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Advancements in Non-Dopaminergic Treatments for Schizophrenia: A Systematic Review of Pipeline Developments

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ABSTRACT

Introduction Conventional antipsychotic drugs that attenuate dopaminergic neural transmission are ineffective in approximately one-third of patients with schizophrenia. This necessitates the development of non-dopaminergic agents.

Methods A systematic search was conducted for completed phase II and III trials of compounds for schizophrenia treatment using the US Clinical Trials Registry and the EU Clinical Trials Register. Compounds demonstrating significant superiority over placebo in the primary outcome measure in the latest phase II and III trials were identified. Collateral information on the included compounds was gathered through manual searches in PubMed and press releases.

Results Sixteen compounds were identified; four compounds (ulotaront, xanomeline/trospium chloride, vabicaserin, and roluperidone) were investigated as monotherapy and the remaining 12 (pimavanserin, bitopertin, BI 425809, encenicline, tropisetron, pregnenolone, D-serine, estradiol, tolcapone, valacyclovir, cannabidiol, and rimonabant) were examined as add-on therapy. Compared to the placebo, ulotaront, xanomeline/trospium chloride, vabicaserin, bitopertin, estradiol, cannabidiol, rimonabant, and D-serine showed efficacy for positive symptoms; roluperidone and pimavanserin were effective for negative symptoms; and encenicline, tropisetron, pregnenolone, tolcapone, BI 425809, and valacyclovir improved cognitive function.

Discussion Compounds that function differently from existing antipsychotics may offer novel symptom-specific therapeutic strategies for patients with schizophrenia.

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Introduction

Schizophrenia is a prevalent psychiatric disorder, affecting 0.7 % of the world population [1]. Pharmacotherapy plays a central role in the treatment of schizophrenia by addressing both acute [2] and maintenance phases [3]. The common mechanism of action among the currently available antipsychotic drugs is the modulation of dopamine neurotransmission. Nevertheless, there are various constraints to the traditional pharmacotherapy for schizophrenia. First, the effectiveness of standard drugs for psychosis is often inadequate, and addressing "treatment-resistant" schizophrenia is a substantial challenge [4]. Approximately one-third of patients diagnosed with schizophrenia experience treatment resistance, and clozapine, intended for treatment-resistant schizophrenia, has a reported response rate of 40 % [5]. Second, antipsychotic drugs are associated with a variety of adverse events, including extrapyramidal symptoms [6], sudden cardiac death [7], and cognitive impairment [8]. Thus, these negative events significantly compromise the quality of life of patients [9]. While the current antipsychotic drugs were devised under the "dopaminergic hypothesis," there is an immediate need for the development of novel drugs that act through mechanisms other than the dopaminergic system. In this review, we systematically searched for non-dopaminergic antipsychotic drugs in the pipeline using the US Clinical Trials Registry and the EU Clinical Trials Register and reviewed the compounds showing positive results in the most recent phase II and III trials.

Methods

A systematic search was conducted to identify double-blind randomized controlled trials (DBRCTs) of non-dopaminergic antipsychotics in patients with schizophrenia. The search was conducted using the US Clinical Trials Registry (https://clinicaltrials.gov/) and the EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). The search filters were: condition or disease, "schizophrenia," and trial phase, "Phase II" and "Phase III" (last search: February 23, 2024). The exclusion criteria were as follows: (1) no final results were available, (2) the compounds tested were already marketed for schizophrenia, (3) non-pharmacological treatments were examined, (4) studies did not recruit patients with schizophrenia, (5) positive symptoms, negative symptoms, or cognitive function were not assessed as primary outcomes, (6) the effectiveness of compounds was not reported, and (7) the compounds tested were antagonists or partial agonists of dopamine receptors. Following the identification of clinical trials that met the selection criteria, compounds that exhibited statistically significant superiority over placebo in the primary outcome measure at the primary endpoint in the latest phase were selected. Collateral information on the included compounds was gathered from published articles via PubMed literature searches and press releases. If the literature searches found that the compounds failed to obtain approval for schizophrenia or their development was discontinued, they were excluded from this review. The search was performed independently by two authors (YK and FU). Conflicts were resolved through discussions with a third author (HU).

Results

A total of 1,243 trials were examined for eligibility, and 1,224 were excluded based on the exclusion criteria or negative study results. The search flow diagram is shown in ▶ **Fig. 1** [10]. Subsequently, a comprehensive evaluation was conducted on 16 drugs across 19 trials that met the selection criteria, including two trials each of roluperidone, xanomeline/trospium, and encenicline. Thus, the exploration of drugs for the treatment of schizophrenia has resulted in a wide range of options, each designed to target a specific mechanism of action (▶ **Table 1**). Overall, our review included nine newly developed compounds whose mechanisms of action were different from those of existing drugs (novel drugs: ulotaront, xanomeline, vabicaserin, roluperidone, pimavanserin, bitopertin, BI425809, encenicline, and tropisetron), three neuroactive steroids that function in the central nervous system (pregnenolone, D-serine, and estradiol), and four drugs already approved and marketed for other diseases (tolcapone, valacyclovir, cannabidiol, and rimonabant) (▶ **Fig. 2**).

