Adjunctive Pregnenolone Ameliorates the Cognitive Deficits in Recent-Onset Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Purpose: This study aimed to examine the effect of add-on treatment with the neurosteroid pregnenolone (PREG) on neurocognitive dysfunctions of patients with recent-onset schizophrenia (SZ) and schizoaffective disorder (SA). **Method:** Sixty out- and inpatients that met *DSM-IV* criteria for SZ/SA were randomized to an 8-week, double-blind, randomized, placebo-controlled, 2-center trial. Participants received either pregnenolone (50 mg/d) or placebo added on to antipsychotic medications. Computerized Cambridge Automated Neuropsychological Test Battery measures were administered at baseline and after 4 and 8 weeks of treatment. ANOVA and paired t- or z-tests were applied to examine between- and within-group differences over time. **Results:** Compared to placebo, adjunctive PREG significantly reduced the deficits in visual attention measured with the Matching to Sample Visual Search task (p=0.002), with moderate effect sizes (d=0.42). In addition, a significant improvement was observed from baseline to end-of-study with respect to the visual (p=0.008) and sustained attention (Rapid Visual Information Processing, p=0.038) deficits, and executive functions (Stockings of Cambridge, p=0.049; Spatial Working Memory, p<0.001) among patients receiving PREG but not among those receiving placebo (all p's>0.05). This beneficial effect of PREG was independent of the type of antipsychotic agents, gender, age, education, and illness duration. **Conclusions:** Pregnenolone augmentation demonstrated significant amelioration of the visual attention deficit in recent-onset SZ/SA. Long-term, large-scale studies are required to obtain greater statistical significance and more confident clinical generalization.

Trial Registration: clinicaltrials.gov Identifier: NCT00847600.

Key Words: Recent-Onset Schizophrenia, Schizoaffective Disorder, Pregnenolone, Clinical Trial

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Introduction

Neurocognitive symptoms or impairments are core presentations of schizophrenia (SZ) and schizoaffective disorder (SA). These symptoms commonly affect visual perception, attention, memory and executive functions and interfere with quality-of-life and functional outcomes (1-3). Although neurocognitive impairments have long been considered core features in patients with SZ, effective treatment has remained an elusive goal. It is known that disturbances in inhibitory gamma-aminobutyric acid (GABA)-mediated or excitatory glutamate-mediated neurotransmission may contribute to the neurocognitive impairments of SZ/SA (e.g., [4]). A

Clinical Implications

This study revealed that adjunctive pregnenolone significantly ameliorated visual attention deficits in comparison to placebo among patients with recent-onset schizophrenia (SZ) and schizoaffective disorder. Owing to concerns regarding clinical versus statistical significance, larger studies should be conducted to establish the potential utility of the treatment. In further studies, differentiating between responses of patients with chronic SZ vs. drug naive first-episode patients and controlling for the effect of different antipsychotic drugs on neurosteroid levels would also yield interesting information.

current model for the pathophysiology of SZ states that N-methyl-D-aspartate (NMDA) receptor hypofunction leads to a dysregulation of GABA fast-spiking interneurons, consequently disinhibiting pyramidal glutamatergic output and disturbing signal-to-noise ratio (5).

Neurosteroids such as pregnenolone (PREG), dehydroepiandrosterone (DHEA), and their sulfates (PREGS, DHEAS) are produced in adrenal glands, gonads, and in situ in the brain (6). These brain neurosteroids showed memory-enhancing properties in aged rodents, elderly humans, and in adults with chronic SZ/SA disorders (7-10).

Several lines of evidence suggest functional interrelationships between neurosteroids and cognitive processes. For example, the neurosteroids PREGS and DHEAS exert their pharmacological effects by modulating $GABA_A$ (type A), AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid), and NMDA receptors (11-14). It has been well established that PREGS is a negative modulator of the $GABA_A$ receptor (15) and a positive modulator of the NMDA receptor (16). Furthermore, peripheral and central administrations of neurosteroids have been implicated as powerful modulators of the basal forebrain and brainstem projection cholinergic neurons, which are related to cognitive processes (17, 18).

