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ORIGINAL RESEARCH

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

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The serotoninergic system as a target for add-on treatment seems to be a promising approach in patients with schizophrenia.

Objective. To clarify if selective 5HT-6 antagonist AVN-211 (CD-008-0173) adds clinical and cognitive effects to stable antipsychotic treatment.

Methods. A randomized, double-blind, placebo-controlled, add-on, 4r-week trial in 47 schizophrenia patients (21 patients receiving study drug and 26 receiving placebo) who were stabilized on antipsychotic medication was performed. Seventeen patients from the study drug group and 25 patients from the placebo group completed the trial. Treatment effects were measured using clinical rating scales and attention tests.

Results. With no differences at baseline, there was a significant difference between the groups in Positive and Negative Syndrome Scale (PANSS) positive subscale score ($p = 0.058$) in favor of patients in the treatment group at the endpoint. The PANSS positive subscore ($p = 0.0068$) and Clinical Global Impression–Severity (CGI-S) ($p = 0.048$) score significantly changed only in the treatment group. Only in the placebo group were significant changes in Calgary Depression Rating Scale (CDRS) total score registered. The indices of attention tests at endpoint did not show differences between the groups, with the exception of the scope of change in the results of the subtest VIII of the Wechsler Adult Intelligence Scale (WAIS), which showed difference between the groups ($p = 0.02$) and was significantly larger in the treatment group. Only inside the study drug group, significant changes in selectivity and continuous attention were observed regarding total correct responses ($p = 0.0038$) and reaction time ($p = 0.058$) in the Continuous Attention Task (CAT) test.

Conclusion. Selective 5HT6 antagonist AVN-211 (CD-008-0173) added antipsychotic and some procognitive (attention) effects to antipsychotic medication.

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Key words: 5HT6 receptor antagonist, add-on, clinical effects, schizophrenia.

Introduction

It is a well-established fact that the existing antipsychotic treatment is more effective against acute psychotic and disorganized symptoms than other psychopathological features of schizophrenia.[1–7] Some studies have demonstrated a direct positive effect of antipsychotic treatment on cognitive dysfunction in schizophrenia, but only in the attention domain.[8–10] Data on the effect produced on other domains are contradictory.[11–13] According to Kane,[14] the level of diverse residual psychopathology, including both residual positive, negative, and cognitive disorders, is a critical factor in determining the long-term therapeutic strategy.

Over the last several years, researchers have repeatedly tried to find a way to expand the profile of therapeutic action of antipsychotics through pharmacological agents

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complimentary to treatment targets other than the dopaminergic system.[15–27] Hypotheses about the role of the serotonin system in the development of various mental disorders[28–31] continue to be relevant. Of recent special interest is one of the serotonergic system structures—the type 6 serotonergic receptors (5-HT6), which are localized primarily in the central nervous system (CNS), particularly in the limbic region.[32] 5-HT6 receptor antagonists have been shown to modulate multiple neurotransmitter systems, the glutamatergic and cholinergic in particular, and therefore to enhance cognition in preclinical studies.[33–36]

It is generally assumed that 5-HT6 receptors may be involved in the pathogenesis of psychosis, cognitive functioning, learning, convulsive disorders, sleep disorders, and appetite control.[34,37] Many antipsychotics and antidepressants have a high affinity to 5-HT6 receptors.[38]

The positive results of the phase II study of the effects of the 5-HT6 receptor antagonist SGS 518 on cognitive dysfunction in 20 patients with schizophrenia were published.[39] In the study of LuAE8054 adding of the study drug to donepezil showed better efficacy of the combined treatment vs donepezil alone in patients with Alzheimer's disease.[40]

Our attempts to treat schizophrenic patients in the period of transition from acute psychosis to remission with non-selective 5-HT6 receptor antagonist dimebon[41] as an add-on to risperidone treatment revealed that dimebon has a positive impact on negative symptoms and some aspects of cognitive functioning.[19]

The data mentioned above underpin our objective in the present study to evaluate the effects of a highly selective 5-HT6 receptor antagonist on residual symptoms and attention in patients with schizophrenia.