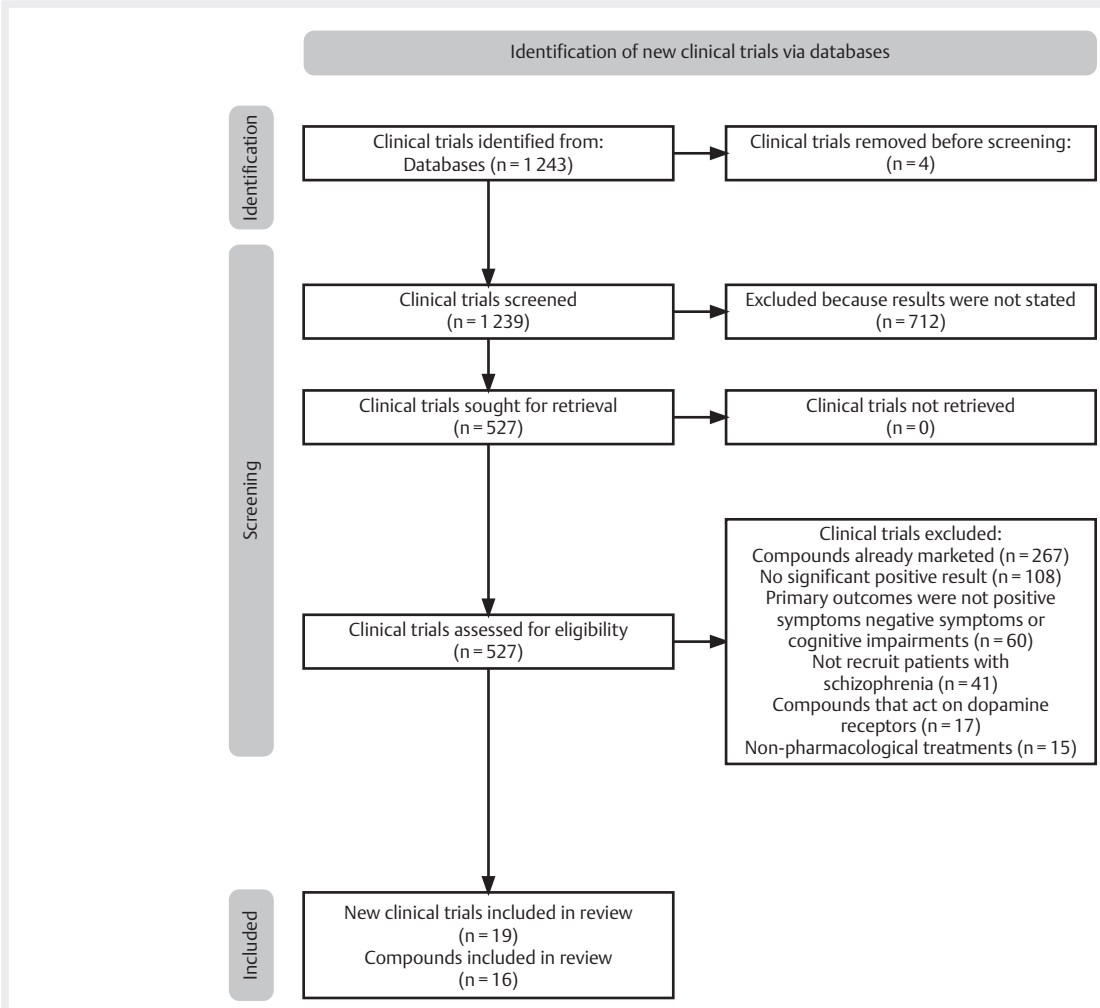
Novel Drugs

Ulotaront (SEP-363856)

Preclinical studies have shown that SEP-363856 exerts agonistic effects on trace amine-associated receptor 1 (TAAR1) (EC50 = 0.140 ± 0.062 µM) and serotonin type 1 A (5-HT_{1A}) receptors (Ki = 0.284 ± 0.056 µM) [11, 12]. A phase II DBRCT was conducted to assess the efficacy of SEP-363856 in the treatment of acute exacerbations of psychosis in patients with schizophrenia (NCT02969382). In this study, a cohort of 245 patients diagnosed with schizophrenia, ranging in age from 18 to 40 years, and exhibiting exacerbation of psychotic symptoms (i. e., Clinical Global Impression of Severity score ≥ 4, and positive and negative syndrome scale (PANSS) total score ≥ 80), were included after hospitalization within 2 weeks of screening. The participants were randomly assigned to receive either 50–75 mg/day SEP-363856 (n = 120) or a placebo (n = 125). After 4 weeks, the SEP-363856 group showed a greater reduction in PANSS total scores compared to placebo group (least-squares mean difference, − 7.5 points; 95 % CI, − 11.9 to − 3.0; $p = 0.001$). During the trial, two adverse events (worsening of schizophrenia and acute cardiovascular insufficiency that resulted in sudden death) occurred in the SEP-363856 group, whereas four serious adverse events (three patients had worsening symptoms of schizophrenia and one patient attempted suicide) occurred in the placebo group.

Xanomeline and trospium chloride

Xanomeline exhibits agonistic effects on M1 (IC50 = 0.006 nM [13]) and M4 muscarinic cholinergic receptors, whereas co-administered trospium chloride, an oral pan-muscarinic receptor antagonist, mitigates approximately 50 % of the adverse cholinergic events linked to xanomeline [14]. One phase II DBRCT in patients with schizophrenia assessed the antipsychotic effects of the combination treatment compared to placebo. The cohort comprised 182 patients with schizophrenia who presented an acute exacerbation (i. e., PANSS total scores of ≥ 80) and required hospitalization within two



▶ **Fig. 1** A Flow diagram of the search process.

months (NCT03697252). The participants were assigned to receive treatment with either xanomeline 250 mg/day, trospium chloride 60 mg/day (n = 90), or placebo (n = 92). After 5 weeks, a greater decrease in the PANSS total score was observed in the treatment group compared to the placebo group (least-squares mean difference, −11.6 points; 95 % CI, −16.1 to −7.1; $p < 0.001$). Adverse events occurred in 54 % and 43 % of the patients in the treatment and placebo groups, respectively. One instance of a severe adverse event was documented in a patient in the treatment group with a worsening of psychotic symptoms. The most frequent adverse events found in the treatment group were constipation (17 %) and nausea (17 %), followed by dry mouth (9 %), dyspepsia (9 %), and vomiting (9 %). None of these adverse events resulted in the discontinuation of xanomeline plus trospium chloride. Thereafter, in a phase III DBRCT, the antipsychotic effects of this combination treatment on patients with schizophrenia were assessed in comparison with placebo. The same criteria as the afore-mentioned phase II trial were applied for a total of 252 patients with schizophrenia (NCT04659161). The participants were assigned to receive treatment with either xanomeline 250 mg/day, trospium chloride 60 mg/day (n = 126), or placebo (n = 126). After 5 weeks, a greater decrease in the PANSS total score was observed in the treatment group compared to the placebo group (least-squares mean difference, −9.6 points; 95 % CI, −13.9 to −5.2; $p < 0.001$). The most frequent adverse events found in the treatment group were constipation (21 %), dyspepsia 19 %), nausea (19 %), followed by headache (14 %) and vomiting (14 %). Adverse event-related discontinuation rates were similar between the treatment and placebo groups (7 % vs 6 %).