Alterations in neurosteroids (PREG and its metabolites) may be involved in the pathophysiology of schizophrenia, mood disorders, dementia and substance abuse (see e.g., [19]). For example, clinical studies demonstrated low circulating levels of PREG in SZ (20), major depression (21), anxiety disorder (22), and dementia (23). Emerging preclinical and clinical evidence suggests that PREG may be a promising novel therapeutic candidate in SZ (e.g., [24, 25]). Two pilot clinical trials revealed contradictory findings regarding the effects of PREG augmentation on neurocognitive impairments. In particular, in an 8-week, randomized, placebo-controlled, add-on trial of chronic SZ patients (44 patients completed the trial), 30 mg/d of PREG improved visual attention deficits (Matching to Sample Visual Search task [MTS]) and memory (Delayed Match to Sample task [DMS]) (26). However, in another 8-week, placebo-controlled, add-on, pilot trial of PREG (fixed escalating doses to 500 mg/day) in 9 patients with schizophrenia (9 in placebo group), PREG and placebo did not differ in effects on the neurocognitive impairments that were measured with the Brief Assessment of Cognition in Schizophrenia and the MATRICS Consensus Cognitive Battery (25).

We conducted a randomized, double-blind, placebo-controlled study using a sample of 60 patients with recent-onset SZ/SA. Add-on PREG (50 mg/d) for 8 weeks was associated with significant improvement in negative symptoms compared with placebo (27). This report presents the effect of add-on PREG on neurocognitive symptoms among patients with recent-onset SZ/SA.

Methods

Study Design

We undertook an 8-week, randomized, double-blind, placebo-controlled study that was initiated by the investigators and was conducted between February 2008 and January 2011, independent of any commercial entities. Our objective was to determine whether PREG ameliorates severity of neurocognitive dysfunctions among patients with SZ/SA.

For inclusion in the study, patients were required to be between the ages of 18 and 40 years (inclusive) and meet criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (28) for a diagnosis of paranoid schizophrenia or schizoaffective disorder and suboptimal response to previous treatment, which was defined by two criteria used in the clinical trials (29): 1) persistent positive symptoms (hallucinations, delusions, or marked thought disorder) after at least 6 continuous weeks of antipsychotic treatment; and, 2) a poor level of functioning over the past 2 years, defined by the lack of competitive employment or enrollment in an academic or vocational program. In addition, patients were required to have: 1) duration of illness *less than 5 years* since onset of first-psychotic episode, which was established based on the first visit to a psychiatrist; 2) a score of at least 3 on the Clinical Global Impression Scale (CGI-S) (30) at entrance to the study; 3) at least two weeks of ongoing treatment with their current antipsychotic medication before the pre-treatment stabilization period; 4) stable symptoms throughout the 2-week pre-treatment stabilization period, with no more than a 20% change in the Positive and Negative Syndrome Scale (PANSS) (31) total score; 5) no change in anticholinergic benzodiazepine, or mood sta-

bilizer medications during the pre-treatment stabilization period, as well as no change in antipsychotics, anticholinergics, benzodiazepines, or mood stabilizers during the 8-week duration of the study; and, 6) ability to participate fully in the informed consent process, or have a legal guardian able to participate in the informed consent process.

Major exclusion criteria included: an unstable medical condition, any significant medical or neurological illnesses, pregnancy, treatment with any steroid or hormonal supplement (e.g., estrogen), and substance abuse and/or dependence. A urine drug screen test was used at baseline assessment to detect illegal substances. The absence of medical or neurologic illnesses was verified by means of a routine laboratory investigation that included differential blood cell counts, liver function tests, glucose and cholesterol levels, physical and neurologic examinations, reports of the patient's family physician, and medical records. It was forbidden to add any other psychoactive medication before entry or during the entire study period.

