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THE CLOZAPINE LEGACY: FUTURE DIRECTIONS IN TREATMENT-RESISTANT SCHIZOPHRENIA AND PARKINSON'S DISEASE PSYCHOSIS

ABSTRACT

Clozapine is an exceptionally potent atypical antipsychotic medication that was developed in the 1950s and is notable for a low affinity for the dopamine D2 receptor. Following multiple fatal cases of agranulocytosis, the drug was withdrawn from the market but later reinstated with strict laboratory monitoring. Despite the risks, clozapine is regarded as the most effective medication in two different types of psychosis: treatment-resistant schizophrenia and psychosis in Parkinson's disease. Although the landmark studies demonstrating the effectiveness of clozapine in both conditions were published decades ago, it remains strikingly underutilized, possibly due to risk of serious adverse effects, clinician reluctance and lack of experience and administrative complexity. It is unlikely that clozapine will ever fully escape these barriers, and continued delays in initiating effective treatment will therefore continue to undermine care. Gladly, novel treatment alternatives are emerging for both disorders. Over the past two decades, focus has shifted from dopaminergic strategies towards pharmacological agents targeting other neurotransmitter receptors that have a role in psychosis. In particular, pimavanserin, a serotonin receptor antagonist/inverse agonist, has been approved for psychosis in Parkinson's disease, and glutamate modulating compounds have been shown to enhance the effectiveness of clozapine in treatment-resistant schizophrenia. Moreover, agonists of acetylcholine receptors may hold theoretical promise for improving outcomes across both conditions. This narrative review explores the future direction that treatment of both disorders may take.

KEYWORDS: CLOZAPINE, PARKINSON'S DISEASE PSYCHOSIS, TREATMENT-RESISTANT SCHIZOPHRENIA, SCHIZOPHRENIA

PATHOGENESIS OF POSITIVE SYMPTOMS

Psychotic episodes are characterized by reality distortion symptoms, known as delusions and hallucinations. Delusions are fixed false beliefs maintained with strong conviction despite clear evidence to the contrary, whereas hallucinations are sensory experiences occurring in the absence of corresponding external stimuli (1). Although commonly discussed in the context of schizophrenia spectrum disorders, these symptoms are transdiagnostic and occur in a variety of psychiatric and neurological disorders, as well as in the context of substance abuse (2).

For decades, impaired dopamine signalling in the midbrain has been considered the central contributor to delusions and hallucinations (3). Dopamine is a widely distributed neurotransmitter, transmitted through four main pathways: the mesocortical pathway (ventral tegmental area to cortex), the mesolimbic pathway (ventral tegmental area to nucleus accumbens), the nigrostriatal pathway (substantia nigra to striatum) and the tuberoinfundibular pathway (hypothalamus to pituitary) (4). Initially, the underlying mechanism was thought to involve an increased number of postsynaptic dopamine receptors, but subsequent studies identified presynaptic dopamine dysregulation as the leading mechanism underlying positive symptoms (3,5). This presynaptic increase in striatal dopamine synthesis and release has formed the theoretical foundation for psychotic symptoms for the past half a century and continues to inform current treatment of delusions and hallucinations.

Since the development of the first antipsychotic medication, chlorpromazine, in 1952, blockade of postsynaptic dopamine D2 receptors in the striatum has been the primary target of antipsychotic pharmacotherapy. Despite the effectiveness of

D2 receptor-blocking therapies, dopaminergic dysfunction provides an incomplete picture of many of the disorders in which psychotic symptoms occur. It is not sufficient to explain complex syndromes such as schizophrenia, where D2 receptor blockade only affects the positive symptom dimension in a meaningful way, while having little effect on what are known as the negative and cognitive symptoms. In addition, despite the strong hereditary components of schizophrenia, genetic studies do not suggest dysfunction of dopamine signalling as the primary cause of the disorder, at least for most individuals (6). Instead, aberrant dopamine signalling is now seen as a final common pathway, where multiple factors such as frontotemporal dysfunction, genetic risk factors, stress and stimulants could converge to give rise to surprisingly similar clinical presentations characterized by positive symptoms (3,6). Other neurotransmitters, including glutamate, serotonin, acetylcholine and histamine, have been suggested to represent upstream regulators of processes leading to schizophrenia.

The shortcomings of the dopamine hypothesis of psychosis are perhaps most clearly seen in two distinct psychotic disorders. Namely, patients with treatment-resistant schizophrenia (TRS) and Parkinson's disease psychosis (PDP) who often either fail to respond to or cannot tolerate commonly used antipsychotic medications. Over the past four decades, no other medication has proved more effective than clozapine, an atypical antipsychotic medication with a relatively low affinity for dopamine receptors, in either condition (7,8). As reflected by numerous negative clinical studies, the dopamine hypothesis of psychosis has ultimately failed to provide both a satisfactory theoretical foundation and novel treatment options for these conditions, and attention is shifting to treatments built on other mechanisms of action. *Table 1* presents the contribution of the most common neurotransmitter systems in both conditions.

