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LEADING ARTICLE

Targeting D-Amino Acid Oxidase (DAAO) for the Treatment of Schizophrenia: Rationale and Current Status of Research

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Abstract

In the brain, D-amino acid oxidase (DAAO) is a peroxisomal flavoenzyme. Through oxidative deamination by DAAO, D-serine, the main coagonist of synaptic *N*-methyl-D-aspartate receptors (NMDARs), is degraded into α-keto acids and ammonia; flavin adenine dinucleotide (FAD) is simultaneously reduced to dihydroflavine-adenine dinucleotide (FADH2), which is subsequently reoxidized to FAD, with hydrogen peroxide produced as a byproduct. NMDAR hypofunction is implicated in the pathogenesis of schizophrenia. In previous studies, compared with control subjects, patients with schizophrenia had lower D-serine levels in peripheral blood and cerebrospinal fluid but higher DAAO expression and activity in the brain. Inhibiting DAAO activity and slowing D-serine degradation by using DAAO inhibitors to enhance NMDAR function may be a new strategy for use in the treatment of schizophrenia. The aim of this leading article is to review the current research in DAAO inhibitors.

Key Points

Sodium benzoate and luvadaxistat (TAK-831) are two potent D-amino acid oxidase (DAAO) inhibitors. Clinical evidence suggests that both may be promising therapeutic agents to treat schizophrenia.

Adjuvant treatment with sodium benzoate improved psychotic symptoms and cognitive impairment in patients with chronic schizophrenia.

The results of INTERACT, a phase II trial, revealed that add-on TAK-831 improved cognitive function but not the negative symptoms of schizophrenia.

The exact mechanism of action of DAAO inhibitors remains unclear.

1 Introduction

Schizophrenia is a severe mental disorder, with an incidence of approximately 1% in all races [1]. In addition to positive and negative symptoms, cognitive impairment plays a major role in determining the overall function of patients

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with schizophrenia [2–4]. However, current antipsychotics developed based on dopaminergic and serotonergic theories have limited efficacy in negative symptoms and cognitive impairment [5, 6]. *N*-methyl-D-aspartate receptor (NMDAR) hypofunction is implicated in the pathogenesis of schizophrenia [7–11]. Ketamine and phencyclidine (PCP), two NMDAR antagonists, produced schizophrenia-like negative symptoms and cognitive impairment [12, 13]. Hyperlocomotion and increased stereotyped behaviors in knockout mice with NR1 subunit deficits were attenuated through treatment with antipsychotics [14]. In a genome-wide association study (GWAS) by the Psychiatric Genomic Consortium [15], 108 loci surpassed genome-wide significance; among them, several genes, including *GRM3*, *GRIN2A*, *SRR* and *GRIA1*, were related to glutamatergic transmission. The results of a recently published GWAS [16] employing a fine-mapping approach supported the pathological roles of two glutamatergic transmission-related genes, *GRIN2A* and *SP4*, in schizophrenia. The structures of NMDARs comprise several different combinations of subunits, such as GluN1/GluN2, GluN1/GluN2/GluN3 and GluN1/GluN3. NMDAR activation requires the simultaneous binding of glutamate and positive allosteric modulators (glycine or D-serine) to the GluN2 subunit and the glycine modulatory site (GMS) on the GluN1 subunit, respectively [17]. In general, GMSs are not fully saturated [18–20], and a small change in the concentrations of coagonists may alter NMDAR activity [21]. Clinical trials have demonstrated that some NMDAR-enhancing agents were beneficial to schizophrenia [22–25], even to antipsychotic-resistant schizophrenia [26, 27]. The results of a meta-analysis [28] which enrolled 40 randomized controlled trials of NMDAR-enhancing agents indicated that add-on treatment of NMDAR-enhancing agents significantly improved the negative symptoms in schizophrenia, even in treatment-refractory schizophrenia.