Prior to starting the study, all subjects provided written informed consent after receiving a full explanation regarding the nature of the study and its potential risks and benefits. The Institutional Review Boards of the two participating centers and the national Ministry of Health Ethical Review Board approved the study.

Participants

Participants were recruited from the inpatient and outpatient services of two large state referral hospitals—Sha'ar Menashe Mental Health Center and Tirat Carmel Mental Health Center—affiliated with the Rappaport Faculty of Medicine, Technion-Israel Institute of Technology (Haifa). Recruitment was initiated in February 2008, ended in November 2010, and the last patient completed treatment in January 2011.

All participants had received an antipsychotic medication for at least three months. At baseline, 24 patients were treated with first-generation antipsychotics (FGAs; chlorpromazine, haloperidol, haloperidol decanoate, perphenazine, zuclopenthixol, zuclopenthixol decanoate, fluphenazine decanoate); 23 patients were treated with second-generation antipsychotics (SGAs; risperidone, olanzapine, quetiapine, ziprasidone, clozapine); and, 13 patients received both types of antipsychotic medications (combined therapy; COMB). Chlorpromazine equivalent (CPZ) doses were calculated based on published data (32, 33). The mean CPZ (±SD) in the FGA group was 443 (±101) mg/day, in the SGA group 392 (±84) mg/day, and in the COMB therapy group 493 (±109) mg/day. Besides antipsychotic medications, the patients continued to take the mood stabilizers (n=14; valproate, carbamazepine, lamotrigine), benzodiazepines (n=19), anti-Parkinson agents (n=33), and antidepressants (n=3) that they received prior to study recruitment.

Study Procedure and Treatment

At the initial screening visit, a thorough clinical and psychiatric examination was performed on patients who met entry criteria. Severity of the disorder and symptoms was evaluated with the CGI-S and the PANSS. Senior psychiatrists (M.S.R., and A.K.) at each site enrolled and established patients' diagnoses according to *DSM-IV* criteria.

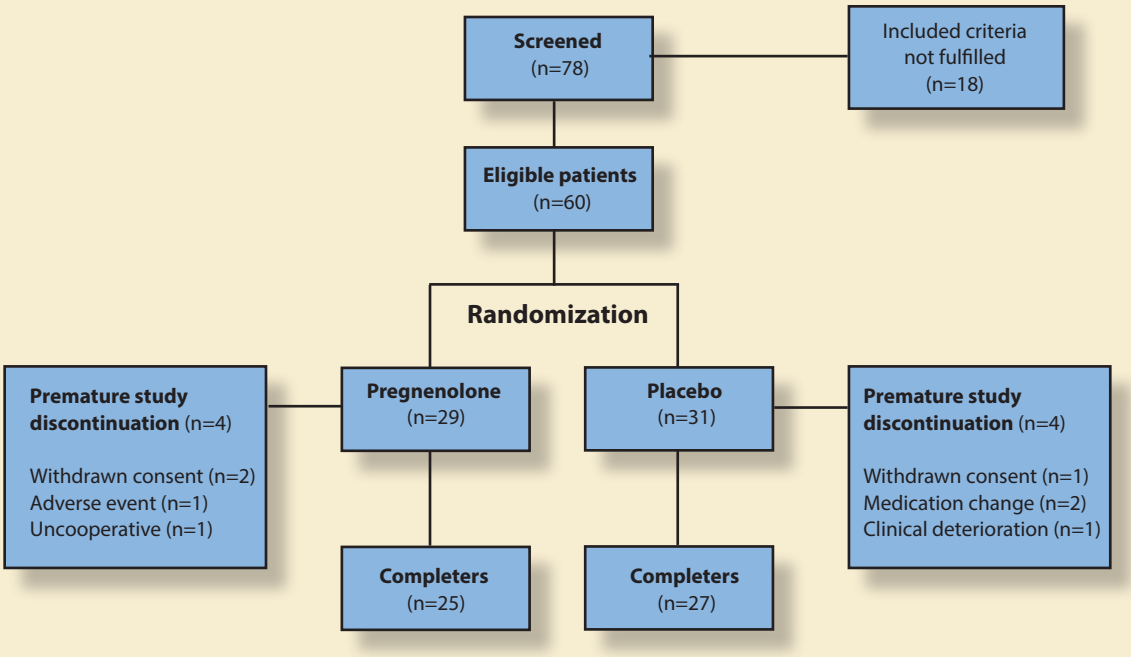
Patients who were clinically stable for the two weeks of the *lead-in phase* (with no more than a 20% change in PANSS total score) were randomized into 2 groups: patients who received PREG and patients who received a placebo, each for 8 weeks in a double-blind manner. The randomization procedure was performed using Random Allocation Software (Version 1.0, May 2004; available at: http://mahmoodsaghaei.tripod.com/Softwares/randalloc.html). We used a low PREG dose (50 mg/day; Biosynergy, Boise, Idaho), taking into account findings from a previous study of the use of PREG (30 mg/day) in schizophrenia, which showed safety and efficacy at a low dose of PREG (12). Patients who received 200 mg/day (26) and a fixed escalating dose up to 500 mg/day (25) of PREG did not show significant improvement in clinical and cognitive domains.