Table 1. Proposed contributions of major neurotransmitter systems to schizophrenia, treatment-resistant schizophrenia and psychosis in Parkinson's disease

System	Proposed role in schizophrenia	Role in pathogenesis and treatment of TRS	Role in pathogenesis and treatment of PDP
Dopamine	Increased dopamine synthesis and signalling in mesolimbic pathways, particularly through dopamine D2 receptors, remains central to positive symptoms. Multiple upstream pathologies may converge on a common dopaminergic abnormality.	Striatal dopamine synthesis appears closer to control levels, suggesting a less central role than in treatment-responsive schizophrenia. D2 receptor blockade often insufficient.	Dopaminergic medications contribute to psychosis but do not solely explain it. D2 receptor antagonists can reduce psychotic symptoms but are limited by motor adverse effects.
Acetylcholine	Modulates dopamine signalling mainly through muscarinic M1 and M4 receptors. Role of nicotinic receptors remains incompletely understood.	Role in pathogenesis uncertain. Direct evidence remains limited, but M1/M4 receptor modulation is a potential therapeutic strategy.	Deficits are strongly associated with cognitive and neuropsychiatric symptoms, including psychosis. Pharmacological modulation is a potential therapeutic strategy.
Serotonin	Regulates dopamine signalling in mesocortical and mesolimbic pathways.	Secondary role to glutamate. 5-HT2A modulation is a potential therapeutic strategy.	Important contribution through 5-HT2A receptors. The role of 5-HT1A and 5-HT3 receptors remains less certain. 5-HT2A modulation represents a leading therapeutic strategy.
Glutamate	The NMDA receptor is a key regulator of cortical and subcortical circuits, including dopaminergic signalling in the midbrain. NMDA receptor antagonists produce a more complete schizophrenia-like syndrome than purely dopaminergic agents such as amphetamine.	Leading mechanistic hypothesis and a major focus of therapeutic development.	Role in pathogenesis uncertain.

System	Proposed role in schizophrenia	Role in pathogenesis and treatment of TRS	Role in pathogenesis and treatment of PDP
TAAR1	Regulates monoaminergic signalling, including dopamine and serotonin pathways. Role in psychosis uncertain.	Role in pathogenesis uncertain.	Role in pathogenesis uncertain. Emerging therapeutic strategy.
Histamine	Histaminergic signalling, especially through the H2 receptor, may modulate glutamatergic and dopaminergic neurotransmission, although its role in schizophrenia remains uncertain.	Role in pathogenesis uncertain.	Role in pathogenesis uncertain.

Abbreviations: 5-HT = 5-hydroxytryptamine receptors (serotonin receptors), NMDA = N-methyl-D-aspartate receptor, PDP = Parkinson's disease psychosis, TAAR1 = Trace amine–associated receptor 1, TRS = Treatment-resistant schizophrenia

TREATMENT-RESISTANT SCHIZOPHRENIA

As many as one third of patients diagnosed with schizophrenia do not respond to traditionally used first- and second-generation antipsychotic medications (9). Patients fulfilling the criteria for schizophrenia who do not respond to two different antipsychotic medications used at an adequate dose over 6 weeks should be considered TRS (10), and evaluated for treatment with clozapine. Whether TRS represents a separate disorder from treatment-responsive schizophrenia, or the most severe aspect of the schizophrenia spectrum, remains uncertain (11). In a study by Demjaha et al., TRS patients displayed normal levels of dopamine in the midbrain when measured with radiolabelled DOPA positron emission tomography (12), suggesting a separate mechanism of action and providing an explanation for why these patients do not respond to D2 blockade (13). TRS has also been shown to present as early- and late-onset types, with an estimated 70% of TRS patients being resistant to treatment at onset of symptoms, while the remaining patients develop it as the disease progresses (14,15). It should also be noted that not all treatment-resistant patients respond to clozapine, and that this condition may comprise multiple different disease pathologies (16).

PARKINSON'S DISEASE PSYCHOSIS

Parkinson's disease (PD) is a common neurodegenerative disorder primarily characterized by motor symptoms. While the root cause of the disorder remains unknown, the disease is known to feature widespread accumulation of intracellular aggregated α-synuclein in the brain. Motor symptoms are primarily associated with degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to a decrease in dopaminergic innervation of the basal ganglia (17). In addition to motor symptoms, PD is associated with a wide range of non-motor symptoms, for many of which the pathogenesis is less well understood. Psychotic symptoms, such as hallucinations and paranoid delusions, occur in approximately 40-60% of patients with PD (18,19) and are associated with worse outcomes (20). These symptoms are exacerbated by antiparkinsonian drug therapies such as dopamine agonists and levodopa but cannot be fully explained as adverse effects of these drugs, as PDP was described before the development of levodopa (21). Furthermore, there is conflicting evidence regarding the correlation with antiparkinsonian drug doses, with some studies reporting a correlation (18,22,23), while others do not (24). Initially, high-dose levodopa infusion did not appear to induce these symptoms (25), but more recent evidence suggests that psychotic symptoms occur more frequently during infusion therapies (26). A characteristic feature of PDP is the presence of visual hallucinations. These are often preceded by milder symptoms such as illusions or a sense of presence; and delusions, when occurring, often do so only at the later stages of the disorder (27).

CURRENT PHARMACOLOGICAL LANDSCAPE

THE SUPERIORITY OF CLOZAPINE

Clozapine was developed in the late 1950s (28), less than a decade after the first antipsychotic medication chlorpromazine (29) was introduced to psychiatric care. Initial studies showed promising results with little extrapyramidal side effects (28), but only a few years later it was withdrawn from the market due to multiple cases of fatal agranulocytosis in Finland in the late 1970s (30). It was reintroduced in limited scale under strict laboratory follow-up regime, but only gained widespread interest after two landmark studies in the late

1980s showed that the adverse effects of clozapine could be mitigated through strict laboratory monitoring, and that it was more effective than chlorpromazine in treating patients with schizophrenia (31,32). A decade later, the effectiveness of using clozapine in treating PDP was demonstrated in two randomized controlled studies (RCTs) (33,34). These studies still constitute the foundation of pharmacological treatment for both conditions, as no other medication has been able to surpass the effectiveness of clozapine in either TRS or PDP despite numerous attempts.