D-Serine, the main coagonist of synaptic NMDARs, is involved in excitatory neurotransmission, synaptic plasticity and cognitive behavior [29–32]. L-Serine is converted into D-serine through isomerization reactions catalyzed by serine racemase (SR) [33, 34]. Thereafter, D-serine is degraded by SR again through an α,β-elimination reaction [33, 35] or by D-amino acid oxidase (DAAO) through oxidative deamination [35, 36] and is ultimately removed from the synapse by the alanine-serine-cysteine transporter (Asc-1) [37, 38]. In the brain, DAAO is a peroxisomal flavoenzyme [35, 36]. Through oxidative deamination by DAAO, D-serine is degraded into α-keto acids and ammonia; flavin adenine dinucleotide (FAD) is simultaneously reduced to dihydroflavine-adenine dinucleotide (FADH2), which is subsequently reoxidized to FAD, with hydrogen peroxide produced as a byproduct [36] (Fig. 1). Compared with control samples, patients with schizophrenia had lower D-serine levels in peripheral blood [39, 40] and the cerebrospinal fluid [41] but higher DAAO expression and activity in the brain [42–46]. Inhibiting DAAO activity and slowing D-serine degradation by using DAAO inhibitors to enhance NMDAR function may be a new strategy for use in the treatment of schizophrenia [47]. The results of INTERACT, a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II trial, showed that luvadaxistat (TAK-831), a highly selective and potent DAAO inhibitor, improved the cognitive function of patients with schizophrenia [47]. Sodium benzoate, another potent DAAO inhibitor, improved not only psychotic symptoms and cognitive impairment in schizophrenia but also cognitive function in early-stage Alzheimer disease and late-life depression [48–51]. DAAO

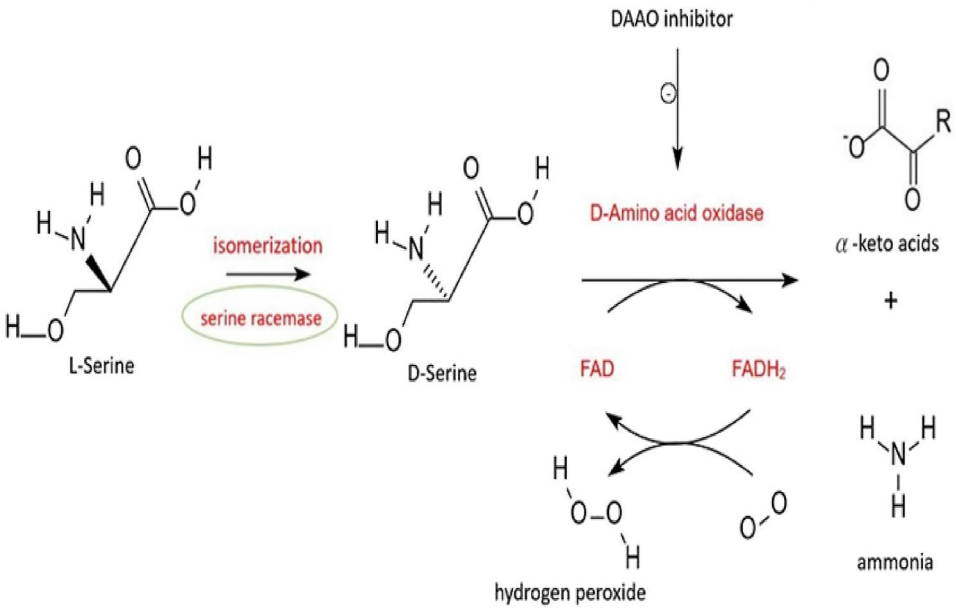

Fig. 1 D-Serine metabolism by D-amino acid oxidase (DAAO). L-Serine is converted into D-serine through isomerization reactions catalyzed by serine racemase (SR) [33, 34]. Thereafter, through oxidative deamination by DAAO [35, 36], D-serine is degraded into α-keto acids and ammonia; flavin adenine dinucleotide (FAD) is simultaneously reduced to dihydroflavine-adenine dinucleotide (FADH2), which is subsequently reoxidized to FAD, with hydrogen peroxide produced as a byproduct [36]

inhibitors may be another promising therapeutic approach [52, 53] capable of overcoming the limitations of current antipsychotics. However, the mechanism of action of DAAO inhibitors remains unclear. Evidence suggested that it may be related to redox modulation instead of an indirect increase in the D-serine level [54].

2 Evidence from Preclinical Studies

Inhibition of DAAO activity reversed schizophrenia-like behavior and prepulse inhibition in mutant mice with NR1 subunit deficits and mice treated with MK-801 [55, 56]. Mutant mice with DAAO deficiency exhibited superior recognition memory performance and elevated D-serine levels in the hippocampus as well as increased anxiety-like behaviors [57, 58].