Follow-up visits for psychiatric and safety assessments were conducted at weeks 2, 4, 6, and 8. Adherence was assessed via verbal report from patients, nurses, and relatives concerning the percentage of doses taken as prescribed. This was believed to be sufficiently accurate given the voluntary basis and cooperative atmosphere of the study.

Outcome Measures

Neuropsychological assessment, a secondary endpoint, was conducted with the computerized Cambridge Automated Neuropsychological Test Battery (CANTAB) (34, 35). The CANTAB battery tasks were run on an IBM-compatible personal computer with a touch-sensitive screen. Participants' performance was tested in six tasks in particular: for assessment attention (MTS=Matching to Sample Visual Search, number correct; RVP=Rapid Visual Information Processing, sustained attention, total hits); visual memory (DMS=Delayed Matching to Sample, total correct; PRM=Pattern Recognition Memory, number correct); and, executive functions (SOC=Stockings of Cambridge, SOC, initial thinking time; SWM=Spatial Working Memory, SWM, strategy). For description of the nature of CANTAB tasks, the performance measures used and how the task scores are derived, see http://www.cantab.com/cantab-tests.asp. CANTAB measures were conducted at baseline and after 4 and 8 weeks of treatment (or at discontinuation of treat-

Figure 1 Patient Flow through the Study



ment). Performance of neurocognitive tasks was presented using the standard z-score, which is given as the number of standard deviations (SD) from the mean performance computed relative to an extensive database of raw scores for normal, healthy adult subjects matched by age and sex. Z-scores were calculated by the CANTAB program on the basis of the extensive normative database included in CANTAB. A negative z-score value indicates poorer than average performance.

Statistical Analysis

Patients who completed the study to its last scheduled visit were included in the statistical analysis. Statistical analysis was performed using NCSS (the Number Cruncher Statistical Systems [36]). Continuous variables were compared using the two-tailed t-test, or the Wilcoxon signed-rank test (z) for assessing the difference in medians. Differences in the frequency of categorical variables were examined with the chi-square test (χ^2). For all analyses, the level of statistical significance was defined as an alpha less than 0.05.

Effects of PREG administration on the CANTAB measures were determined by analysis of variance (ANOVA). The linear ANOVA model 2 × 3 included the two treatment arm effects (pregnenolone versus placebo) by time (3 visits: at baseline, 4 and 8 weeks). In addition, we used ANOVA model 2 × 3 × 2 (with the gender effect), or model 2 × 3 × 3 (type of antipsychotic agents, FGAs/SGAs/COMB), or controlling age and education (years). Post hoc analysis was carried out in cases of significant outcomes, using the Tukey-Kramer method. Paired t- or z-tests were applied to examine within-group changes over time. In addition to the linear ANOVA model, we also evaluated a mixed model (also known as a hierarchical linear model), which revealed similar findings in this sample (27).