Increased dopamine signalling in the midbrain has traditionally been seen as the main mechanism underlying positive symptoms of psychosis, and consequently blockade of the D2 receptor in the striatum has been considered as the main mechanism of action for antipsychotic medications (3). Clozapine is regarded as one of the most potent antipsychotic medications but has a relatively low affinity for the D2 dopamine receptor when compared to other antipsychotic medications (35), making it something of a pharmacological enigma. Clozapine has a broad receptor affinity profile, working as an antagonist or inverse agonist at the dopamine D2 and D4 receptors, the serotonin 5-HT2A and 5-HT3 receptors, the histamine H1 and H2 receptors and the muscarinic M1 receptor, but an agonist at the muscarinic M4 and the serotonin 5-HT1A receptors, as well as a moderate protean agonist at histamine H3 receptor. Its metabolite norclozapine, however, is a full agonist at the M1 receptor. Further, there is evidence suggesting that clozapine partakes in modulation of glutamate metabolism (36). This unique repertoire of receptor affinities has made it difficult to decipher which effects underlie its positive effects (37-39).

Clozapine is associated with several potentially severe side effects, which in addition to agranulocytosis, include myocarditis, paralytic ileus, pneumonia, seizures, venous thromboembolism and significant weight gain. A fourth of patients with schizophrenia on clozapine discontinue the medication, many due to adverse effects. Severe adverse events, such as agranulocytosis, myocarditis and thromboembolism, are relatively rare, affecting only a small minority of patients (40). Longer follow-ups have, however, highlighted the cumulative risk of paralytic ileus and pneumonia, and highlighted these as among the most important causes of clozapine-related mortality during long-term treatment (41). Historically, the risk of agranulocytosis has mandated frequent monitoring of neutrophil counts during clozapine treatment. However, these recommendations have recently been revised as the risk of agranulocytosis is relatively low in patients with stable neutrophil counts. As the risk for agranulocytosis declines markedly after the first years of treatment (42), annual monitoring may be safe for patients without neutropenia after two years of treatment (43). Currently, the European Medicines Agency (EMA) suggests weekly monitoring during the first 18 weeks of treatment, monthly monitoring until the end of the first treatment year, monitoring every 12 weeks during the second year, and annual monitoring after the first two years in patients without neutropenia. These recommendations are currently being implemented in Finland. Reflecting the concerns about these risks and the need for frequent laboratory follow-up, delays in initiating clozapine treatment in TRS are still common (44,45), and clinicians often resort to less effective options in treating PDP (46,47). As clozapine remains markedly underused in PDP, less is known about its safety profile in PDP when compared to TRS (48). While the risk of agranulocytosis does not seem to be dose dependent, the risk of metabolic complications appears to be lower in PDP, where the required dose is often a tenth of that needed in TRS (48,49). In a small follow-up study on 32 PDP patients using clozapine, the main reason for discontinuation of treatment was not the occurrence of adverse events, but the inconvenience of frequent laboratory testing (49).

Since clozapine was developed, numerous attempts have been made to mimic its effects. Despite the development of dozens of dopaminergic antipsychotic drugs over the past four decades, arguably, none of them fully mimics the receptor affinity profile of clozapine, nor has any drug been able to provide equal therapeutic efficacy, especially for TRS and PDP. The atypical or second-generation antipsychotic medications were brought to the market among great anticipation, and while they have become the primary treatment option for psychotic disorders, they have not provided a clear alternative in TRS or PDP. During the past two decades, the focus has shifted from mimicking the full spectrum towards more precise compounds targeting a specific receptor, yet often in a manner similar to clozapine. It should be noted that not all novel treatment options aim to mimic or replace clozapine (50), as many options are non-pharmacological, and many aim to augment the effect of clozapine. But as initiation of clozapine remains one of the key barriers, and delays are associated with worse outcomes (51), a major unmet need is an effective antipsychotic medication for TRS that clinicians feel comfortable prescribing and whose initiation is not delayed due to a fear of side effects. Whether or not this will be the same medication that alleviates psychotic symptoms in PDP without aggravating motor symptoms remains to be seen.

SHORTCOMINGS OF SECOND-GENERATION ANTIPSYCHOTICS IN PDP

The emergence of atypical or second-generation antipsychotic medications in the 1990s sparked a new interest in the treatment of PDP. Whereas the categorization is ambiguous (52), many of the antipsychotic medications developed during the past three decades do display a lower D2 receptor affinity (53), which was theorized to result in a lower risk of extrapyramidal complication — a common side effect of early first-generation antipsychotic medications. In theory, these new medications could provide a similar effect to clozapine, while maintaining the low risk of extrapyramidal symptoms, but without the potentially fatal side effects.

Risperidone, being the first of the novel medications developed, initially showed great promise in PDP. Multiple open-label studies showed improvement in psychotic symptoms with no worsening of motor symptoms (54-57), while others highlighted the risk for motor complications (58,59). A small RCT comparing risperidone to clozapine did not observe significant differences between alleviation of positive symptoms (60). While not statistically significant, motor symptoms improved in the clozapine group while they worsened in the risperidone group. Olanzapine, sharing a more similar receptor affinity profile to clozapine than risperidone (53), was subsequently theorized to have a more favourable side-effect profile. An open-label trial on 15 patients with PDP initially showed a positive response on psychotic symptoms with no motor deterioration (61). Later studies, however, showed a significant negative effect on motor symptoms (62,63), which was later verified in double-blinded RCT studies, both compared to placebo (64,65) and clozapine (66). In a recent meta-analysis, both risperidone and olanzapine were associated with significant extrapyramidal side effects, and neither drug is recommended for use in PDP (7).

Quetiapine was released a few years after risperidone, and more closely mimics clozapine's relatively low D2 receptor affinity and relatively strong antagonism at the 5-HT2A receptor (53). Due to this similarity, quetiapine was hypothesized to mirror the effects of clozapine. Open-label studies (67-73) and studies comparing quetiapine to clozapine (74,75) suggested that quetiapine might be as effective as clozapine in the treatment of PDP. The effectiveness of clozapine could, however, not be replicated in multiple placebo-controlled studies on PDP patients (76-79) or patients with parkinsonism and psychosis (80). Three reviews (81-83) and one meta-analysis (84) analysing the effectiveness of quetiapine have reached the same conclusion: quetiapine is not significantly more effective than placebo in treating PDP. A later version of the meta-analysis, employing a Bayesian network analysis, suggested that quetiapine may be more effective than placebo, but less effective than clozapine (7). Many previous individual studies have not shown a significant worsening of motor function in association with quetiapine, a result supported by the meta-analysis by Iketani et al. (7). Despite the evidence supporting the use of clozapine, most physicians rely on second-generation antipsychotics such as quetiapine or risperidone in the treatment of PDP (46,47). The use of antipsychotic medications in PDP remains controversial since quetiapine is associated with a significant increase in mortality in the elderly (85).