Materials and Methods

The study, entitled "Double Blind Placebo-Controlled Pilot Phase IIa Study of Efficacy and Safety of Orally Administered AVN-211 (CD-008-0173) in Stable Patients with Schizophrenia Receiving Stable Antipsychotic Treatment," was conducted in 2010 in outpatient male subjects diagnosed with schizophrenia under *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV) criteria. All patients provided signed a written informed consent form. Clinical study approval was obtained from the Ministry of Health of the Russian Federation (# 404 from 07.10.2009).

AVN-211 (CD-008-0173) is a small molecule, 3-sulfonyl-pyrazolo[1,5-a]pyrimidine (number of international publication WO 2009/093206 A2), MW = 333.44, serotonin receptor antagonist with specifically high activity in respect to 5-HT6 and 5-HT2b (Ki = 2.1 nM and Ki = 125 nM, respectively) AVN 211 (CD-008-0173). Bioavailability of the compound is 24%, and protein binding is 88%. The compound weakly interacts with cytochromes 2C19 P 450.

The compound was tested for anti-amnestic, anxiolytic, and antipsychotic effects in various in vivo models: the passive avoidance test, the Morris water maze test, the elevated plus maze test, and prepulse inhibition of acoustic startle.

The passive avoidance test

Male adult BALB/c mice (24–25 g) were used in the experiments. A passive avoidance cage (Ugo Basile, Italy Comerio VA) was used. On the first day, mice were treated intraperitoneally with pro-amnesic agent scopolamine (0.3 mg/kg) 30 min before training. Independent groups of mice were treated additionally with one of the reference drugs (tacrine, 10 mg/kg, 30 min before training or memantine, 5 mg/kg, 60 min before training) or with AVN-211, which was administered 5 min before training. The control animals were injected with physiological solution. According to the results of the test performed, AVN-211 (CD-008-0173) was more effective than Memantine or Tacrine. The most pronounced effect of AVN-211 (CD-008-0173) was observed in 0.05 mg/kg (i/p) and 0.2 mg/kg (p/o) doses.

The Morris water maze test

Male adult BALB/c mice (24–25 g) were used in the experiments. On every day of testing, mice were treated intraperitoneally with (a) scopolamine (1.5 mg/kg) or (b) scopolamine (1.5 mg/kg) combined with tacrine (3 mg/kg), donepezil (3 mg/kg), or AVN-211 (0.05, 0.2, or 1 mg/kg). Scopolamine was administered 30 min before training, tacrine and donepezil were administered 60 min before training, and AVN-211 was administered 5 min before training. The control group animals were injected with physiological solution. The Morris water maze test AVN-211 (CD-008-0173) (0.05 and 0.2 mg/kg p.o) revealed a pronounced anti-amnestic effect comparable to that of acetylcholinesterase inhibitor donepezil (trade name Aricept).

Elevated plus maze test

Male BALB/c mice weighing approximately 25 g were used in the experiment. Mice were treated with either placebo, buspirone (5 mg/kg, i.p. 30 min before the training), lorazepam (0.05 mg/kg, i.p. 60 min before the training), fenobam (5 mg/kg, 60 min before the training), rufinamide (15 mg/kg, 60 min before the training), or AVN-211 (0.05, 0.2, or 1 mg/kg, i.p. 5 min before the training). Buspirone and lorazepam were administered at the maximum dose; sedative side-effects were not seen at this dose, ie, there was no decrease in general exploratory activity in the test.

Buspirone, lorazepam, fenobam, rufinamide, and AVN-211 (CD-008-0173) (0.05 and 0.2 mg/kg) produced a clear anxiolytic effect in the elevated plus maze test. They significantly increased the number of visits to the open arms of the maze, time spent in the open arms, and decreased the number of defecations. AVN-211 (CD-008-0173), lorazepam, buspirone, fenobam, and rufinamide did not affect locomotor activity, thus their anxiolytic activity does not produce a sedative effect. The most prominent anxiolytic effect was observed in the case of AVN-211 (CD-008-0173) injected i.p. in the doses of 0.01–0.2 mg/kg, lorazepam injected i.p. at the dose of 0.05 mg/kg, and fenobam injected i.p. in the dose of 5 mg/kg.

