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REVIEW

A Clinically Oriented Review of New Antipsychotics for Schizophrenia

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Background: Currently available antipsychotics, mainly targeting the dopaminergic pathway, fail to address the complexity of schizophrenic symptoms and can lead to burdening adverse events. The need for innovative pharmacological options remains critical and research is now focusing on the development of non-dopaminergic antipsychotics. This review aims to summarize the current literature on the most promising non-dopaminergic new APs (muscarinic agonists, Trace Amine Associated Receptor 1 agonists, Glycine Transporter Type 1 inhibitors and 5-HT2A antagonists) and provide a clinically oriented overview of their efficacy, safety and potential use in schizophrenia.

Methods: A preliminary search was conducted through the Clinical Trials Database, in order to identify a representative (at late-stage clinical development) for each pharmacological class. The following drugs were selected: bitopertin (GlyT-1 inhibitor), pimavanserin (5-HT2A antagonist), ulotaront (TAAR1 agonist) and xanomeline-trospium (muscarinic agonist). Then, a literature search was conducted through PubMed, in order to retrieve current literature focusing on the efficacy and safety of these drugs.

Results: The clinical development of bitopertin and pimavanserin was halted despite the early promises. Xanomeline-trospium chloride was recently approved by the FDA for the treatment of schizophrenia. Ulotaront showed mixed results, although analysis is ongoing.

Conclusion: The findings of our review indicate that research on the treatment of schizophrenia is gaining momentum. However, it is crucial to remain cautious about over-optimism, as many compounds have failed to deliver the expected results. A balanced approach is recommended when dealing with new APs, whether under investigation or approved. In the latter case, clinicians should carefully evaluate the cost–benefit ratio. Since several agents are still being tested, there is hope that additional data may present new therapeutic opportunities.

Keywords: schizophrenia, antipsychotics, negative symptoms, cognitive symptoms, adverse events, unmet needs

Introduction

Historically, and up to these days, the treatment of schizophrenia has mainly relied on pharmacological agents modulating dopaminergic transmission.[1–3]

While first-generation antipsychotics (APs) primarily target dopamine D_2 receptors, second-generation ones have a broader mechanism of action, as in the case of clozapine, a potent AP (typically used in treatment-resistant schizophrenia) that combines dopaminergic and serotonergic modulation with effects on other neurotransmitters.[4–8]

However, the neurotransmitter alterations of schizophrenia are rather heterogeneous, as reflected in the heterogeneity of positive, negative and cognitive symptoms.[9]

Currently available APs do not address the complexity of schizophrenia and present considerable limitations. In particular, since both first and second-generation APs can cause troublesome side-effects,[10] the reduction of psychotic symptoms may paradoxically come at a cost in terms of patients' quality of life.[11] Moreover, even recent compounds fail to significantly improve negative and cognitive symptoms.[10,12] To further complicate matters, nearly a quarter of people at their first psychotic episode can develop treatment resistance from the very early therapeutic stages.[13] Therefore, more

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successful and tolerated pharmacological agents, also targeting negative symptoms and cognitive dysfunction, still represent medical unmet needs.[2,10]

In order to address such unmet needs, research is increasingly focusing on a plethora of new compounds that go beyond the classic dopaminergic paradigm.[1,9,14]

A recently published review[1] presented the most promising pharmacological classes of new non-dopaminergic APs, namely: muscarinic agonists, Trace Amine Associated Receptor 1 (TAAR1) agonists, Glycine Transporter Type 1 (GlyT-1) inhibitors and 5-HT2A antagonists. This paper focused primarily on the biological substrates supporting the potential efficacy of new APs while summarizing the study results for several compounds (grouped per pharmacological class).

These compounds are at various stages of testing and show a wide variety of mechanisms of action, safety profiles and potential use in the specific symptoms of schizophrenia. In light of this complex scenario, precision medicine would require to match each compound with a specific patient clinical profile,[15–17] bearing in mind the balance between effectiveness and adverse events (AEs). Building on this, and covering the same innovative pharmacological classes as the aforementioned paper,[1] we conducted a narrative review of each class representative (in late-stage clinical development), providing an in-depth, clinically oriented overview of their efficacy, safety and potential use in schizophrenia.

Methods

Aim

Summarize current literature on the most promising non-dopaminergic new APs and provide a clinically oriented overview of their efficacy, safety and potential use in schizophrenia.

Preliminary Search

As previously stated, this review focuses on a limited number of pharmacological classes that, for their characteristics, might attract the interest of potential readers. Indeed, by combining both subjective evaluations and insights from previous studies,[1] we decided to prioritize the selection of compounds being: a) innovative; b) prominent in the research landscape; c) responsive to critical clinical needs (eg negative symptoms).

In order to identify a representative per pharmacological class to be a priori selected as the focus of our review, we conducted a preliminary search using the National Institutes of Health US National Library of Medicine Clinical Trials Database, narrowing the search to the condition/disease "schizophrenia" and applying the filter "Phase 3" (access: 13th September 2024). The search involved the currently known drugs belonging to each pharmacological class, until one eligible compound (having completed Phase III clinical trials, with or without available results) was found and selected as a representative of that class (the only selection criteria being the previously mentioned advanced stage of development).