Vabicaserin

Vabicaserin acts as an agonist of 5-HT_{2C} receptors (Ki = 3 nM) [15, 16]. A phase II DBRCT included 289 patients with schizophrenia who presented acute exacerbations and then were hospitalized (i. e., PANSS total scores of 70 to 120 and PANSS positive syndrome scores of ≥ 20) (NCT00265551). After a 1-week washout period, the participants were assigned to the following four groups: 200 mg/day vabicaserin (n = 82), 400 mg/day vabicaserin (n = 77), 15 mg/day olanzapine (n = 77), or placebo (n = 77). Both the 200 mg/day vabicaserin group and the 15 mg/day olanzapine group showed a greater reduction in the PANSS positive syndrome score compared to the placebo group (vabicaserin 200 mg/day: -4.22,

▶ **Table 1** Summary of clinical trial results of 16 drugs for schizophrenia identified in this review.

Investigational Substances (monotherapy or add-on)	Presumed mechanism of action	No. of DBRCTs	Comparison Groups	Study Cohort	Findings of Studies
(1) Novel Drugs					
Ulotaront (monotherapy)	Agonistic effects on TAAR1, 5-HT_{1A}	1	Treatment vs. placebo	245 patients, aged 18–40 years, hospitalized within 2 weeks of screening	− 7.5 in PANSS total score vs. placebo ($p = 0.001$)
Xanomeline and trospium chloride (monotherapy)	Agonistic effects on M_1 and M_4 cholinergic receptors	2	Treatment vs. placebo	(Phase II) 182 and (Phase III) 252 patients, hospitalized within 2 months	(Phase II) − 11.6 in PANSS total score vs. placebo ($p < 0.001$) (Phase III) − 9.6 in PANSS total score vs. placebo ($p < 0.001$)
Vabicaserin (monotherapy)	Agonist for 5-HT_{2C} receptors	1	Treatment (200 mg/day, 400 mg/day), olanzapine 15 mg/day, placebo	289 patients with PANSS total scores of 70 to 120	200 mg/day: − 4.22 (SE = 0.76) in PANSS positive syndrome score vs. placebo ($p = 0.03$) 400 mg/day: no significant difference vs. placebo
Roluperidone (monotherapy)	Affinities for σ2 (sigma-2) and 5-HT_{2A} receptors	2	Treatment (32 mg, 64 mg) vs. placebo	(Phase II) 244 and (Phase III) 513 patients, with symptomatically stable and manifest negative symptoms	(Phase II) 32 mg: − 3.07 in PANSS negative factor score vs. placebo ($p = 0.024$) 64 mg: -3.50 in PANSS negative factor score vs. placebo ($p = 0.004$) (Phase III) 32 mg: − 4.0 in the PANSS-derived Negative Symptom Factor Score vs. placebo ($p = 0.064$) 64 mg: − 4.5 in the PANSS-derived Negative Symptom Factor Score vs. placebo ($p = 0.044$)
Pimavanserin (add-on)	Inverse agonist and antagonist at 5-HT_{2A} receptors	1	Treatment vs. Placebo	403 outpatients with predominantly negative symptoms after at least 8 weeks of treatment	− 10.4 in NSA-16 score reduction vs. placebo ($p = 0.043$)
Bitopertin (add-on)	Selective inhibitor of glycine reuptake	1	Treatment (10 mg/day, 20 mg/day) vs. placebo	596 outpatients with PANSS total score ≥ 70; scores ≥ 4 in at least two specific PANSS subscales	10 mg/day: −1.37 in PANSS Positive Syndrome score vs. placebo 20 mg/day: no significant difference vs. placebo
BI 425809 (add-on)	Selective glycine transporter-1 inhibitor	1	Treatment (2 mg/d, 5 mg/day, 10 mg/day, 25 mg/day) vs. placebo	509 outpatients, aged 18–50 years, on stable conventional antipsychotic treatment, 12 weeks	2 mg/day: no significant difference vs. placebo 5 mg/day: no significant difference vs. placebo 10 mg/day: + 1.98 in MCCB overall composite T-score vs. placebo 25 mg/day: + 1.73 in MCCB overall composite T-score vs. placebo
Encenicline (add-on)	Selective agonist for α7 nicotinic acetylcholine receptors	2	Treatment (1 mg/day, 2 mg/day) vs. placebo	(i) 753 and (ii) 766 patients, aged 18–64 years, on atypical antipsychotic treatment	(i) + 3.9 (1 mg/day), + 4.0 (2 mg/day) vs. + 3.2 (placebo) in MCCB ($p < 0.05$) − 4.4 (1 mg/day), − 5.0 (2 mg/day) vs. − 3.9 (placebo) in SCoRS ($p < 0.05$) (i) + 3.4 (1 mg/day), + 3.4 (2 mg/day) vs. + 3.0 (placebo) in MCCB ($p < 0.05$) − 3.3 (1 mg/day), − 3.7 (2 mg/day) vs. − 3.4 (placebo) in SCoRS ($p < 0.05$)
Tropisetron (add-on)	5-HT_3 receptor antagonist; agonistic effects at α7-nicotinic acetylcholine receptor	1	Treatment vs. placebo, add-on to risperidone 6 mg/day	179 patients, aged 18–64 years, with moderate or greater severity on one or more psychotic items in BPRS	96 vs. 95 in MATRICS Cognition Domains scores ($p < 0.05$)
(2) Neuroactive Steroids					

▶ **Table 1** Continued.