An effect size (Cohen's d) was calculated for raw scores of outcome variables at the last examination (week 8) for between-group comparisons by the estimated pooled standard deviation (SD). A small effect size was defined as d≥0.2, a moderate effect size as d≥0.5, and a large effect size as d≥0.8 (37).

Results

Characteristics of the Groups

Of 78 screened subjects with ongoing residual symptoms, 18 patients did not enter the study. Two subjects were excluded due to organic brain damage, and 5 patients due to comorbidity with substance abuse; 4 patients had serious medical illnesses, and 7 patients did not agree to participate (see Figure 1).

Table 1 Baseline Characteristics of the Population Being Sampled and Patients Completing the Clinical Trial

	Patients Completing the Clinical Trial					
	Pregnenolone (N=25)		Placebo (N=27)		Significance	
Baseline Values of Variables	Mean	SD	Mean	SD	t (z)	P
Age (years)	26.9	5.2	27.8	6.0	0.6	0.58
Education (years)	11.3	1.4	11.4	2.2	0.2	0.80
Age of onset (years)	24.7	5.0	23.9	5.5	0.5	0.60
Number of admissions	2.6	1.5	2.9	1.7	0.8	0.44
Duration of illness (years)	2.5	1.4	2.8	1.5	0.7	0.50
CGI-S score	3.4	0.8	3.5	0.7	0.6	0.56
PANSS total score	58.2	11.9	63.7	10.5	0.8	0.45
Negative scale score	15.6	3.3	16.7	2.8	0.9	0.36
Positive scale score	13.2	2.9	14.4	3.1	0.3	0.74
General scale score	30.2	6.7	31.3	5.6	0.8	0.32
SANS total score	34.9	7.0	34.0	6.4	1.1	0.24
GAF score	59.3	12.5	58.1	7.1	0.3	0.76
ESRS score	5.6	3.9	6.8	5.9	0.8	0.43
Gender (male/female)*	22/3		23/4		χ^2=0.08, df=1, p=0.77	
Married	12.0%		14.8%		χ^2=1.3, df=1, p=0.76	
Schizophrenia, paranoid type	15	60.0%	19	70.4%	χ^2=0.62, df=1, p=0.43	
Schizoaffective disorders	10	40.0%	8	29.6%		
Antipsychotic drugs: FGAs/SGAs/COMB†	10/8/7		9/13/5		χ^2=1.5, df=2, p=0.47	

*Single=never married, separated, divorced, and widowed †All participants had received an antipsychotic medication for at least three months: first-generation antipsychotics (FGAs: chlorpromazine, haloperidol, haloperidol decanoate, perphenazine, zuclopenthixol, zuclopenthixol decanoate, fluphenazine decanoate); second-generation antipsychotics (SGAs: risperidone, olanzapine, quetiapine, ziprasidone, clozapine); and, both types of antipsychotic medications (combined therapy: COMB).

Sixty patients with a suboptimal response to antipsychotic agents were randomized. Baseline characteristics of the population sampled and patients completing the clinical trial are presented in Table 1. Fifty-two patients (7 women and 45 men) completed the trial. Of the 8 subjects who dropped out, 4 patients received PREG and 4 patients received placebo. More specifically, 3 patients from the PREG group and 1 patient from the placebo group dropped out during the first 2 weeks of the study. Another 4 patients (1 patient from the PREG group and 3 patients from the placebo group) dropped out between the 4th and 6th weeks. Reasons for dropping out were not related to the PREG or placebo administration: three patients withdrew consent, two patients had a change in antipsychotic drugs, one patient dropped out because of clinical deterioration, one patient because of an extrapyramidal adverse event, and one more due to noncompliance. There were no notable imbalances between the two treatment groups (PREG=25 and placebo=27) in the baseline characteristics, or between the 52 completers and the 8 noncompleters.