SHORTCOMINGS OF SECOND-GENERATION ANTIPSYCHOTICS IN TRS

Second-generation antipsychotic medications have been extensively studied in TRS patients. The original study by Kane et al. showed statistically significant improvement in both positive and negative symptoms in patients using clozapine when compared to chlorpromazine, a first-generation antipsychotic medication (32). Regarding second-generation antipsychotic medications the situation is less clear. Two meta-analyses published a decade ago reached different conclusions, with results supporting (86) and contradicting (87) the superiority of clozapine when compared to other second-generation antipsychotic medications. Olanzapine, which most closely mimics the receptor affinity profile of clozapine (53), was shown to be at least almost as effective in treating positive and negative symptoms. A more recent meta-analysis reached a similar conclusion: clozapine is more effective in TRS patients than first-generation antipsychotics and seems to be more effective than second-generation antipsychotics other than olanzapine (8). The authors of the meta-analyses highlight limitations, such as many studies being industry sponsored, omitting measurements of plasma levels of clozapine increasing the risk of using inadequate doses of clozapine, and the varying definitions of TRS used in individual studies. Further, it is likely that many of the patients included in the study most likely do not fulfil the widely used Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines for TRS (10). In two critical subgroup analyses of the most recent meta-analysis — when industry-sponsored studies were excluded and when including only double-blinded studies with high doses of clozapine in very treatment resistant patients — clozapine was shown to be more effective than olanzapine (8).

CURRENT GUIDELINES FOR TRS AND PDP FROM A EUROPEAN PERSPECTIVE

At the time of writing, no antipsychotic medications that do not rely on direct D2 blockade have been approved for the treatment of schizophrenia or PDP in Europe. In contrast, in the United States, such approaches have entered clinical use, with xanomeline–trospium recently approved for use in schizophrenia, and pimavanserin being approved for PDP almost a decade ago. For both PDP and TRS, multiple treatment guidelines have been published, reflecting differently on the available evidence. A recent treatment algorithm for PDP from a European perspective — where pimavanserin is not an option — recommends a trial of quetiapine prior to initiating treatment with clozapine (88). Conversely, the TRRIP guidelines for TRS do not make suggestions regarding which two antipsychotic medications should be trialled before clozapine, although this question was discussed and differing viewpoints presented (10). Adhering strictly to the available evidence, one could argue that a trial of quetiapine prior to clozapine in PDP is not supported, and that olanzapine may warrant consideration as one of the two antipsychotics trialled before clozapine in schizophrenia. However, strict adherence to available evidence may not always be feasible in clinical practice. Trials of quetiapine in PDP have generally been small and underpowered; nevertheless, the drug is well tolerated, widely familiar to clinicians and requires minimal laboratory monitoring. Conversely, although recent meta-analyses highlight olanzapine as an alternative to clozapine in TRS, this evidence is constrained by the heterogeneous definition of TRS in these studies and the role of industry sponsorship.

Taken together, olanzapine most closely mimics clozapine both from a pharmacological and clinical perspective but still seems to be less effective than clozapine in TRS (8) and is hindered by motor complications in PDP (7). Ultimately, it seems unlikely that a medication which primarily relies on dopamine receptor antagonism will achieve the same level of efficacy and tolerability as clozapine in these two conditions. Promising multi-receptor modulators such as brilaroxazine, a serotonin-dopamine modulator currently in late-stage development (NCT05184335), continue to be developed and may ultimately prove effective in one or both conditions. However, as with other atypical antipsychotics, it remains uncertain whether they can overcome the limitations associated with dopamine receptor modulation. Consequently, increasing attention has been directed toward medications that selectively target glutamate, serotonin, acetylcholine and histamine receptors. *Table 2* presents those treatment options that have been developed furthest, while the next section describes these and other promising treatment options in detail.

Table 2. Main new medications that do not rely on dopamine D2 receptor blockade developed for the treatment of schizophrenia or PDP

Medication	Mechanism of action	Results from research on patients with schizophrenia	Results from research on patients with TRS	Results from research on patients with PDP
Xanomeline - trospium	M1 and M4 agonist	Phase III: Significant reduction in PANSS score. Approved by the FDA in 2024 for the treatment of schizophrenia in the United States	No RCTs Conflicting results from case reports	No RCTs No case reports
Emraclidine	M4 allosteric modulator	Phase Ib: Significant reduction in total PANSS score Phase IIb: Failed to meet primary endpoint (reduction in PANSS score) in two studies	No RCTs No case reports	No RCTs No case reports
Pimavanserin	5-HT2A antagonist / inverse agonist	Phase II: Significant reduction in NSA-16 score Phase III: Failed to meet primary endpoint (reduction in NSA-16 score)	No RCTs Positive case report series	Phase III: Significant reduction in SAPS-PD. Approved by the FDA in 2016 for the treatment of PDP in the United States Two ongoing RCTs comparing efficacy to quetiapine