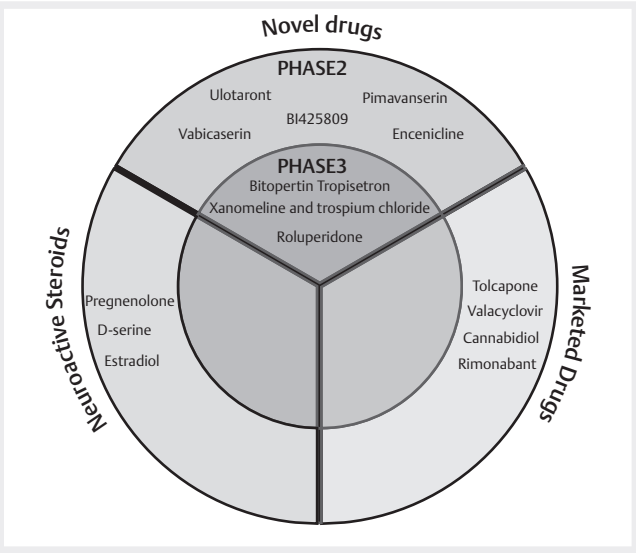
Investigational Substances (monotherapy or add-on)	Presumed mechanism of action	No. of DBRCTs	Comparison Groups	Study Cohort	Findings of Studies
Pregnenolone (add-on)	Mitigates GABA dysregulation and NMDA receptor dysfunction	1	Treatment vs. placebo	120 outpatients, aged 21–65 years, on antipsychotics for at least eight weeks	+ 3.25 points in UPSA-B vs. placebo ($p = 0.03$)
D-serine (add-on)	Endogenous agonist at glycine-site of NMDA receptors	1	Treatment vs. placebo in a crossover design	16 patients	Reduction in PANSS total scores vs. placebo (effect size 0.8, $p = 0.023$)
Estradiol (add-on)	Elevates serotonin levels, activates metabotropic glutamate receptors, enhances dopamine synthesis	1	Treatment (100 µg/day, 200 µg/day) vs. placebo	183 women with treatment-resistant schizophrenia	100 µg/day: − 8.9 vs. − 5.64 in PANSS Total, − 2.82 vs. − 1.82 in PANSS Positive, − 4.26 vs. − 2.5 in PANSS General scores (all $p < 0.01$) 200 µg/day: − 13.23 vs. − 5.64 in PANSS Total, − 4.13 vs. − 1.82 in PANSS Positive, − 5.63 vs. − 2.5 in PANSS General scores (all $p < 0.01$)
(3) Marketed Drugs					
Tolcapone (add-on)	Central inhibitor of COMT, enhancing dopamine levels	1	Treatment vs. placebo in a cross-over design.	59 patients, aged 18–50 years	80.9 ± 1.9 vs. 76.2 ± 2.3 in N-Back Task Performance ($p = 0.034$)
Valacyclovir (add-on)	Antiherpes drug	1	Treatment vs. placebo	24 HSV1-seropositive patients	+ 2.13 in 2-back working memory accuracy scores vs. placebo ($p = 0.037$)
Cannabidiol (add-on)	Cannabinoid	1	Treatment vs. placebo	88 patients, aged 18–65 years, with a positive response to a single antipsychotic treatment ≥ 4 weeks	− 1.4 in PANSS Positive scores vs. placebo ($p = 0.019$)
Rimonabant (add-on)	Cannabinoid-1 receptor antagonist	1	Treatment vs. placebo	15 patients, aged 18–55 years, on second-generation antipsychotics	− 1.9 in BPRS total scores vs. placebo ($p = 0.02$)

Abbreviations: DBRCTs: double-blind randomized controlled trials, TAAR1: trace amine-associated receptor 1, 5-HT: 5-hydroxytryptamine, PANSS: Positive and Negative Syndrome Scale, SE: standard error, NSA-16:16-item Negative Symptom Assessment, MCCB: Measurement and treatment research to improve cognition using the schizophrenia (MATRICS) Consensus Cognitive Battery, SCoRS: Schizophrenia Cognition Rating Scale, BPRS: Brief Psychiatric Rating Scale, GABA: Gamma-amino butyric acid, NMDA: N-methyl-D-aspartic acid, UPSA-B: UCSD Performance-Based Skills Assessment: Brief, COMT: catechol-O-methyl-transferase, HSV1: herpes simplex virus type 1.

SE = 0.76, $p = 0.03$; olanzapine 15 mg/day: − 4.97, SE = 0.78, $p = 0.01$). In contrast, there was no difference in the changes in PANSS positive syndrome scores between the vabicaserin 400 mg/day group and the placebo group (− 2.13, SE = 0.80, $p = 0.80$). The most frequently reported treatment-emergent adverse events in the vabicaserin group were dyspepsia and headache. Dyspepsia (13.4 %, 200 mg/day; 16.9 %, 400 mg/day) and diarrhea (8.5 %, 200 mg/day; 5.2 %, 400 mg/day) were reported more than twice as frequently after vabicaserin treatment than after the placebo (dyspepsia, 5.2 %; diarrhea, 2.6 %). Serious adverse events were reported in six subjects in the vabicaserin 200 mg/day group, seven subjects in the vabicaserin 400 mg/day group, and seven subjects in the placebo group. Three subjects receiving vabicaserin experienced serious adverse events, and two withdrew from the study because of serious treatment-related adverse events.

Roluperidone

Roluperidone is a compound that exhibits affinities towards both σ2 (sigma-2) (Ki = 8.19 nmol/L) and 5-HT_{2A} receptors (Ki = 7.53nmol/L) [17]. In a phase II DBRCT, roluperidone substantially improved negative symptoms in patients with schizophrenia compared with a placebo (EudraCT Number: 2014-004878-42). This study included 244 patients, aged 18–60 years, diagnosed with schizophrenia. These patients were considered symptomatically stable by their treating psychiatrist and exhibited persistent negative symptoms for a minimum of three months. Patients at baseline scored ≥ 20 points on the seven-item negative symptom scale (items N1-N7) and < 4 points on agitation, hyperactivity, hostility, suspiciousness, uncooperativeness, and poor impulse control on the PANSS. Following a minimum washout period of five days, patients were allocated to receive daily doses of 32 mg (n = 78) or 64 mg (n = 83) roluperidone or placebo (n = 83), respectively. Compared to the placebo group (mean ± standard error, -1.53 ± 0.47), significantly greater reductions in the PANSS negative syndrome score were found at week 12 in the roluperidone 32 mg/day group (mean ± standard error, − 3.07 ± 0.49; $p = 0.024$) and the 64 mg group (mean ± standard error, -3.50 ± 0 · 48; $p = 0.004$). Serious adverse events were observed in two patients in the placebo group and in six patients in the roluperidone group. Two patients in the placebo group and four in the roluperidone 32 mg/day group were



▶ **Fig. 2** An overview of non-dopaminergic agents for schizophrenia.