Numerous DAAO inhibitors, including 5-methylpyrazole-3-carbo-xylic acid (AS057278) [59], 6-chlorobenzo[d] isoxazol-3-ol (CBIO) [56, 60, 61], 4H-thieno[3,2-b] pyrrole-5-carboxylic acid (compound 8) [62], sodium benzoate [63], 4-hydroxy-6-{2-[4(trifluoromethyl)phenyl]ethyl}-pyridazin-3(2H)-one (TAK-831) [64] and 4-hydroxypyridazin-3(2H)-one (compound 30) [65] have been investigated.

Chronic administration of AS057278, a selective DAAO inhibitor, increased D-serine in the cortex and normalized PCP-induced hyperlocomotion in rats [59]. Sershen et al. [61] employed the PCP-treated mouse model to explore whether CBIO and sodium benzoate increase the D-serine level in the brain and inhibit PCP-induced locomotor activity or not. The results indicated that D-serine inhibited PCP-induced hyperactivity and suggested an interaction between sodium benzoate and D-serine with unknown mechanisms other than DAAO inhibition. Fradley et al. [66] showed that TAK-831 improved cognitive deficits and negative symptoms in an animal model of schizophrenia. Nagy et al. [65] investigated the effects of a novel DAAO inhibitor (compound 30) on cognitive function (measured by passive avoidance learning) and neuronal firing activity in rats. Their results revealed that low doses of DAAO inhibitor (compound 30) seemed to exhibit efficacy similar to that of high doses of D-serine, with fewer side effects. The results also revealed a relationship between the neural and behavioral action of DAAO inhibition.

3 Evidence from Clinical Trials

3.1 Sodium Benzoate

Clinical evidence supported that sodium benzoate improved not only psychotic symptoms and cognitive impairment in schizophrenia but also cognitive function in early-stage Alzheimer disease and late-life depression [48–51, 54, 67, 68]. The contents of those studies are briefly summarized in Table 1.

Lane et al. [48] conducted a 6-week, randomized, double-blind, placebo-controlled trial in which sodium benzoate (1 g/day) was administered as an adjuvant therapy to patients with chronic schizophrenia who had been stabilized with antipsychotics for at least 3 months. The results revealed that sodium benzoate improved both the positive and negative symptoms of schizophrenia and enhanced cognitive function in the domains of processing speed and visual memory. Lin et al. [50] conducted a 12-week, randomized, double-blind, placebo-controlled trial in which dual NMDAR enhancers, sarcosine and sodium benzoate, were applied to treat chronic schizophrenia. The results showed that patients treated with a combination of sarcosine and sodium benzoate exhibited greater cognitive improvement than did those treated with sarcosine alone or placebo.

In clinical practice, clozapine is used as the last-line antipsychotic for patients with schizophrenia previously observed to be refractory to standard treatments with at least two specific antipsychotics [1]. Previous studies have indicated that the efficacy of clozapine could not be augmented with NMDAR-enhancing agents [69–71]. This finding may be attributed to the fact that clozapine itself already acts as a potential NMDAR enhancer [72–75], thus attenuating the effectiveness of glycine, D-serine, and glycine transporter-1 (GlyT1) inhibitor. A 6-week, randomized, double-blind, placebo-controlled trial [54] investigated the efficacy of sodium benzoate as adjunctive therapy for clozapine-resistant schizophrenia. The enrolled patients were allocated into three treatment groups: sodium benzoate 1 g/day, sodium benzoate 2 g/day and placebo. The results were more promising than those of previous studies on clozapine augmentation with other NMDA-enhancing agents [70–72]; both doses of sodium benzoate improved the negative symptoms and benzoate 2 g/day improved positive symptoms. The serum DAAO levels of the patients in the 2 g/day sodium benzoate group decreased more compared with those of the patients in the placebo group. However, the blood levels of five amino acids (D-serine, L-serine, glycine, D-alanine and L-alanine) in each of the groups did not change significantly from baseline to the endpoint. Importantly, the changes of serum catalase (CAT), a vital antioxidant, were correlated with the improvement of overall symptoms and positive symptoms in the sodium benzoate groups [54].