Prepulse inhibition of acoustic startle

AVN-211 (CD-008-0173) was also tested for antipsychotic effect in the acoustic startle reflex. Naive male SHK, weighing 24–30 g, were used. All experiments were conducted in the light phase of a dark/light cycle. Apomorphine and haloperidol were obtained from Sigma Chemicals (St. Louis, MO, USA). Haloperidol was administered 60 min prior to the testing (volume of injection was 10 mL/kg). Apomorphine was administered s.c. 20 min before the testing (volume of injection was 1 mL/kg.). AVN-211 was administered i.p. 5 min before the testing (volume of injection was 10 mL/kg). The results demonstrated about 53% prepulse inhibition in the placebo group. The propsychotic agent apomorphine reduced this variable, which showed a deterioration of the ability for filtration of sensory signals. Haloperidol (1 mg/kg) and AVN-211 (CD-008-0173) (0.05 and 0.2 mg/kg) prevented the disruptive effect of apomorphine on the startle prepulse inhibition.

AVN-211 (CD-008-0173) was studied in Phase I and Phase Ib in 2–8 mg doses. Both studies demonstrated that AVN-211 (CD-008-0173) was well tolerated, and had a long half-life exceeding 24 hrs. Steady-state plasma concentration was achieved on day 3 of q.d. administration and equaled 13–18 ng/mL. AVN-211 (CD-008-0173) metabolism leads to the formation of 2 metabolites: M1, which is a reversible metabolite and can serve as an AVN-211 (CD-008-0173) plasma depot, and M2 metabolite, which is 3 orders of magnitude less potent than AVN-211 (CD-008-0173).

Twenty-one patients were randomized into the study drug group, and 26 were randomized in the control group. Randomization was performed with the help of randomization tables by the specially assigned independent person, who did not participate in other study procedures. It was a double-blind, placebo-controlled study.

AVN-211 (CD-008-0173) (4 mg) or placebo were administered orally q.d. as comedication to the patients' stable antipsychotic treatment (basic therapy). The basic therapy included mostly risperidone, quetiapine, haloperidol, or zuclopenthixol; in a few cases, the patients' current therapy included paliperidone, olanzapine, sulpiride, flupentixol, chlorpromazine, trifluoperazine, perphenazine, levomepromazine, or chlorprothixene.

Key inclusion criteria included willingness to give written informed consent, age between 18 and 60, male sex, initial diagnosis of schizophrenia according to DSM-IV, Positive and Negative Syndrome Scale (PANSS) remission criteria (fewer than 80 points overall, 3 or fewer points in 2, 3, 4, and 6 positive subscale symptoms), stable antipsychotic treatment (constant therapy with one antipsychotic drug without changing the dose during the last 2 months or more), and pronounced disorders of selective attention. The study included patients with attention test results that were lower than the lower limit of normal level of performance. Six patients were excluded after the screening due to failure to fulfill this requirement.

Positive and Negative Syndrome cale (PANSS),[42] Clinical Global Impression–Severity (CGI-S),[43] Clinical Global Impression–Improvement (CGI-I),[43] Negative Symptoms Assessment (NSA-16),[44] and Calgary Depression Rating Scale (CDRS)[45] were used as tools to study the possible influence of AVN-211 (CD-008-0173). A battery of 5 attention tests was chosen for the evaluation of attention and its properties (switching, volume, concentration, productivity, stability, resistance, fatigue, selectivity, and errors of attention). Other considerations our choice of tests were the duration of testing (16–23 min) and the possibility of obtaining quantitative results for statistical evaluation. Clinical assessment and psychological testing were performed by qualified and certified clinicians and clinical psychologists, respectively, whose inter-rater reliability was previously established. One patient dealt with the same clinician and the same psychologist throughout the study.

The mean age of participants at baseline was 36.16 ± 10.4 years (see Table 1). In the group receiving the study drug, the mean age was 34.93 ± 9.98 years (with a range of 23–52 years), while in the placebo group the mean age was 37.1 ± 1.8 years (with a range of 19–59 years). The mean age of onset of the disease was 20.2 ± 8.84 years. In the AVN-211 (CD-008-0173) group, this was 21 ± 10.36, while in the placebo group the mean age of onset was 19.62 ± 7.56. Statistically significant differences were observed in neither the first nor the second parameters.