hospitalized because of worsening schizophrenia symptoms. The remaining two serious adverse events occurred in the group receiving a daily dose of 64 mg roluperidone: one involved vomiting and abdominal pain and the other involved syncope and bradycardia. Subsequently, a phase III DBRCT also showed that roluperidone substantially improved negative symptoms in patients with schizophrenia compared with a placebo (NCT03397134). This study included 513 patients, aged 18–55 years, diagnosed with schizophrenia. The criteria for the study population were the same as the above phase II trial. Following a minimum washout period of two days, patients were allocated to receive daily doses of 32 mg (n = 170) or 64 mg (n = 171) of roluperidone or placebo (n = 172), respectively. A significantly greater reduction in the PANSS-derived Negative Symptom Factor Score (i. e., N1 to N4, N6, G7, and G16 of the PANSS) was observed in the roluperidone 64 mg/day group (mean ± standard error, − 4.5 ± 0.35; p = 0.044) compared to the placebo group (mean ± standard error, − 3.5 ± 0.35), but not in the roluperidone 32 mg group (mean ± standard error, − 4.0 ± 0 · 35; p = 0.286). Severe treatment-emergent adverse events were reported in 17 patients (3 %) overall, with similar incidences in all treatment groups. There were 25 (5 %) patients with serious adverse events, 5 (3 %) in the placebo group, and 20 (6 %) in the roluperidone groups. There were two deaths during the trial in the roluperidone 32 mg dose, one patient committed suicide, and another died from gastrointestinal bleeding 6 days after he withdrew consent and discontinued the trial. Neither death was considered to be related to treatment by investigators.

Pimavanserin

Pimavanserin is an inverse agonist and antagonist of 5-HT_{2A} receptors (pKi = 9.3 ± 0.14) [18, 19]. A phase II DBRCT was conducted to examine the efficacy of pimavanserin combined with currently available antipsychotics for the negative symptoms of schizophrenia (NCT02970305). The trial included 403 outpatients with schizophrenia who presented a predominance of negative symptoms (i. e., PANSS Marder negative factor item score of ≥ 20 and PANSS Marder positive factor item score of ≤ 22) after at least 8 weeks of antipsychotic treatment. In addition to their ongoing antipsychotic treatment, 201 and 202 patients were assigned to receive treatment with 10–34 mg/day pimavanserin (initial dose of 20 mg/day) or placebo, respectively, for 26 weeks. The pimavanserin group showed a greater score reduction in the Negative Symptom Assessment-16 (NSA-16) at week 26, compared to placebo (least squares mean difference, − 1.9; standard error, 0.95; $p = 0.043$). The incidence of adverse events was 71 out of 202 (35 %) in the placebo group and 80 out of 201 (40 %) in the pimavanserin group; the most common adverse events were headache (10 of 202 [5 %] in the placebo group vs. 13 of 201 [6 %] in the pimavanserin group) and somnolence (10 [5 %] vs. 11 [5 %]). No fatal adverse events were reported. One serious adverse event occurred in the placebo group (< 1 %) and four (2 %) in the pimavanserin group, all of which were classified as psychiatric disorders. Adverse events leading to discontinuation occurred in six (3 %) of the 202 patients in the placebo group and in 10 (5 %) of the 201 patients in the pimavanserin group. However, most adverse events were mild or moderate in severity. In the pimavanserin group, one patient reported severe toothache (< 1 %) and two patients reported worsening schizophrenia (1 %).

Bitopertin

Bitopertin functions as a selective inhibitor of glycine reuptake and modulates the neurotransmission of glutamate (IC50 = 25 nM) [20] and dopamine in animal models [21]. One study has examined the efficacy of a combination of currently available antipsychotics and bitopertin in patients with schizophrenia. The 12-week phase III DBRCT (NCT01235559) involved 596 outpatients who were prescribed antipsychotic medication and displayed severe symptoms (i. e., the PANSS total score of ≥ 70 and a score of ≥ 4 of at least two of the following PANSS subscales: delusions, hallucinatory behavior, suspiciousness, and unusual thought content). In addition to their ongoing treatment, patients were randomly assigned to receive 10 mg/day bitopertin (n = 199), 20 mg/day bitopertin (n = 198), or placebo (n = 199). The reduction of PANSS Positive Symptom Factor Score (i. e., calculated from delusions [P1], hallucinatory behavior [P3], grandiosity [P5], suspiciousness [P6], fixations [N7], physical interest [G1], abnormal thought content [G9], and lack of judgment and insight [G12]) at 12 weeks was greater in the bitopertin 10 mg/day group compared with the placebo (mean difference in the score –1.37, 95 % CI, –2.27 to –0.47, $p = 0.0028$), while there were no differences in the reduction of PANSS Positive Symptom Factor Score between the bitopertin 20 mg/day and placebo groups (mean difference in score –0.46, 95 % CI, -1.34 to 0.43, $p = 0.3142$). The adverse events reported during the trial included one case each of aspiration pneumonia, psychiatric symptoms, psychotic disorder, schizophrenia, suicidal ideation, completed suicide, and hallucinations.

BI 425809

BI425809 acts as a selective glycine transporter-1 (GlyT1) inhibitor (IC50 = 5.0 nM) [22]. GlyT1 inhibitors are thought to elevate synaptic glycine levels and consequently enhance glutamatergic neurotransmission and downstream neuroplastic processes, which represent potential treatment targets for cognitive impairment

associated with schizophrenia [23]. Additionally, BI425809 enhances extracellular glycine levels in the cerebrospinal fluid of both rodents and healthy volunteers (NCT02362516). One phase II DBRCT assessed the effects of once-daily add-on treatment with oral BI425809 in patients with schizophrenia. A total of 509 outpatients aged 18–50 years who were on stable treatment with a conventional antipsychotic were assigned to receive 2 mg (n = 85), 5 mg (n = 84), 10 mg (n = 85), or 25 mg (n = 85) of BI425809 or placebo (n = 170) for 12 weeks and were followed up for 4 weeks (NCT02832037). With regard to the change from baseline in the MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score at week 12, five of six dose-response models were statistically significant (linear [t = 2.55, $p = 0.015$], linear in log [t = 2.56, $p = 0.015$]; Emax [t = 2.75, $p = 0.0089$], sigmoid Emax [t = 2.98, $p = 0.0038$], and logistic [t = 2.77, $p = 0.0085$]). Pairwise comparisons found greater improvement from baseline in MCCB overall composite T-score at week 12 with 10 mg and 25 mg, compared to placebo (adjusted mean difference [95 % CI]: 1.98 [0.43–3.53] for 10 mg and 1.73 [0.18–3.28] for 25 mg). However, there were no significant differences in changes from baseline to week 12 in the Schizophrenia Cognition Rating Scale (SCoRS) interviewer-rated total score, PANSS total and subscale scores, or Personal and Social Performance scores between any BI 425809 dose group and placebo. The most frequently observed adverse events by the system organ class were nervous system disorders (86 patients, 17 %) and the most frequent adverse event was headache (42 patients, 8 %). No worsening of schizophrenia symptomatology was observed in terms of the PANSS total score.