Medication	Mechanism of action	Results from research on patients with schizophrenia	Results from research on patients with TRS	Results from research on patients with PDP
Roluperidone	5-HT2A antagonist α1 antagonist σ2 antagonist	Phase IIb: Significant reduction in PANSS negative score Phase III: Numerical but non-significant reduction in PANSS negative score; further Phase III evaluation ongoing	No RCTs No case reports	No RCTs No case reports
Ondansetron	5-HT3 antagonist	Multiple positive RCTs showing reduction in negative symptoms	Two RCTs show reduction in negative symptoms	Positive open-label studies Ongoing RCT
Ulotaront	TAAR1 agonist 5-HT1A agonist	Phase II: Significant reduction in PANSS score Phase III: Failed to meet primary endpoint (reduction in PANSS score) in two studies	No RCTs No case reports	Pilot study: Non-significant reduction in SAPS-PD score when compared to placebo
Iclepertin	GlyT1 inhibitor	Phase II: Significant improvement in MCCB Phase III: Failed to meet primary endpoint (improvement in MCCB) in three studies	No RCTs No case reports	No RCTs No case reports
Bitopertin	GlyT1 inhibitor	Phase II: Significant reduction in PANSS negative score Phase III: Failed to meet primary endpoint (reduction in PANSS negative score) in multiple studies	No RCTs No case reports	No RCTs No case reports
Evenamide	Voltage-gated sodium channel modulator	Phase II&III: Significant reduction in PANSS score in patients with worsening symptoms on stable second-generation antipsychotic medication	Phase II: One-year open-label, rater-blinded study Significant reduction in PANSS score Phase III: Ongoing	No RCTs No case reports

Abbreviations: 5-HT= 5-hydroxytryptamine receptors (serotonin receptors), FDA = Food and Drug Administration, GlyT1 = Glycine transporter type 1, MCCB = MATRICS Consensus Cognitive Battery, M1 and M4 = Muscarinic acetylcholine receptors M1 and M4, NSA-16 = Negative Symptom Assessment-16, PANSS = Positive and Negative Syndrome Scale, PDP = Parkinson's disease psychosis, RCT = Randomized controlled trial, SAPS = Scale for the Assessment of Positive Symptoms, SAPS-PD = Scale for the Assessment of Positive Symptoms - Parkinson's Disease, TAAR1 = Trace amine–associated receptor 1, TRS = Treatment-resistant schizophrenia

NEW PHARMACOLOGICAL TARGETS

GLUTAMATE

Glutamate is the principal excitatory neurotransmitter in the brain, with its actions mediated through fast excitatory AMPA receptors and NMDA receptors, the latter essential for synaptic plasticity. Multiple studies have demonstrated abnormal levels of glutamatergic metabolite levels across schizophrenia spectrum patients compared with control subjects, particularly in brain areas such as the basal ganglia and anterior cingulate cortex (89). Impaired NMDA receptor function has been suggested as one of the main mechanisms leading to an increase in dopamine signalling in the mesolimbic dopamine pathway (90). Moreover, symptoms caused by disruptions of glutamate signalling through the NMDA receptor support a central role for glutamate in the formation of

psychotic symptoms. For example, prolonged use of ketamine, an NMDA receptor antagonist, and autoimmune encephalitis caused by NMDA receptor antibodies can induce syndromes resembling schizophrenia (91). Crucially, these syndromes often present a more complete mimicry of schizophrenia, with negative and cognitive symptoms often present. The NMDA receptor requires simultaneous binding of glutamate and glycine or D-serine to activate (92). Thus, molecules enhancing NMDA receptor function through the glutamate and/or glycine binding sites have been studied. Multiple molecules have shown promising results in schizophrenia, but so far only a few have been trialled specifically in TRS. Furthermore, most novel pharmacological interventions in TRS have been trialled as add-ons to clozapine in cases with inadequate response (93,94).

Glycine has been studied as a potential add-on to antipsychotic treatment in multiple studies. While it does not seem to alleviate symptoms in TRS patients when added to clozapine (95,96), there is evidence of significant reduction in negative symptoms when used in combination with other antipsychotic medications (50). D-Amino acid oxidase (DAAO) inhibitors, which block the breakdown of D-serine, have been highlighted as one potential target for novel therapies. An RCT on the use of sodium benzoate, a DAAO inhibitor, as an add-on to clozapine in TRS patients with inadequate response showed improvement in both positive and negative symptoms (97). Ω-NaBen is a crystalline form of sodium benzoate with a higher central nervous system exposure (98). A Phase II/III study on its efficacy as an add-on to clozapine in TRS is currently ongoing (NCT03094429). Luvadaxistat, a selective DAAO inhibitor, was originally developed to treat Friedreich ataxia but has recently been studied in schizophrenia. A Phase II trial as an add-on to antipsychotic medication (other than clozapine) showed improvement in cognitive symptoms (99), but these results were not replicated in a more recent trial (100), with no further trials ongoing. Neither trial investigated the effectiveness of luvadaxistat in TRS.

Sarcosine is an inhibitor of the type 1 glycine transporter (Glyt1), which increases the synaptic availability of glycine, leading to an augmentation of glutamate binding to the NMDA receptor. Sarcosine was shown to be an effective add-on to antipsychotic treatment in a small placebo-controlled study (101), but these results were not replicated when patients were using clozapine (102). As clozapine itself already modulates glutamate transmission, the negative results in trials investigating the combination of other glutamate agonists with clozapine may reflect a ceiling effect where further glutamate augmentation provides little benefit (103). Supporting this line of thinking, a clinical case report described a positive response to sarcosine in a TRS patient after clozapine had to be discontinued due to myocarditis (104). A placebo-controlled trial on sarcosine in patients with Parkinson's disease dementia showed initial favourable effects on hallucinations, which were, however, not retained at the 8-week follow-up (105). Iclepertin is a selective Glyt1 inhibitor, which initially showed significant reduction in cognitive symptoms in schizophrenia (106). These results were, however, not replicated in Phase III studies (107). Bitopertin, another Glyt1 inhibitor, failed to translate positive Phase II results — which showed a significant reduction in negative symptoms (108) — to larger Phase III trials (109). It seems unlikely that iclepertin or bitopertin will be trialled in either PDP or TRS.