Lin et al. [49] conducted a 24-week, randomized, double-blind, placebo-controlled trial which showed that sodium benzoate significantly improved cognitive function in patients with early-stage Alzheimer disease. Recently, sodium benzoate was also found to improve cognitive function in women (but not in men) with behavioral and psychological symptoms of dementia [67]. Lane et al. [68] performed the resting-state

Table 1 Brief summary of the clinical trials of sodium benzoate

Diagnosis	Study weeks	Dosage	Results	References
Chronic schizophrenia $n = 52$	6	Add-on sodium benzoate 1 g/day or placebo	Compared with placebo, sodium benzoate had greater improvement in total PANSS score, positive subscale, negative subscale, SANS and the cognitive domains of processing speed and visual learning	[48]
Amnestic MCI or mild AD $n = 60$	24	Sodium benzoate (250–1500 mg/day) or placebo	Compared with placebo, sodium benzoate had better improvement in ADAS-cog subscale at week 16, week 24 and endpoints	[49]
Chronic schizophrenia $n = 63$	12	Adjunctive sarcosine 2 g/day plus sodium benzoate 1 g/day, adjunctive sarcosine 2 g/day or placebo	Compared with placebo or sarcosine alone, adjunctive sarcosine 2 g/day plus benzoate 1 g/day had better improvement in cognitive function	[50]
Late-life depression $n = 117$	8	Sodium benzoate (250–1500 mg/day), sertraline (25–150 mg/day) or placebo	Compared with placebo, sodium benzoate, but not sertraline, showed better improvement in perceived stress scale scores and cognitive function than placebo	[51]
Clozapine-resistant schizophrenia $n = 60$	6	Add-on sodium benzoate 1 g/day, sodium benzoate 2 g/day or placebo	Compared with placebo, both doses of sodium benzoate produced better improvement in negative symptoms Sodium benzoate 2 g/d also produced better improvement in total PANSS score, PANSS-positive score and QOL	[54]
AD or VaD with BPSD $n = 97$	6	Sodium benzoate (250–1500 mg/day) or placebo	Compared with placebo, among 62 women, but not 35 men, 6-week sodium benzoate treatment had significant improvement in ADAS-cog performance and also increased estradiol to follicle-stimulating hormone ratios. Neither women nor men in the sodium benzoate group had a significant difference in BEHAV-AD scores	[67]
Amnestic MCI $n = 21$	24	Sodium benzoate (250–1500 mg/day) or placebo	In sodium benzoate group: 1. decreased resting-state ReHo in right OFC 2. the change in working memory was positively correlated with the change of ReHo in right precentral gyrus and right middle occipital gyrus 3. the change in verbal learning and memory was positively correlated with the change in ReHo in left precuneus	[68]

AD Alzheimer's disease, *ADAS-cog* Alzheimer`s Disease Assessment Scale – cognitive subscale, *BEHAV-AD* Behavioral Pathology in Alzheimer`s Disease rating scale, *BPSD* behavioral and psychological symptoms of dementia, *MCI* mild cognitive impairment, *OFC* orbitofrontal cortex, *PANSS* Positive and Negative Syndrome Scale, *QOL* Quality of Life scale, *SANS* Scale for the Assessment of Negative Symptoms, *ReHo* regional homogeneity, *VaD* vascular dementia

functional magnetic resonance imaging to analyze regional homogeneity and local functional connectivity in patients with mild cognitive impairment. The results showed that sodium benzoate was able to alter the brain activity; the alteration of brain activity was correlated with the change in cognitive function of the patients. In another study [51], patients with geriatric depression were treated with sodium benzoate, sertraline (a commonly used antidepressant) or placebo for 8 weeks; the results showed that compared with the placebo group, those treated with sodium benzoate (but not those treated with sertraline) had substantial improvements in cognitive function and perceived stress scores.