Encenicline

Encenicline acts as a selective agonist of the α_7-nicotinic acetylcholine receptor (Ki = 9.98 nM) [24, 25]. Its efficacy as an adjunctive treatment for cognitive impairment in patients with schizophrenia was tested in two phase II DBRCTs (IND Number: 076939, Sponsor protocol codes EVP-6124-015 and EVP-6124-016). Patients aged 18–64 years who were receiving atypical antipsychotic treatment were randomized to receive 1 mg/day or 2 mg/day encenicline or placebo (n = 753 in one study; n = 766 in the other). The primary outcomes were changes in MCCB and SCoRS scores at 26 weeks. The arithmetic mean ± standard error of the MCCB in the first trial was 3.9 ± 0.41 for the EVP-6124 1 mg group, 4 ± 0.47 for the 2 mg group, and 3.2 ± 0.42 for the placebo group ($p < 0.05$), while the second trial showed 3.4 ± 0.42 for the EVP-6124 1 mg group, 3.4 ± 0.46 for the 2 mg group, and 3 ± 0.41 for the placebo group ($p < 0.05$). The arithmetic mean (full range (min-max)) of SCoRS was the first trial was − 4.4 (− 26 to 14) for the EVP-6124 1 mg group, − 5 (− 33 to 21) for the 2 mg group, and -3.9 (− 42 to 21) for the placebo group ($p < 0.05$), while the second trial found − 3.3 (− 21 to 30) for the EVP-6124 1 mg group, − 3.7 (− 23 to 27) for the 2 mg group, and − 3.4 (− 28 to 17) for the placebo group ($p < 0.05$). In the two trials, one case with ECG signs of myocardial ischemia and two cases of psychiatric decompensation were reported.

Tropisetron

The antiemetic drug tropisetron, a serotonin 5-HT_3 receptor antagonist (Ki = 5.3 nM) [26], has also been shown to have agonistic effects on the α_7-nicotinic acetylcholine receptor (Ki = 6.9 nM) [27] that might enhance cognitive function in patients with schizophrenia. This was evaluated in one phase III DBRCT using adjunctive tropisetron treatment in 179 patients with schizophrenia or schizophreniform disorder aged 18–64 years who presented with moderate or greater severity on at least one of the five psychotic items in the Brief Psychiatric Rating Scale (BPRS) (NCT00435370). Further inclusion criteria included a duration of illness of less than five years and a lifetime antipsychotic treatment history of less than 14 days. Antipsychotics other than risperidone, psychostimulants, and antidepressants were not permitted during the trial. Ninety and 89 patients were assigned to receive 10 mg/day tropisetron or placebo, respectively, in addition to 6 mg/day risperidone. The primary outcome was the change in the MATRICS Cognition Domains, which consisted of eight existing scales (that is, Brief Assessment of Cognition in Schizophrenia (BACS) Symbol-Coding, Trail Making Test: Part A, Attention/Vigilance Continuous Performance Test-Identical Pairs (CPT-IP), Wechsler Memory Scale-3rd Ed. (WMS-III) Spatial Span + Letter-Number Span, Hopkins Verbal Learning Test-Revised (HVLT-R), Brief Visuospatial Memory Test-Revised (BVMT-R), Neuropsychological Assessment Battery (NAB), and Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEI)), from baseline to 12 weeks. The tropisetron group showed significantly higher MATRICS Cognition Domain scores than the placebo group (mean ± standard deviation, tropisetron group 96 ± 16 vs. placebo group 95 ± 15], $p < 0.05$). Dry mouth, constipation, blurred vision, and nausea were observed in 8 of 90 patients in the tropisetron group and 6 of 89 patients in the placebo group; however, no serious adverse events were observed.

Neuroactive Steroids

Pregnenolone

The naturally occurring neurosteroid pregnenolone has been hypothesized to mitigate gamma-aminobutyric acid dysregulation and N-methyl-d-aspartate (NMDA) receptor dysfunction in patients with schizophrenia [28]. In a phase II DBRCT, the combination of antipsychotics and pregnenolone resulted in a significant enhancement of social function in patients with schizophrenia, in contrast to antipsychotic monotherapy (NCT00894842). The trial included 120 outpatients with schizophrenia aged 21–65 years who had been receiving antipsychotic drugs for at least 8 weeks. Sixty patients each were allocated to the antipsychotic plus pregnenolone and antipsychotic plus placebo groups. Pregnenolone was initiated at a dose of 100 mg/day and increased to 500 mg/day by the fourth week. A greater improvement in UCSD Performance-based Skills Assessment-Brief composite scores was observed in the pregnenolone group compared to the placebo group after 8 weeks of treatment (least-square means [standard error] 72.29 [1.03] in the pregnenolone group and 69.03 [1.02] in the placebo group, with a difference between least-square means, 3.25 points; 95 % CI, 0.40–6.10; $p = 0.03$). Conversely, no significant differences were found in changes in the MCCB composite and Scale for Assessment

of Negative Symptoms (SANS) total scores between the two groups. There were no serious adverse events related to the study medication, and the number of participants experiencing treatment-emergent adverse events was comparable between the placebo and pregnenolone groups (58 % and 55 %, respectively).

D-serine

D-serine is an endogenous agonist for the glycine site of NMDA receptors [29]. During the initial treatment phase of a phase II DBRCT (NCT00817336) employing a crossover design, 16 participants with schizophrenia or schizoaffective disorders were randomly categorized into two groups (1:1 ratio) and administered either D-serine (60 mg/kg/day) or a placebo. The initial phase was followed by a 2-week single-blind placebo washout period, followed by the alternative treatment in the second phase. Two participants prematurely withdrew from the study. A significant treatment-by-time interaction was observed for PANSS total scores in the double-blind study ($p = 0.023$). D-serine treatment led to a reduction in the PANSS total score from 82.2 ± 7.9 to 77.9 ± 9.3, whereas no significant change was found with the placebo treatment (from 79.3 ± 9.0 to 80.0 ± 10.3), yielding an effect size of 0.8. While no substantial treatment-by-time interaction was detected for the PANSS negative symptom scores ($p = 0.36$), a significant treatment effect emerged when accounting for baseline scores ($p = 0.047$). Other PANSS subscale scores did not exhibit any notable effects and there were no adverse effects of clinical significance.

