Morosini PL, Magliano L, Brambilla L, et al. Development, reliability and acceptability of a new version of the *DSM-IV* Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand*. 2000;101:323–329.
36. Keefe RS, Harvey PD, Goldberg TE, et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). *Schizophr Res*. 2008;102:108–115.
37. Cornblatt BA, Risch NJ, Faris G, et al. The Continuous Performance Test, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. *Psychiatry Res*. 1988;26:223–238.
38. Yokomaku D, Numakawa T, Numakawa Y, et al. Estrogen enhances depolarization-induced glutamate release through activation of phosphatidylinositol 3-kinase and mitogen-activated protein kinase in cultured hippocampal neurons. *Mol Endocrinol*. 2003;17:831–844.
39. Adams MM, Fink SE, Janssen WG, et al. Estrogen modulates synaptic *N*-methyl-D-aspartate receptor subunit distribution in the aged hippocampus. *J Comp Neurol*. 2004;474:419–426.
40. Smith SS, Woolley CS. Cellular and molecular effects of steroid hormones on CNS excitability. *Cleve Clin J Med*. 2004;71(suppl 2): S4–S10.

41. Lu NZ, Shlaes TA, Gundlah C, et al. Ovarian steroid action on tryptophan hydroxylase protein and serotonin compared to localization of ovarian steroid receptors in midbrain of guinea pigs. *Endocrine*. 1999;11:257–67.
42. Bethea CL, Lu NZ, Gundlah C, et al. Diverse actions of ovarian steroids in the serotonin neural system. *Front Neuroendocrinol*. 2002;23:41–100.
43. Chakos M, Roy M, Dargani N. Selective benefit of estrogen augmentation in persistently symptomatic schizophrenic women: occurs in treatment with second generation antipsychotics, but not with first generation antipsychotics. *Schizophr Bull*. 2007;33:425.
44. Kulkarni J, Sheppard S, White S, et al. The estrogen 100. *Acta Neuropsychiatr*. 2006;18:258–259.
45. Fink G, Sumner B, Rosie R, et al. Androgen actions on central serotonin neurotransmission: relevance for mood, mental state and memory. *Behav Brain Res*. 1999;105:53–68.
46. Batrinos ML. Testosterone and aggressive behavior in man. *Int J Endocrinol Metab*. 2012;10:563–568.
47. Benmansour S, Privratsky AA, Adeniji OS, et al. Signaling mechanisms involved in the acute effects of estradiol on 5-HT clearance. *Int J Neuropsychopharmacol*. 2014;17:765–777.
48. Lee MA, Jayathilake K, Sim MY, et al. Decreased serotonin 2C receptor responses in male patients with schizophrenia. *Psychiatry Res*. 2015;226: 308–315.
49. Evans D. *Placebo: The Belief Effect*. London: HarperCollins; 2003.
50. Kemp AS, Schooler NR, Kalali AH, et al. What is causing the reduced drug-placebo difference in recent schizophrenia clinical trials and what can be done about it? *Schizophr Bull*. 2010;36: 504–509.
51. Bugarski-Kirola D, Wang A, Abi-Saab D, et al. A phase II/III trial of bitopertin monotherapy compared with placebo in patients with an acute exacerbation of schizophrenia—results from the CandleLyte study. *Eur Neuropsychopharmacol*. 2014;24: 1024–1036.
52. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373:31–41.
53. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Eng J Med*. 2001; 344:1594–1602.