In contrast to other clinical trials for chronic, treatment-resistant, or clozapine-resistant schizophrenia [48, 50, 54], a 12-week, randomized, double-blind, placebo-controlled trial [76] that evaluated the efficacy of sodium benzoate (1000 mg/day) as an adjuvant treatment for early psychosis revealed that compared with placebo controls, add-on treatment of sodium benzoate did not produce better outcomes. The results were possibly influenced by recruiting patients who were younger (mean age of 21 years) with recent-onset disorder and a broader range of diagnoses in this study, including schizophrenia, schizophreniform disorder, affective psychosis, delusional disorder and other forms of psychosis not otherwise specified. The previous study reported the difference between bipolar disorder and schizophrenia on D-serine levels. Compared with the control subjects, patients with bipolar disorder had higher D-serine levels [77].

3.2 TAK-831

TAK-831is a highly selective DAAO inhibitor. Yoneyama et al. [64] investigated the brain distribution of TAK-831 in rats. The results showed remarkably different distribution between target (cerebellum) and reference (frontal cortex) regions. At a daily dose of 600 mg, TAK-831 achieved a target occupancy rate of over 90% [78] and was well tolerated with mild adverse events [79]. The results of the phase II trial released in March 2021 revealed that add-on luvadaxistat (TAK-831) improved not negative symptoms but cognitive function in patients with schizophrenia [47]. Further, there has been an ongoing randomized, double-blind, parallel, placebo-controlled phase II trial with a 12-month open-label extension to evaluate the efficacy of add-on luvadaxistat (TAK-831) in treating cognitive impairment in patients with schizophrenia [80].

4 Analysis of the Mechanism of Action of DAAO Inhibitors

The exact mechanism of action of DAAO inhibitors remains unclear [53]. Preclinical and clinical studies revealed that TAK-831 increased D-serine levels [66, 79], whereas sodium benzoate did not change D-serine levels [61, 63]. Instead, the correlation between the changes in the catalase and the improvements of overall symptoms and positive symptoms was found in patients treated with sodium benzoate [54]. Overall, the mechanism of action of DAAO inhibitors may still be related to the enhancement of NMDAR function [53]. Schizophrenia is a highly heterogeneous disease in which oxidative stress may play a central role in pathogenesis [81]. Accumulating evidence suggests that schizophrenia is associated with redox imbalance [81, 82]. Lower aconitase, nicotinamide adenine dinucleotide dehydrogenase (NADH), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) levels were identified in patients with schizophrenia than in people without schizophrenia in postmortem studies [83]. Analyses of plasma and cerebrospinal fluid revealed that patients with schizophrenia had lower glutathione (GSH) levels and higher oxidized glutathione levels than people without schizophrenia [84, 85]. Higher levels of thiobarbituric acid–reactive substances (TBARS) and lower catalase (CAT) and superoxide dismutase (SOD) activity were observed in schizophrenia [86, 87]. Changes in GSH, SOD and CAT levels were associated with changes in clinical symptoms of schizophrenia, indicating that these redox-involved factors may have potential to be biomarkers of schizophrenia and may be helpful in monitoring disease progression [54, 86–90]. There is a reciprocal connection between NMDAR activity and redox modulation. Cysteine residues of NMDAR are involved in redox modulation [91], and NMDAR dysfunction may lead to decreased antioxidant capacity, resulting in oxidative stress which in turn causes downregulation of NMDARs [82, 92]. Both ketamine and phencyclidine decreased glutathione levels in rat models of schizophrenia [93, 94]. Deficiency of the NMDAR subunit GluN2A resulted in vulnerability to redox dysregulation and delayed the maturation of paravalbumin interneurons [95, 96] which is considered to be a key pathophysiological mechanism of schizophrenia [82, 97, 98].

4.1 Sodium Benzoate Enhances NMDAR Function Through its Antioxidant Properties

DAAO inhibitors, such as sodium benzoate, may enhance NMDAR function through antioxidant activity instead of by inhibiting DAAO. Evidence showed that sodium benzoate modulates antioxidant defense mechanisms in a dose-dependent manner [99–103]. El-Shennawy et al. [99] administered sodium benzoate to male rats at doses of 0, 1, 10, 50, 100, 250, 500 and 1000 mg/kg/day for 90 consecutive days. The results revealed that subchronic use of sodium benzoate was risky at both low and high doses, and the toxicity of it was dose dependent. Sodium benzoate impaired the reproductive system, resulting in decreased sperm count, sperm motility, testicular 17β-hydroxysteroid dehydrogenase (17β-HSD) and