Evenamide —which modulates glutamate release through blockade of voltage-gated sodium channels — is arguably one of the most promising novel pharmacological treatment options in TRS. In the Phase II trial, addition of evenamide to current second-generation antipsychotic treatment, in patients with schizophrenia experiencing worsening symptoms, was associated with a significant reduction in positive symptoms when compared to placebo (110). These results were replicated in a recent Phase III trial (111). Furthermore, in an open-label study, evenamide was well tolerated in TRS patients with minimal side effects and maintained efficacy even after 12 months of use (112). Evenamide appears to be an effective and safe option for treating TRS as an adjunct therapy to second generation antipsychotic medication (including clozapine) (113). A larger Phase III study to assess its efficacy in TRS patients (as defined by the TRRIP guidelines) is currently ongoing (NCT07184619).

Despite promising results in patients with schizophrenia (114), N-acetylcysteine, a glutamate-modulating agent proposed to restore glutamatergic homeostasis by increasing the delivery of cysteine, did not improve outcomes in patients with TRS when combined with clozapine (115).

Levetiracetam binds to the intracellular synaptic vesicular protein 2A, leading to a reduction in excitatory signalling and neuromodulation mainly through reduced glutamate signalling. It is mainly used in patients with epilepsy but has been shown to normalize hippocampal hyperactivity associated with psychosis in schizophrenia (116). Despite psychosis being a known side effect, preliminary results suggest that it could be effective in treating negative and cognitive symptoms in schizophrenia (117), and a placebo-controlled trial in PDP patients is currently ongoing (NCT05824728).

Memantine is an NMDA receptor antagonist used in advanced stages of Alzheimer's disease, often in combination

with an acetylcholinesterase inhibitor (AChEI). Results are mixed, but it seems to be effective in treating negative symptoms in schizophrenia (118) and TRS patients with a suboptimal response to clozapine (119). Unlike other NMDA receptor antagonists such as ketamine, memantine does not seem to induce psychotic symptoms. The reason for this is not fully understood but may be related to a low affinity for the NMDA receptor, rapid dissociation from the receptor, as well as an uncompetitive mechanism of antagonism (120). No trials specifically studying PDP patients have been conducted.

SEROTONIN

Serotonin is synthesized in the raphe nuclei in the brainstem, with widespread connections across the cortex. There are 14 known serotonin receptors, and serotonin has been implicated in multiple neurological conditions (121). Most centrally for psychosis, it is thought to be a central regulator of dopamine signalling in the mesocortical pathway and has thus been strongly linked to the presence of negative and cognitive symptoms. Stimulation of the 5-HT2A receptor has been shown to lead to an increase of dopamine signalling in both the mesocortical and mesolimbic pathways (121), and administration of 5-HT1A agonists increases dopamine function especially in the mesocortical pathway.

Due to the lower risk of motor complications, medications targeting the serotonergic system of the brain have been extensively studied in psychotic disorders during the past two decades. Pimavanserin, a 5-HT2A receptor antagonist/inverse agonist, has been approved for the treatment of PDP in the US (122). Multiple studies show effectiveness when compared to placebo (123,124), and the lack of direct effect on the dopaminergic system results in a low risk for aggravation of motor symptoms when compared to dopamine antagonists (7). Two large studies comparing pimavanserin to quetiapine in PDP are currently ongoing (NCT04373317, CTRI/2022/04/041968). An RCT of pimavanserin in patients with schizophrenia showed a trend towards improvement in negative symptoms (125). However, these findings were not replicated in the Phase III study (126), leading to the termination of research on pimavanserin use in schizophrenia. No randomized studies were conducted specifically in TRS patients, but a case series of 10 patients with refractory psychosis — six of whom had not responded to clozapine — showed a reduction in positive symptoms following treatment with pimavanserin (127). Further support for the role of serotonin in the emergence of negative symptoms comes from studies of roluperidone (MIN-101), an antagonist of 5-HT2A, α1-adrenergic and σ2 receptors. Although it shares serotonergic activity with pimavanserin, antagonism of σ2 receptors may additionally influence signalling in glutamatergic and dopaminergic pathways. Similarly to pimavanserin, promising Phase IIb results (128) were not fully replicated in the subsequent Phase III trial, where the primary endpoint narrowly missed statistical significance (129). Consequently, the Food and Drug Administration (FDA) concluded that there was insufficient evidence to support approval. A new confirmatory Phase III trial was subsequently initiated in 2026 (NCT07565428). Remlifanserin (ACP-204), a selective 5-HTA2 inverse agonist, has recently been developed to treat psychosis in Alzheimer's disease, and a study on dementia with Lewy bodies (DLB) patients with psychotic symptoms is currently ongoing (NCT07029581).

Trace amines are found in low concentrations in the central nervous system and are thought to play a role in the modulation of monoaminergic neurotransmission (130). Thus, the trace amine-associated receptor 1 (TAAR1) has been considered a potential target in schizophrenia, where dysregulation of dopaminergic, serotonergic and glutamatergic signalling has been theorized to underlie the development of psychosis. Ulotaront, a TAAR1 and 5-HT1A agonist, has been shown to be significantly more effective than placebo in treatment of schizophrenia (131), and a pilot study found a non-significant numerical reduction in the severity of PDP when compared to placebo (132). Two Phase III trials in schizophrenia did, however, fail to meet the primary endpoint, possibly in part due to an unusually large reduction in symptoms in the placebo groups. Whether the efficacy of ulotaront is achieved through serotonergic effects or mediated through the TAAR1 receptor is uncertain. Ralmitaront, a selective TAAR1 agonist, failed to show efficacy in a Phase II trial in patients with schizophrenia and further studies do not seem to be planned (NCT04512066).