After the patients signed the informed consent form, they were subjected to the screening procedures and then randomized into either the AVN-211 (CD-008-0173) group or the placebo group. Patients received 4 mg of AVN-211 (CD-008-0173) or placebo q.d. in the morning

Table 1. *Tests used in the study and evaluated parameters*

Test	Measures features	Evaluated parameters
Digit Symbol Coding[46]	Psychomotor speed and visual-motor coordination	Raw scores Standard scores
Schulte tables[47]	Shifting and stability	Total time in sec (shifting) Total error Stability attention Fatigability Learning to be attentive
Continuous Attention Task (CAT)[48]	Selectivity and continuous attention	Total correct responses Total false responses Reaction time, msec (correct responses)
Subtest VIII of Wechsler Adult Intelligence Scale (WAIS)[49]	Selectivity	Raw scores Standard scores
Bourdohn test[50]	Productivity, stability, and concentration	Productivity Stability Concentration of attention

Table 2. *Psychometric scores*

PANSS scores	Group	Baseline	Endpoint	P
Positive subscale	AVN-211 (CD-008-0173)	10.8 ± 2.64	9.41 ± 2.53	0.0068
	Placebo	11.72 ± 2.41	10.84 ± 2.46	0.07
Negative subscale	AVN-211 (CD-008-0173)	20.12 ± 6.42	16.06 ± 5.14	0.0072
	Placebo	20.04 ± 5.18	17.68 ± 5.19	0.016
General psychopathology subscore	AVN-211 (CD-008-0173)	31.53 ± 5.55	27.00 ± 5.79	0.014
	Placebo	32.28 ± 4.28	28.52 ± 7.87	0.014
Total PANSS score	AVN-211 (CD-008-0173)	62.53 ± 9.05	52.41 ± 11.27	0.0018
	Placebo	64.08 ± 7.80	57.04 ± 13.98	0.0032
CGI-S	AVN-211 (CD-008-0173)	3.76 ± 0.75	3.24 ± 1.03	0.047
	Placebo	3.84 ± 0.8	3.64 ± 1.04	0.13
CDRS	AVN-211 (CD-008-0173)	3.06 ± 3.13	2.53 ± 2.74	0.59
	Placebo	3.08 ± 3.04	2.36 ± 2.83	0.015
NSA (total score)	AVN-211 (CD-008-0173)	60.65 ± 19.02	51.59 ± 17.51	0.0076
	placebo	68.6 ± 15.51	58.72 ± 15.48	0.003

during a period of 28 days, in addition to their stable antipsychotic monotherapy. The patients had their final visit to the hospital 7 days after the completion of drug administration.

Findings

At the beginning of the trial, there was no difference between the groups either in terms of clinical or cognitive test indices. Seventeen patients from the study drug group (80.95%) and 25 patients from the placebo group (96.15%) completed the study. Four patients from the study drug group prematurely discontinued the trial. The reasons for discontinuation were as follows: 2 patients due to patient decision and 2 due to emerging side effects. In the placebo group, only 1 patient decided to drop out. The mean PANSS score at the beginning of the study in the study drug group was 62.53 ± 9.05, and in the placebo group was 64.08 ± 7.80; this proves that this was a stable patient population. The indices of clinical assessment are presented in Table 2.

The only difference between the groups at endpoint was registered on the PANSS positive subscale score ($p = 0.058$, effect size $d = 0.57$). Intragroup analysis showed that, in the study drug group, there was a difference between the baseline and the endpoint both in the positive and the negative subscale PANSS scores and in CGI-S score, though in the placebo group the difference was observed only in the negative subscale