Estradiol

In animal studies, estradiol elevates serotonin levels, activates metabotropic glutamate receptors, and enhances dopamine synthesis, release, and turnover [30]. A phase II placebo-controlled DBRCT evaluated the effectiveness of estradiol in women with treatment-resistant schizophrenia who were concurrently taking antipsychotic medications (NCT00357006). This study involved 183 female participants diagnosed with either schizophrenia or schizoaffective disorder, exhibiting a PANSS total score > 60 despite receiving a consistent dosage of antipsychotics for a minimum of 4 weeks. In addition to their ongoing treatment, patients were randomly assigned to take 100 (n = 59) or 200 µg/day of transdermal estradiol (n = 62) or placebo (n = 62). At 8 weeks, both the 200 µg/day and 100 µg/day estradiol groups demonstrated significant decreases in PANSS total, positive symptom, and general psychopathology scores when compared to the placebo group (200 µg/day: total, − 13.23 vs. -5.64; positive symptom, − 4.13 vs. − 1.82; general psychopathology, − 5.63 vs. − 2.5; and 100 µg/day: total, -8.9 vs. − 5.64; positive symptom, − 2.82 vs. -1.82; general psychopathology, − 4.26 vs. − 2.5; all $p < 0.01$). A greater effect was observed in the 200 µg/day than in the 100 µg/day treatment group. There were no significant differences in the PANSS-negative symptoms. No between-group or interaction effects were observed in relation to changes in the Repeatable Battery of Neuropsychological Status total scale score or any domain score at week 8. With the exception of irregular menstrual cycles in the 200 µg/day estradiol group (68 % vs 38 % $p = 0.001$), there were no statistically significant variances in the frequency of adverse events compared to placebo.

Marketed Drugs

Tolcapone

Tolcapone, currently used as an adjuvant therapy for the symptomatic management of idiopathic Parkinson's disease, acts as a central inhibitor of catechol O-methyltransferase (COMT) (Ki = 30 nM) [31], thereby potentially enhancing dopamine levels in the brain. In a phase II DBRCT (NCT00044083), tolcapone enhanced working memory in patients diagnosed with schizophrenia. The trial was conducted in a crossover fashion and included 59 patients with schizophrenia aged 18–50 years. The study involved 30 patients who received placebo for 1 week, followed by a 1-week washout period. Subsequently, they were administered 200 mg/day of tolcapone for an additional week. The remaining 29 patients were administered the reverse regimen. The patients in the tolcapone-treatment session were found to have higher N-Back Task Performance scores compared to those in the placebo session (mean ± standard error, 80.9 ± 1.9 vs. 76.2 ± 2.3, $p = 0.034$). No serious adverse events were observed. Adverse events were detected in 37 % of patients receiving tolcapone and 29 % of those receiving placebo. Adverse events that occurred more frequently than 5 % in the tolcapone and placebo groups included nausea (8.33 % and 13.56 %), diarrhea (11.67 % and 6.78 %), appetite problems (8.33 % and 10.17 %), stiffness (18.33 % and 10.17 %), sleep problems (28.33 % and 10.17 %), and hallucinations (15.00 % and 16.95 %).

Valacyclovir

Valacyclovir is an L-valyl ester prodrug of acyclovir, an antiherpes virus-specific drug (IC50 = 0.01-1.25 µg/mL) [32]. A phase II, placebo-controlled DBRCT assessed the efficacy of add-on valacyclovir in 24 neurotropic herpes simplex virus, type1 (HSV1)-seropositive individuals with schizophrenia or schizoaffective disorder. In addition to ongoing treatment with antipsychotic drugs, patients were randomly assigned to receive valacyclovir (n = 12) or placebo (n = 12) (NCT00514449). Valacyclovir (1.0 g) was administered orally twice daily for the first 2 weeks and 1.5 g orally twice daily for the next 16 weeks. The valacyclovir group exhibited a significantly greater improvement in 2-back working memory accuracy scores at 18 weeks than the placebo group (valacyclovir, mean ± standard deviation 2.13 ± 2.68; placebo, 0.13 ± 2.97; effect size, 0.72; $p = 0.037$). In addition, valacyclovir exhibited a trend-level improvement in total working memory accuracy scores (valacyclovir, 3.76 ± 4.90; placebo, 0.25 ± 4.90; effect size, 0.79; $p = 0.10$) and significant improvements in the processing speed of immediate verbal memory (valacyclovir, -0.11 ± 0.09; placebo, -0.01 ± 0.08; effect size, 1.21; $p = 0.036$), but there was no significant difference in delayed verbal memory. Regarding the other four cognitive domains (visual object learning, face memory, spatial processing, and emotion recognition), post-hoc analyses showed significant improvement only in the accuracy of delayed visual object learning (valacyclovir, 2.44 ± 2.62; placebo, -0.49 ± 3.11; effect size, 0.91; $p = 0.026$), but not in the other three domains. For changes in psychiatric symptoms, there were no significant differences in the PANSS score changes between the valacyclovir and placebo groups (total, − 7.88 ± 15.01 vs. − 14.33 ± 18.42; positive symptoms, − 2.91 ± 4.73 vs. − 3.35 ± 4.84; negative symptoms, − 2.15 ± 3.21

vs. − 4.22 ± 3.21; general symptomatology, − 3.05 ± 8.60 vs. − 5.60 ± 10.18) (all $p > 0.05$). The reported side effects in one patient each were constipation, stomach pain, motion sickness, occasional muscle twitch, tremor, and upset stomach, none of which were serious and required treatment discontinuation.