The searched drugs were: "xanomeline-trospium chloride" (for muscarinic agents); "ulotaront/SEP-363856" (for TAAR1); "bitopertin" (for GlyT-1); "pimavanserin" (for 5-HT2A).

According to the database, all the searched drugs were eligible (having completed phase III clinical trials).

Inclusion Criteria

Original studies and post-hoc analyses focusing on the a priori selected new APs (bitopertin, xanomeline-trospium chloride, pimavanserin, ulotaront) and addressing their clinical effects and potential use in schizophrenia (eg efficacy on negative symptoms, use as augmentation therapy), as well as their safety profile (in individuals with schizophrenia or healthy volunteers); papers written in English.

Exclusion Criteria

Grey literature; review studies; letters; case-reports and case-studies; animal models; in-vitro studies; papers focusing on disorders other than schizophrenia; papers focusing exclusively on clinical effects unrelated to the treatment of schizophrenia (eg effects on REM sleep, gastric emptying, etc).

Search Strategy

A literature search was performed on PubMed, using the terms: ((schizophrenia OR psychosis) AND (xanomeline-trospium chloride OR ulotaront OR bitopertin OR pimavanserin)).

Selection of the Relevant Papers

All the papers retrieved through PubMed underwent a screening for eligibility, in order to exclude all papers clearly meeting the exclusion criteria. The remaining, potentially eligible papers (according to article type, language, topic) were subjected to an in-depth screening (revision of abstract and full-text) aimed at reaching a definite decision in terms of inclusion/exclusion. Being the present paper a narrative review, no quantitative synthesis nor critical appraisal of the selected studies were conducted.

Additional Search Strategy

In order to retrieve any potentially relevant papers not already identified through our PubMed search, we checked the reference list of the papers included in the review.

In the paper, we report the main findings pertaining to the efficacy and safety profile of the APs focus of our review, also providing some clinical specificities (Figure 1) pertaining to each compound. These specificities are by no means guidelines, nor are they intended as such. However, they do represent memos/generic suggestions for the clinicians dealing with new APs. With due distinctions in relation to the different molecules considered, some tips could be transferred to several compounds belonging to the same pharmacological class, considering the shared mechanism of action.

Results

Glycine Transporter 1 Inhibitors (Bitopertin, a.k.a. RG1678)

What is Bitopertin?

A reduced N-methyl-D-aspartate (NMDA) signaling could relate to positive symptoms but also be crucially involved in the pathogenesis of negative ones. Since the activation of NMDA glutamate receptors also requires the binding of