Thirty-four of 52 patients met the criteria for paranoid type of schizophrenia and 18 for schizoaffective disorders. Overall, among the completers there were no notable imbalances between the two treatment groups (PREG=25 and placebo=27) in age, gender, marital status, age of illness onset, number of hospital admissions, illness duration, distribution of diagnoses, or antipsychotic drugs. Seven female subjects completed the trial and had no disturbances in their menstrual cycles.

Table 2 CANTAB Mean Z-Scores Ratings of Participants Who Completed this Trial at Baseline and after 8 Weeks of Treatment

Cognitive Domains	Cognitive Tasks		Placebo (N=27)			Pregnenolone (N=25)			Significance Between-Group Differences			
									Baseline		Throughout the Trial ANOVA (df=2,133)	
			Baseline	Week 8	t (z) p	Baseline	Week 8	t (z) * p	t /z	p	F	p
Visual Memory	DMS	N	25	24		24	23					
		Mean	-1.0	-0.2	**3.3**	-1.4	-0.2	**2.4**	0.7	0.50	0.5	0.49
		SD	1.1	1.6	**0.004**	1.3	1.3	**0.028**				
	PRM	N	26	25		25	24					
		Mean	-1.0	-0.87	0.5	-0.99	-1.0	0.1	0.2	0.87	0.01	0.93
		SD	1.5	1.6	0.62	1.1	1.1	0.94				
Attention	MTS	N	25	25		25	23					
		Mean	-0.35	-0.17	1.4	-0.69	-0.34	**2.9**	1.8	0.061	9.2	**0.002**
		SD	0.5	0.3	0.074	1.1	0.4	**0.008**				
	RVP	N	25	24		24	23					
		Mean	-1.7	-1.5	0.7	-1.2	-0.6	**1.8**	1.7	0.092	3.7	0.052
		SD	1.2	1.1	0.47	0.9	1.2	**0.038**				
Executive Functions	SOC	N	22	22		23	21					
		Mean	1.0	1.5	1.5	0.52	1.2	**1.6**	1.4	0.15	1.1	0.28
		SD	0.4	3.2	0.071	1.4	1.2	**0.049**				
	SWM	N	24	25		25	23					
		Mean	-0.22	0.19	2.1	-0.39	0.26	**4.0**	0.9	0.39	0.9	0.33
		SD	0.7	0.9	0.051	0.9	0.9	**<0.001**				

*Significance of the within-group differences. DMS=Delayed Matching to Sample (total correct); PRM=Pattern Recognition Memory (number correct); MTS=Matching to Sample Visual Search (number correct); RVP=Rapid Visual Information Processing (total hits); SOC=Stockings of Cambridge (initial thinking time); SWM=Spatial Working Memory (strategy). N=number of subjects who were able to complete specific tasks in the CANTAB.

Pregnenolone Ameliorates the Visual Attention Deficits

Table 2 presents the CANTAB mean z-scores of participants who completed this trial at baseline and after 8 weeks of treatment. At baseline, neurocognitive performance of the patients showed pronounced neurocognitive impairment in various cognitive domains, including attention (MTS, PRV), memory (DMS, PRM), and executive function (SWM). No significant differences in the performance of CANTAB tasks at baseline assessment between two treatment groups were observed (all p values >0.05).

Compared to placebo, adjunctive PREG significantly reduced the deficits in visual attention measured with the Matching to Sample Visual Search task (MTS; p=0.002), with moderate effect sizes (d=0.42, 95% CI: from -1.01 to 0.17). The mean (±SD) z-score reduced on the MTS task throughout the trial in the PREG group (on 0.53±0.38 scores, t=2.9, p=0.008) was significantly greater than those in the placebo group (z-score changed on 0.18±0.17 scores, z=1.4, p=0.074). In addition, CANTAB also demonstrated between-group differences in performance on the Rapid Visual Information Processing task (sustained attention) that did not reach a significant level ($F_{2,133}$=3.7, p=0.052; effect size d=0.37, 95% CI: from -0.22 to 0.96). A significant improvement was observed in the PREG group from baseline to end-of-study with respect to sustained attention (p=0.038) deficits, but not among those receiving placebo (p=0.47).