Table 3. *Results of attention measurements*

Test	Index type	Group	Baseline	Endpoint	P
Digit Symbol Coding (psychomotor speed and visual-motor coordination)	Raw scores	AVN-211 (CD-008-0173)	32.76 ± 13.3	37.71 ± 13.77	0.04
		Placebo	34.96 ± 12.17	38.28 ± 14.03	0.027
	Standard scores	AVN-211 (CD-008-0173)	6.12 ± 2.67	7.00 ± 2.65	0.17
		Placebo	6.8 ± 2.64	7.08 ± 2.87	0.03
Continuous Attention Task (CAT) (selectivity and continuous attention)	Total correct responses	AVN-211 (CD-008-0173)	4.94 ± 1.73	6.5 ± 1.32	0.0038
		placebo	5.6 ± 2.22	6.2 ± 1.63	0.1
	Reaction time, msec (correct responses)	AVN-211 (CD-008-0173)	786.41 ± 209.31	699.81 ± 190.71	0.058
		Placebo	674.66 ± 231.86	682.34 ± 201.47	0.9
Subtest VIII of WAIS ("Missing details")	Raw scores	AVN-211 (CD-008-0173)	12.06 ± 4.44	15.18 ± 4.67	0.0001
		Placebo	13.44 ± 3.79	13.2 ± 4.04	0.001
	Standard scores	AVN-211 (CD-008-0173)	8.82 ± 2.81	11.12 ± 3.3	0.0001
		Placebo	9.88 ± 2.35	11.08 ± 2.71	0.0004
Bourdohn test	Productivity of attention	AVN-211 (CD-008-0173)	502.095 ± 166.14	610.33 ± 200.07	0.008
		placebo	490.14 ± 194.3	569.57 ± 241.33	0.0007

PANSS score (Table 2). The CDRS scores significantly changed only in the placebo group, though positive difference was observed in both groups (Table 2). Analysis of the individual PANSS scores at endpoint revealed a difference in the delusion score in favor of the study drug group ($p = 0.02$). The changes in the delusion score from baseline to endpoint in this group reached the level of tendency ($p = 0.062$), and in the placebo group no changes were observed ($p = 0.78$). Intragroup analysis showed a difference in the set of symptoms that demonstrated changes in severity. In the study drug group, significant changes were observed with regard to grandiosity ($p = 0.03$), blunted affect ($p = 0.04$), difficulty in abstract thinking ($p = 0.0039$), stereotyped thinking ($p = 0.01$). In the placebo group, significant changes were observed with regard to suspiciousness ($p = 0.03$), emotional withdrawal ($p = 0.007$), anxiety ($p = 0.03$), and poor attention ($p = 0.00067$).

Passive/apathetic social withdrawal significantly decreased in both groups (study drug group: $p = 0.027$; placebo group: $p = 0.0027$).

The cognitive indices that showed significant changes in any group are shown in Table 3.

It is notable that the Digit Symbol Coding scores in the placebo group worsened, while no change was observed in the AVN-211 (CD-008-0173) group. Selectivity of attention and continuous attention improved in the AVN-211 (CD-008-0173) group (effect size $d = 0.21$), and showed no change in the placebo group.

In analyzing the magnitude of changes in both groups (differences of cognitive parameter between baseline and endpoint visits), we find that the experimental group showed better results ($p = 0.02$) in Subtest VIII of WAIS. The magnitude of standard score changes was 31.27% ± 26.77% in the AVN-211 (CD-008-0173) group and 12.72% ± 17.24% in the placebo group ($d = 0.84$).

We found that there was no difference between the groups depending on the type of primary pharmacotherapy (typical or atypical antipsychotics) with respect to clinical symptoms (though there was a difference in the results of cognitive tests). By the end of the study, this difference remained for most cognitive tasks in the placebo group, but not in the experimental group.

There was no difference in the total PANSS score between patients who took typical antipsychotics and those who took atypical ones, either at the beginning or at the end of the study, nor was there a difference between the AVN-211 (CD-008-0173) group and the placebo group, or within study groups.

At the beginning of the study those patients who were given atypical therapy (in both groups) demonstrated better results in Digit Symbol Coding ($p = 0.01$), total time ($p = 0.01185$) and "learning to be attentive" (0.03469) in Schulte tables, correct responses' mean reaction time ($p = 0.00409$) and the number of correct responses ($p = 0.00806$) in Continues Attention Task (CAT), attention productivity in the Bourdohn test ($p = 0.01287$) in the beginning of the study. At the end of the study, these differences were intact in the placebo group but were leveled in the AVN-211 (CD-008-0173) group in Digit Symbol Coding, total time and "learning to be attentive" in the Schulte tables, and attention productivity in the Bourdohn test. Differences in the number of correct responses in CAT disappeared in both study groups. The number of incorrect responses in CAT did not differ at the beginning of the study, but

the patients in the placebo group who took typical antipsychotics gave a significantly greater number of erroneous answers ($p = 0.02716$).