Cannabidiol

Cannabidiol (CBD) is one of at least 85 active cannabinoids identified in cannabis plants [33]. It has demonstrated potential as a therapeutic and pharmaceutical target, specifically as an analgesic, anticonvulsant, anxiolytic, antipsychotic, anti-inflammatory, and antioxidant agent [34]. Only one phase II DBRCT study has been conducted to evaluate the efficacy of adjunctive CBD in the treatment of psychotic symptoms (NCT02006628). This study included 88 patients aged 18–65 years who were diagnosed with schizophrenia or related psychotic disorders. These patients had responded positively to a stable dosage of a single antipsychotic treatment for at least 4 weeks. A total of 43 patients were assigned to receive a daily dose of 1,000 mg CBD in conjunction with their ongoing antipsychotic treatment, while the remaining 45 patients were instructed to maintain their current medication regimen for 6 weeks. The PANSS positive score (week 6) displayed a marked decrease in the CBD combination group in contrast to the comparison group (mean difference, − 1.4; 95 % CI, -2.5 to − 0.2; $p = 0.019$). Adverse events were reported by one-third of the patients in the CBD group, showing no significant difference compared to the placebo group. Dyslipidemia and nausea were found to be adverse events associated with the treatment. One patient in the CBD group experienced nausea, diarrhea, abdominal pain, and vomiting, which subsequently resolved.

Rimonabant

Rimonabant is an anorectic anti-obesity drug that acts as a cannabinoid-1 receptor antagonist [35]. The efficacy of rimonabant in overweight individuals with schizophrenia who were receiving second-generation antipsychotic drugs was evaluated in a phase II placebo-controlled DBRCT (NCT00547118). This study included 15 individuals diagnosed with schizophrenia or schizoaffective disorder who had a body mass index (BMI) of ≥ 30 kg/m^2, or a BMI of ≥ 27 kg/m^2 with hyperlipidemia or hypertriglyceridemia. Patients were randomly assigned to receive add-on treatment with 20 mg/day rimonabant (n = 7) or placebo (n = 8). Rimonabant treatment resulted in a greater reduction in the BPRS total score at 16 weeks compared to placebo (mean ± standard deviation: treatment difference, − 1.9 ± 0.8; t = 2.5, $df = 30.7$, $p = 0.02$). Among the BPRS factors, there were group differences in anxiety/depression (treatment difference, − 1.4 ± 0.4; t = 4.0, $df = 29.5$, $p = 0.0004$) and hostility (treatment difference, − 0.7 ± 0.3; t = 2.5, $df = 26.9$, $p = 0.02$). No significant differences were found in the Calgary Depression Scale total score, SANS total score and subscales, or Clinical Global Impression. Fourteen participants (seven each for rimonabant and placebo) underwent an assessment of neurocognition using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Iowa Gambling Task (IGT), Probabilistic Learning (PL), and N-Back Task. A significant treatment effect was observed for the RBANS total scale score at 16 weeks; however, no significant difference was observed in any of the RBANS domain scores or the IGT. On the other hand, those treated with rimonabant were significantly more likely to choose the most frequently rewarded item in PL tasks than those receiving placebo (F = 5.45; $df = 1,10.7$; $p = 0.04$; ES: 1.29; CI: − 2.07, 4.60). No significant differences were observed on the N-Back working memory task. The most common adverse effects of rimonabant were enuresis (n = 4), headache (n = 3), anorexia (n = 3), and abdominal pain (n = 3). None of the cases were serious or resolved without treatment.

Discussion

In our systematic search for non-dopaminergic medications for schizophrenia, 16 compounds showed positive results in phase II and phase III trials. Of these compounds, eight (bitopertin, estradiol, ulotaront, xanomeline, trospium chloride, vabicaserin, cannabidiol, rimonabant, and D-serine) showed effects on positive symptoms, two (roluperidone and pimavanserin) affected negative symptoms, and six (encenicline, tropisetron, pregnenolone, tolcapone, BI 425809, and valacyclovir) affected cognitive function. Four of the 16 treatments (ulotaront, xanomeline and trospium chloride, vabicaserin, and roluperidone) were superior to the placebo when administered as single agents. Of the three drugs that were effective in treating positive symptoms when administered alone, ulotaront has agonistic effects on TAAR1 and 5-HT$_{1A}$, vabicaserin has agonistic effects on 5-HT$_{2C}$ receptors, and xanomeline and trospium chloride have agonistic effects on the M_1 and M_4 muscarinic cholinergic receptors. In addition, roluperidone, which showed an effect on cognitive function, has affinities for σ2 (sigma-2) and 5-HT$_{2A}$ receptors.

The adverse events of all the previously mentioned compounds were comparable to those of placebo, except for the marked increase in menstrual irregularities observed with estradiol compared to placebo. Typical adverse events associated with conventional antipsychotics include extrapyramidal symptoms and hyperprolactinemia as these drugs, exhibit a common mechanism of action of suppressing dopaminergic neural transmission. The drugs discussed in this review possess a novel mechanism of action that is not mediated by dopamine receptors, thus potentially reducing the likelihood of those adverse events.

This review had several limitations. First, although ClinicalTrials.gov and the EU Clinical Trials Register contain more than 447,000 and 43,000 clinical trials, respectively, some local clinical trials may not have been captured. Second, some compounds were administered as adjuncts to the ongoing regimen, making it challenging to compare their efficacy with that of existing antipsychotics. Third, the participants included in these studies were not always well characterized in terms of diagnosis and severity of illness, which limits the extrapolation of the results to other populations with schizophrenia. Fourth, a qualitative, rather than quantitative, assessment of the clinical trials was conducted in the present review because of limited, heterogeneous data.

In conclusion, this review identified promising compounds that showed positive results in phase II or III trials for schizophrenia or treatment-resistant schizophrenia. These compounds, which function differently from existing antipsychotics that antagonize dopamine receptors to varying degrees, could effectively address the unmet requirements of patients with schizophrenia, offering more symptom-specific novel therapeutic strategies with fewer side effects.

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Conflict of Interest

Dr. Ueno has received grants from the Discovery Fund, Nakatani Foundation, Canadian Institutes of Health Research (CIHR), and Brain & Behavior Research Foundation (BBRF); manuscript fees from Dainippon Sumitomo Pharma; and consultant fees from WCG Clinical and Uchiyama Underwriting within the past three years. Dr. Uchida has received grants from Daiichi Sankyo, Eisai, Mochida, Otsuka, and Sumitomo Pharma; speaker fees from Eisai, Lundbeck, Meiji Seika Pharma, Otsuka, Boehringer Ingelheim Japan, MSD, and Sumitomo Pharma; and advisory board fees from Lundbeck, Sumitomo Pharma, Takeda Pharmaceutical Company, and Boehringer Ingelheim Japan over the past three years.

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