No significant between-group differences in the memory (DMS, PRM) and executive functions (SOC, SWM) were observed throughout the trial time (all p's>0.05). After Bonferroni corrections for the six cognitive measures (p=0.05/6=0.008), between-group differences on the MTS task (p=0.002) remained significant.

Paired t- (z-) tests were applied to examine within-group changes over time. For the PREG sample—in addition to MTS and RVP—there were significant improvements from baseline to end-of-study with respect to executive functioning (SOC, z=1.6, p=0.049; SWM, t=4.0, p<0.001) but not among patients who received placebo (all p's>0.05). For both

groups there were no significant improvements on the PRM task, though significant improvement was observed on the DMS task ($p<0.05$). The type of the antipsychotic agents (FGAs, SGAs, and COMB), gender, age, education, and illness duration did not show a significant effect on within- and between-group differences in cognitive performance.

Discussion

In this study, we investigated the effect of adjunctive PREG compared to placebo on cognitive impairments using a sample of patients with recent-onset SZ/SA in an 8-week, randomized trial. The main results of this study are:

1) compared to the placebo group, adjunctive PREG significantly ameliorated *visual attention deficit* as assessed by the CANTAB's MTS task ($p=0.002$), with a moderate effect size ($d=0.42$, 95% CI: from -1.01 to 0.17);

2) a significant positive effect of adjunctive PREG was observed from baseline to end-of-study with respect to the executive functioning (SOC and SWM tasks), but not among patients who received placebo; and,

3) the ameliorative effect of PREG on cognitive performance was independent of effects of age, gender, type of antipsychotics (FGAs, SGAs, and COMB), education, and short illness duration among patients with recent-onset SZ/SA.

Findings from the present study are consistent with improvement in visual attention deficits (measured with MTS task) of chronic patients with SZ/SA who were treated with 30 mg/d of PREG (26). Furthermore, add-on DHEA—an active metabolite of PREG—improved a sustained attention (RVP) task of chronic patients with SZ/SA throughout a randomized, double-blind, placebo-controlled, crossover trial (9).

The mechanisms by which oral add-on PREG might exert its effects on cognitive dysfunctions have not been clearly elucidated in the scientific literature. While it remains poorly understood at this stage what precisely may account for PREG's influence on cognitive improvement, various aspects of the involvement of PREG and its sulfate in neurophysiological function should be considered.

First of all, one possibility is through an effect of elevated circulating PREG levels. Pregnenolone and its neuroactive metabolites (PREGS, DHEA, DHEAS, progesterone, allopregnanolone) have modulatory effects on the release of multiple neurotransmitters. There are data demonstrating that adjunctive PREG and DHEA administration significantly elevates the serum levels of PREG and DHEA (25, 26), which are associated with sustained attention, visual memory tasks, and executive functions (38). More specifically, PREG may act as a potential signaling molecule for neocortical organization and through modulation of the $GABA_A$, NMDA, and sigma-1 receptors (6, 11, 12), and cholinergic (8, 18) and dopamine systems (39).

Second, PREG, PREGS, and DHEA regulate the growth of neurons and cerebral brain-derived neurotrophic factor (BDNF) levels, enhance the myelination and synaptogenesis in the CNS, and produce neuroprotective properties (40, 41). Although we do not have any definitive explanation for the mechanisms underlying the beneficial effects of the addition of neurosteroids to antipsychotics, it may be hypothesized that the neuromodulatory effects of PREG are relevant to the clinical activity, as was demonstrated for clozapine (42).