The patients who underwent typical antipsychotic therapy with the add-on of AVN-211 (CD-008-0173) revealed more evident positive changes than those receiving combination of typical antipsychotics and placebo in the following parameters: PANSS positive subscale ($p = 0.004$), PANSS negative subscale ($p = 0.03$), and Subtest VIII of WAIS score ($p = 0.03$). There was no difference in the changes of clinical or cognitive parameters between the study groups for patients receiving atypical antipsychotics as primary pharmacotherapy.

Discussion

The 5-HT6 receptor appears to be a prospective pharmacological target for treatment of different CNS diseases. More and more experimental and clinical studies have examined the effects of 5HT6 agonists and antagonists in neurodegenerative diseases, depression, anxiety, and schizophrenia.[38]

The main goal of the present study was to reveal the additional clinical effects of the selective 5HT6 AVN-211 (CD-008-0173) in patients with schizophrenia who were stabilized on the antipsychotic medication. The results showed that AVN-211 (CD-008-0173) improved a significant aspect of functioning of this group of schizophrenia patients regarding residual psychotic symptoms. The most important changes were decrease in the severity of the residual delusions accompanied by a decrease in overall severity of the disease (no changes in CGI-S score in the placebo group and significant changes in the study drug group). Similar data were obtained in the study which showed that the combined treatment of clozapine and aripiprazole had advantages over the monotherapy of clozapine measured by CGI score.[51]

In relation to cognitive dysfunction, this study aimed to assess the impact of the study drug (AVN-211) attention in schizophrenia patients. This aspect of cognitive dysfunction was chosen for two reasons: First, attention was considered to be the only cognitive target for antipsychotic treatment, and second, attention is the most basic cognitive function. Some authors consider that one of the aspects of attention, vigilance, should be tested before all other more complicated functions are examined.[52]

Our attempt to homogenize the group by the level of attention dysfunction and gender was not fully successful, as the individual variability of indices regarding the cognitive tests was still very large. Therefore, it was clear that we needed many more patients to obtain reliable evidence that our pharmacological agent really has an effect on patients' cognition. More significant seem to be the results of CAT, where, even in spite of the relatively small number of patients, we registered significant intragroup changes in respect to selectivity and maintenance of attention. We consider the difference between the groups in the scale of improvement in the results of the Subtest VIII of WAIS ("Missing details") to be important. We think that this test is one of the most relevant in the case of the typical for schizophrenia disorder regarding selectivity of attention, considering the context of the task.

In the context of the current discussion on the similarity or difference in effects of typical and atypical antipsychotics, of special interest is the difference in the results of attention tests depending on the form of basic treatment. At baseline, the patients receiving the typical antipsychotic treatment performed worse than the patients receiving atypical antipsychotic treatment. Adding the 5HT6R inhibitor graded the difference, possibly due to the optimization of the efficacy of typical antipsychotics.

Conclusion

The data that we presented here can be regarded as additional proof in favor of the hypothesis that 5-HT6 receptors play a role in the pathogenesis of psychotic disorders and elements of cognitive dysfunction.

We suggest that the dysfunction of 5-HT6 receptors plays a role in the pathogenesis of both psychopathological manifestation and some aspects of cognitive dysfunction in schizophrenia. Though we did not get robust data on the effects of the compound AVN-211 (CD-008-173) with strong 5HT6 antagonist activity, new trials in more selective groups of patients, for example, patients with acute psychotic symptoms and patients with residual delusions, are advisable. A wider range of dosages would be important to test as well.

Limitations

The present study is a pilot one and has many limitations. We examined a clinically mixed group of patients, since they were chosen according to the criterion of stability of condition but not the criterion of predominance of residual positive or negative symptoms. The randomization system was organized in such a way that more patients were in the placebo group than in the treatment group, so the treatment group appeared to be small. The basic treatment varied depending on the patient. Also, we examined only one aspect of cognitive dysfunction, that of attention.

Disclosures

The authors do not have an affiliation with or financial interest in any organization that might pose a conflict of interest.

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