17-ketosteroid reductases (17-KSR) activity; increased abnormal sperm and alteration of hormone levels. Overall, as the dose of sodium benzoate increased from 100 mg/kg/day, testicular nitric oxide (NO), malondialdehyde (MDA), xanthine oxidase (XO), tumor necrosis factor (TNF)-α, interleukin (IL)-6, p53 protein, and caspase-3 activity increased significantly; by contrast, levels of the antioxidant enzymes glutathione peroxidase (GPx), glutathione S-transferase (GST), CAT, SOD, GSH and total antioxidant capacity (TAC) decreased significantly. Olofinnade et al. [102] distributed 40 male rats into four groups: the control group and three groups that received sodium benzoate at doses of 125, 250 and 500 mg/kg/day, respectively, for 8 consecutive weeks. Consequently, the hematological effects of and oxidative stress induced by sodium benzoate were also dose dependent. Significant decrease in serum MDA levels and increase in TAC were found as the dose of sodium benzoate increased. In addition, a significant increase in serum SOD and decrease in serum TNF-α were found in the group that received sodium benzoate at 125 mg/kg/day. However, the caspase-3 levels and renal function of the sodium benzoate groups did not differ significantly from those of the control group. Khan et al. [104] distributed 25 male rats into five groups: the control group and four groups that received sodium benzoate at doses of 70, 200, 400 and 700 mg/kg/day, respectively, for 30 consecutive days. The activities of antioxidant enzymes SOD, CAT, GST and GPx in the liver gradually decreased in the groups receiving the daily doses of 200 mg/kg and higher. These changes were not observed in the group that received sodium benzoate at 70 mg/kg/day. The mitochondria are the primary sites of intracellular reactive oxygen species (ROS) production [105, 106]. Mitochondrial dysfunction causes excessive ROS production, resulting in oxidative stress. Protein DJ-1, with antioxidant properties, is involved in regulating the quality of and oxidative stress in mitochondria [107]. Xu et al. [103] observed that a single dose of sodium benzoate (i.e., 100 mg or 200 mg/kg) improved cognitive function, upregulated mitochondrial DJ-1 and the antiapoptotic factor Bcl-2 and reduced the levels of proapoptotic factors (e.g., cleaved caspase-3 and cleaved caspase-9) and ROS production in rats with intracranial hemorrhage. By contrast, with higher doses and prolonged use of sodium benzoate, the production of excessive levels of mitochondrial transcription factor A (mtTFA) and mitochondrial uncoupling protein 2 (UCP2), proteins associated with mitochondrial function, may lead to mitochondrial dysfunction [99].

5 Conclusions

An animal study showed that D-serine had poor ability to pass the blood–brain barrier (BBB) and higher doses were thus required [108]; administration of D-serine, particularly at high doses [109], increased the risk of nephrotoxicity in rats [110]. However, clinical trials reported nonsignificant increases in nephrotoxicity induced by high-dose (>60 mg/kg/day) D-serine administration [111–113]. Whether long-term administration of D-serine in high doses inflicts nephrotoxicity or peripheral nerve injury [114] in humans remains uncertain. Co-administration of DAAO inhibitors reduced the required D-serine dose and DAAO activity, thus attenuating the risks of side effects [56, 115]. D-Serine-induced nephrotoxicity was not reported in DAAO knockout rats [116]. Possibly, high-dose D-serine degraded by DAAO may increase the production of hydrogen peroxide [117] and reduce glutathione concentrations [118], leading to cell damage and oxidative stress. Antioxidant properties of sodium benzoate may also prevent oxidative stress which may be induced by high-dose D-serine. Collectively, DAAO inhibitors have the potential to serve as an effective treatment for schizophrenia. The efficacy and safety of TAK-831 and sodium benzoate are dose-dependent [66, 79, 102, 103]. In rat models, the toxicity of sodium benzoate on the reproductive system and liver and renal function were dose- and duration-dependent [99, 104, 119, 120]. No side effects have been observed in previous clinical trials [48–51, 54, 76], which may be due to the doses used being below the maximum dose recommended by the Food and Drug Administration [121]. In the future, researchers should conduct trials that involve various populations and test several dosages of DAAO inhibitors with longer study duration to further elucidate the clinical efficacy and safety of DAAO inhibitors as a potential treatment for schizophrenia and other neurocognitive disorders.

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