Third, a glutamatergic model may be useful for understanding the effects of PREG administration on cognitive symptoms. According to the glutamatergic model of schizophrenia, psychotic and neurocognitive symptoms—similar to those of schizophrenia—emerge by blocking neurotransmission at NMDA-type glutamate receptors (43). In preclinical studies, memory-enhancing effects of PREGS and DHEAS have been attributed to their NMDA-agonistic properties (44, 45). PREGS can act via nongenomic mechanisms by binding to the NMDA and $GABA_A$ receptors to enhance neuronal excitability (46). Additional evidence has accumulated supporting the ability of PREGS to enhance long-term potentiation by accentuating the activity of NMDA receptors (13).

Next, evidence from lesioning studies and neuroimaging has linked attention deficits and decision-making to dysfunctions of the prefrontal, right parietal and temporal cortex (47-49) and the hippocampus (50). Most neurosteroids, including PREG and its metabolites (PREGS, DHEA, and DHEAS), have been shown to be produced in the hippocampal formation and have exhibited *modulatory effects* on brain functions (19, 51). Neuromodulators that alter the balance between lower-frequency glutamate-mediated excitatory and higher-frequency GABA-mediated inhibitory synaptic transmission are likely to participate in core mechanisms for CNS function and may contribute to the pathophysiology of neurological disorders such as SZ and Alzheimer's disease. For instance, PREGS modulates both ionotropic glutamate and $GABA_A$ receptor-mediated synaptic transmission (52). Although the exact pathophysiology of schizophrenia is unknown, the NMDA receptors have received great attention since they play a critical role in synaptic plasticity associated with learning and memory, as well as cortical plasticity and maturation (53). PREGS acts as a cognitive enhancer by enhancing NMDAR activity, and may participate in the reduction of schizophrenia's negative symptoms by systemic pregnenolone (54). Furthermore, Marx et al. (42) demonstrated that serum PREG levels are closely correlated with hippocampal PREG levels in rats. PREGS infused into the

medial septum nucleus increases hippocampal acetylcholine and spatial memory in rats (55). Likewise, cerebrospinal fluid PREG levels are positively correlated with temporal cortex PREG levels ($r=0.57$, $p<0.0001$) in patients with Alzheimer's disease (56).

Another possibility is that, although the molecular mechanisms of neurodegeneration and pathogenesis of schizophrenia remain largely unknown, a significant body of literature indicates that the main mechanisms implicated in the disease process may include oxidative stress and inflammation. Oxidative stress or a disturbance in the pro-oxidant–antioxidant balance in favor of the former—leading to potential damage (57, 58)—has been suggested to contribute to the pathophysiology of schizophrenia (59-61). Many lines of evidence now support the hypothesis that inflammation-related pathways are involved in the pathophysiology of psychiatric disorders (62, 63). A number of studies have shown anti-inflammatory and antioxidant roles of neurosteroids (64-67). Recently, successful clinical trials were conducted with anti-inflammation adjunctive agents (see review, e.g., [68]).

The present findings should be considered cautiously. The relatively modest sample size of this trial should be carefully examined before generalizing the findings to other groups. It would be important in the future to investigate benefits of neurocognition over a longer period of time following PREG administration in order to explore whether improvement in neurocognition progresses over time. Long-term, large-scale studies are required to obtain greater statistical significance and more confident clinical generalization. The population enrolled was 87% male. The sex prevalence of SZ is approximately equal, and yet clinical trials of new therapeutic drugs have been conducted, for the most part, with male participants. Based on 67 published clinical trials, the median percentage of women in the total sample was 33.3%, the minimum was 6.7%, and the maximum was 71.2% (69). The increasing shift toward outpatient rather than inpatient drug trials may help to increase the proportion of women.

In conclusion, the present study revealed that adjunctive PREG significantly ameliorated visual attention deficits in comparison to placebo among patients with recent-onset SZ/SA. Owing to concerns regarding clinical versus statistical significance, larger studies should be conducted to establish the potential utility of the treatment. In further studies, differentiating between responses of patients with chronic SZ vs. drug naive first-episode patients and controlling for the effect of different antipsychotic drugs on neurosteroid levels would also yield interesting information.

Statement of Interest

None of the authors have any conflicts of interest to report.

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