Ondansetron is a selective 5-HT3 receptor antagonist used primarily as an antiemetic. 5-HT3 receptors have been implicated in the modulation of dopaminergic signalling within the mesolimbic pathway, as well as nicotinic receptor-mediated cholinergic neurotransmission (133). In the 1990s, three open-label studies suggested that ondansetron could be effective in the treatment of PDP (133). Despite these promising initial findings, no randomized controlled trials were conducted for several decades. However, an RCT investigating ondansetron in the treatment of PDP was initiated in 2024 (NCT04167813). In schizophrenia, ondansetron has been shown to reduce negative symptoms in multiple RCTs (134). Similar findings have been shown for TRS, where two RCTs demonstrated a significant reduction in negative symptoms when ondansetron was added to either haloperidol or risperidone (135,136). Nevertheless,

a recent meta-analysis concluded that the available evidence for the use of ondansetron in TRS remains insufficient and highlighted the need for high-quality RCTs (50).

ACETYLCHOLINE

The cholinergic system of the central nervous system originates in the basal forebrain and upper brainstem. The effects of acetylcholine are mediated through fast-acting, ligand-gated nicotinic receptors and G protein-coupled muscarinic receptors (M1-M5), which facilitate slower modulations of neural signalling. Nicotinic receptors in the central nervous system exist in a wide variety of combinations of multiple α and β subunits. Peripheral muscarinic and nicotinic receptors are widely distributed within the autonomic nervous system and in the neuromuscular junctions respectively, giving rise to many of the side effects associated with cholinergic medications.

Widespread changes in the level of both nicotinic and muscarinic receptors have been observed in schizophrenia (137), and the effect of clozapine on muscarinic receptors has been suggested to, at least partially, account for its effectiveness (38). M1 and M4 receptor agonism reduces dopamine signalling in the mesolimbic pathway and could represent a pathophysiological explanation for the emergence of positive symptoms as well as a target for antipsychotic medications (138). The evidence for the involvement of nicotinic receptors in the development of psychosis is less clear (139). Stimulation of nicotinic receptors in the ventral tegmental area seems to increase dopamine signalling in the ventral striatum (140), and nicotine consumption is more prevalent in patients with schizophrenia than in the general population (141). Patients with a recent psychosis show lower availability of the α7 receptor in the hippocampus (142), and multiple α7 receptor agonists are in development, especially for treating cognitive symptoms in schizophrenia (143).

Imbalances in the cholinergic system have also been suggested to underlie the formation of visual hallucinations in PD (144) and DLB (145), which shares both clinical and neuropathological aspects with PD. In addition, the prevalence of psychotic symptoms in PD correlates with cognitive decline (19,24), which has been tightly linked to alterations in the cholinergic system.

Additional support for the targeting of the cholinergic system comes from the recent approval of xanomeline-trospium, a combination of the M1/M4 agonist xanomeline and the peripheral muscarine antagonist trospium, for the treatment of schizophrenia (146,147). This represents the first approval of an antipsychotic drug whose primary mechanism of action is not based on D2 antagonism, marking a major breakthrough in the treatment of psychotic disorders. Currently, there are no ongoing studies assessing its effectiveness in TRS, but a case report described a case of successful use of xanomeline-trospium in a patient with TRS (148). A more recent case series of 20 treatment-resistant patients did not show significant improvements, but most of the patients discontinued the medication due to side effects (149). These in turn, were attributed to factors such as predominance of schizoaffective disorder diagnoses, concurrent use of anticholinergic medication and not taking xanomeline-trospium with food (150). Moreover, xanomeline-trospium is currently being studied in treating psychosis in Alzheimer's disease (NCT06947941) but has not been trialled in PDP. Emraclidine, a selective M4 allosteric modulator, recently failed to meet the primary endpoint in two Phase II trials (NCT05227690, NCT05227703) following a successful placebo-controlled Phase 1b trial (151), which demonstrated significant improvements in positive and negative symptoms in patients with schizophrenia.

Despite evidence supporting a central role of cholinergic dysfunction in the emergence of psychotic symptoms, relatively few studies have examined the use of AChEIs in the treatment of PDP. AChEIs act more broadly on the cholinergic system by increasing the availability of acetylcholine in the synaptic cleft, thereby enhancing signalling though both nicotinic and muscarinic receptors. While donepezil (152) and rivastigmine (153) do not appear to prevent the development nor slow the progression of PDP, three small open-label studies investigating the effect of donepezil and rivastigmine in PDP reported significant improvement in symptom severity (154-156). Similar results have been described in case series (157-159). Furthermore, in DLB, donepezil has been shown to alleviate visual hallucinations (160,161). Notwithstanding, given the tendency toward substantial improvement in placebo groups in previous double-blind studies (83), results from open-label studies should be approached with caution.

HISTAMINE

Among the principal transmitter substances of the brain, histamine is arguably the least well characterized. Histamine-containing neurons originate in the tuberomammillary nucleus (TMN), extend broadly throughout the cortex, and exert their effects through four receptor subtypes, designated H1 through H4 (162). Increased levels of histamine metabolites have been observed in cerebrospinal fluid in patients with schizophrenia, and histamine receptors H1-3 have been suggested to possibly take part in the formation of psychotic symptoms (163).

Following a case report (164) describing a patient with schizophrenia and a peptic ulcer who improved clinically after treatment with famotidine, an H2 antagonist, an open-label trial subsequently showed improvement in 12 subjects with schizophrenia when famotidine was added to current treatment (165). Two RCTs studying the effects of famotidine in TRS patients showed significant amelioration of positive and negative symptoms when compared to placebo (166,167). Despite these promising results, to our knowledge, no follow-up studies have been conducted. Famotidine has not been trialled in PDP. Instead, famotidine has been studied for the treatment of dyskinesias in PD (168). While famotidine did not result in a significant decrease in dyskinesias, it was well tolerated and no significant adverse events were observed.

Both H2 and H3 receptors remain potential therapeutic targets, but enthusiasm for H3 receptor modulation has waned following several negative Phase II studies of H3 inverse agonists for cognitive symptoms in schizophrenia (163). Furthermore, the discontinuation of 40 mg famotidine tablets means that patients would need to take twenty 10 mg tablets daily to reach the 200 mg dose used by Meskanen et al., potentially limiting the feasibility of clinical implementation (167).

CONCLUSIONS AND FUTURE PERSPECTIVES

Arguably, the major challenges associated with clozapine use are not a lack of evidence for its effectiveness, nor solely its side-effect profile, but rather the hesitancy in initiating treatment and structural difficulties in arranging the required laboratory follow-up. Approximately one fifth of patients presenting with a first-episode psychosis will develop TRS (9,169), and a substantial proportion of these patients already exhibit treatment resistance during the first presentation (14). Thus, from a theoretical perspective, as many as one in ten patients with a first-episode psychosis could be candidates for clozapine within the first six months if guidelines were strictly adhered to. In clinical practice, however, initiation is often delayed (44,45), which has been associated with worse outcomes, including increased risk of suicide and less favourable long-term prognosis (51). In PDP, the situation is similar. Clozapine is an unfamiliar drug for many neurologists, and it is possible that many clinics struggle to cope with the intense initial laboratory follow-up that is required. Patients thus end up using medications that are arguably safer and require less monitoring (46,47), but whose efficacy has not been proven and may even be harmful (7,83). Although the evidence supporting the use of clozapine in both conditions has been available for decades, substantial barriers to its implementation persist in clinical practice. Consequently, there remains a clear need for novel treatment options.

Xanomeline-trospium (146) for schizophrenia and pimavanserin for PDP (123) represent the first FDA-approved antipsychotic medications that do not rely on direct D2 receptor blockade. Xanomeline-trospium could potentially be beneficial for patients with TRS or PDP and could warrant pilot studies in these populations. Unfortunately, regarding pimavanserin, all studies on schizophrenia seem to have been halted, and it will most likely not be trialled in TRS in the near future despite promising results from a small case series (127).

Developing novel drug therapies for the treatment of schizophrenia has proved to be extremely difficult. Many promising drugs — such as pimavanserin, roluperidone, bitopertin, iclepertin, ulotaront and emraclidine — have failed to meet primary endpoints in schizophrenia patients in Phase III studies despite encouraging Phase II or Ib studies (106,151,170). For iclepertin and bitopertin, development in patients with schizophrenia appears to have slowed. Clinical trials demonstrated effects primarily on cognitive and negative symptoms rather than positive symptoms (106-108), and it is thus unlikely that they will be pursued in PDP. Roluperidone is currently undergoing a new Phase III trial after narrowly failing to reach statistical significance in the original Phase III trial. Given its serotonergic mechanism, which it shares with that of pimavanserin, it may represent a candidate for the treatment of PDP. Similarly, a new Phase III trial studying ulotaront in patients with schizophrenia is currently ongoing (NCT06894212). A small encouraging pilot study on ulotaront in PDP has been conducted (132), but these results have not yet led to a larger trial. For emraclidine, no trials in PDP have yet been registered, although there could be a theoretical rationale for investigating its efficacy in PDP. Three decades after the original open-label studies of ondansetron in PDP, there is now renewed interest. Positive results from the ongoing RCT could provide a valuable addition to the limited repertoire of pharmacological treatments for PDP.

Clinical trials on novel antipsychotic drugs focus primarily on schizophrenia, and clozapine users and TRS patients are often excluded. Given that TRS may involve pathophysiological mechanisms less directly connected to dopaminergic dysfunction, these failed trials in schizophrenia may risk limiting research into therapies that could benefit this subgroup. The argument could be made that many of these drugs could be considered a candidate for a Phase II trial in TRS. Results from the Phase III study on evenamide are eagerly awaited and could potentially come to form part of the standard of care in TRS patients

who do not fully respond to clozapine. Other glutamatergic treatment options will hopefully emerge in the coming years. The theoretical support for using them in PDP is less strong, but clinical trials may still be warranted. Further studies on the effect of famotidine in TRS have, perhaps somewhat surprisingly, not followed the two positive RCTs. A large multi-centre RCT could be justified based on these findings, but a lack of commercial incentive makes this unlikely in the near future. The research on famotidine in TRS nevertheless highlights the value of clinical observations and case reports, but also underscores the challenges of translating promising signals into large-scale trials in the absence of industry sponsorship.

Arguably, one the largest discrepancies between PDP pathogenesis and clinical trials is the lack of studies on cholinergic medications. There is robust support for abnormal cholinergic signalling underlying the formation of psychosis in PD (144), but so far, no RCTs on treating these symptoms with anticholinergic drugs have been done. While it would be of utmost value to trial xanomeline-trospium in PDP, there is enough support from case reports and open-label studies to warrant an RCT on whether AChEIs could be effective in treating these symptoms. Psychotic symptoms in PD often precedes dementia, and it is likely that these patients would require AChEI treatment within a few years. AChEIs are often well tolerated in these patients, and clinicians have extensive experience with using this class of medication.

Despite great promise from multiple Phase II studies, it should be ensured that patients receive the best possible treatment while the field is awaiting the arrival of possible positive results from Phase III trials. Clozapine is effective in treating PDP (33,34), perhaps more so than pimavanserin (7). The doses required in PDP are lower than those used in TRS, and while agranulocytosis remains a significant risk, other risks such as metabolic complications seem to be less common, and many movement disorder clinics report a clear clinical benefit with low risks of adverse effects (48,49). Further, clozapine seems to be effective in treating rest tremor in PD (48,171). Considering this evidence, it may be advisable for clinics treating patients with PD to either ensure access to the expertise and infrastructure required to initiate clozapine in PDP patients when required, or to establish a clear referral pathway in case a trial of quetiapine is unsuccessful (88).

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