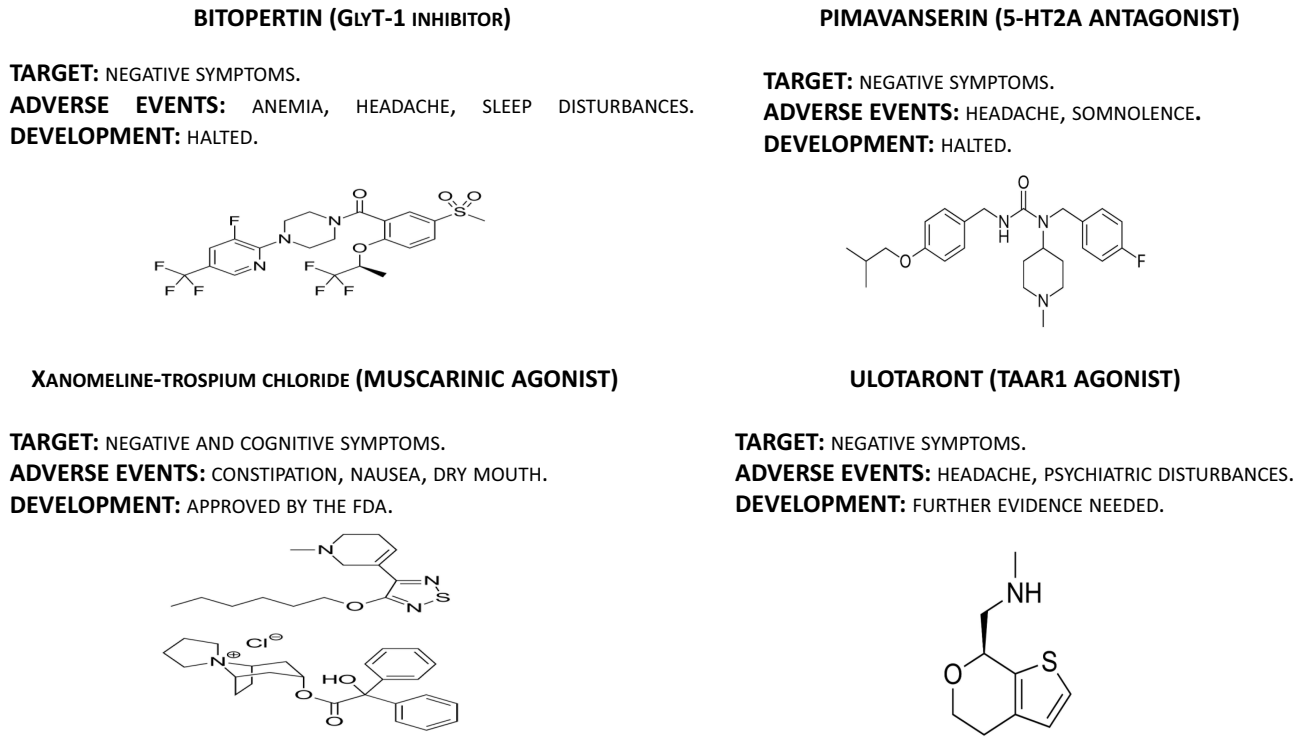

Figure 1 The Figure summarizes the main characteristics of bitopertin, pimavanserin, ulotaront and xanomeline-trospium chloride.
Abbreviations: 5-HT, 5-hydroxytryptamine; GlyT-1, Glycine Transporter Type 1; TAAR1, Trace Amine Associated Receptor 1.

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glycine, inhibitors of glycine transporter type 1 (GlyT-1), such as bitopertin, may show therapeutic potential via the modulation of glutamatergic (but also dopaminergic) neurotrasmission.[1,18,19]

Clinical Efficacy of Bitopertin: Overview of Literature Data

An 8-week randomized, placebo-controlled, double-blind Phase II study[20] tested the effect of bitopertin added to current antipsychotic therapy (with the exclusion of clozapine) in adults with schizophrenia and predominant negative symptoms. The primary efficacy measure was the change in the Positive and Negative Syndrome Scale negative symptom factor score (PANSS NSFS).

Secondary measures included, among others, response criterion (≥20% improvement from baseline in the PANSS NSFS), clinical global impression (CGI) and functioning. Considering the per-protocol population, subjects were randomly assigned to oral placebo (n = 61) or bitopertin 10, 30 or 60 mg/per day (n = 60, 57 and 53, respectively). Overall, the findings indicated that patients treated with the therapeutic regimen of bitopertin 10 mg showed greater clinical improvement.[20] More specifically, the reduction of the PANSS NSFS reached trend-level significance compared to placebo (−25% versus −20%, p = 0.07). Moreover, the response criterion was met by 65% of the patients (versus 43% placebo, p = 0.01), who were also more frequently rated as "much" or "very much" improved at the CGI (36.6% versus 23%, p = 0.03) and scored better at the functioning scale (8.76 versus 5.96 mean change, p = 0.07).

A following double-blind, randomized study assessing the efficacy of 52-week adjunctive bitopertin (5, 10 or 20 mg/day) in patients with persistent negative or suboptimally controlled symptoms[21] reported an improvement in all the efficacy endpoints. However, the value of these findings is limited since no placebo arm was established in this study (probably because testing the drug efficacy was a secondary aim, with safety being the primary one).

Moreover, several other studies did not report encouraging results pertaining to the potential efficacy of bitopertin.

A randomized, double-blind, 4-week phase II/III trial (CandleLyte study) evaluated the efficacy of bitopertin monotherapy (10 or 30 mg) versus placebo or olanzapine (15 mg) among inpatients with an acute exacerbation of schizophrenia.[22] In this study, improvement of positive symptoms and readiness for hospital discharge were associated with both bitopertin and olanzapine treatment. However, the study failed since no statistical separation from placebo was recorded for bitopertin nor olanzapine on the primary endpoint (change from baseline in the PANSS total score), mostly due to a stronger than expected placebo response.

The SearchLyte clinical trial program produced three randomized, double-blind, placebo-controlled, 12-week phase III studies (Twilyte, NightLyte and MoonLyte) investigating the efficacy of bitopertin (5 or 10 mg in MoonLyte; 10 or 20 mg in TwiLyte and NightLyte) in outpatients with schizophrenia and positive symptoms suboptimally controlled by current treatment. Only NightLyte (n = 199 placebo, n = 198 bitopertin 10 mg, n = 199 bitopertin 20 mg) met the primary endpoint (mean change from baseline in the PANSS positive symptom factor score) versus placebo, and only in the bitopertin 10 mg arm ($p < 0.01$).[23]

Finally, the phase III FlashLyte and DayLyte studies (randomized, 24-week, double-blind, placebo-controlled) did not provide evidence of superior efficacy of adjunctive bitopertin over placebo in stable patients with persistent predominant negative symptoms.[18]

Safety Profile of Bitopertin

GlyT-1 inhibitors can lead to a reduction of hemoglobin, the latter requiring glycine for its biosynthesis. Consistent with this, all studies investigating the safety profile of bitopertin reported this AE. Overall, evidence suggests a small, gradual, dose-dependent and reversible bitopertin-related hemoglobin reduction, with few cases reaching the withdrawal criteria of hemoglobin decrease of 25% and more from baseline.[18,20–24]

The most common AEs (incidence ≥5%), typically being dose-dependent, were sleep disturbances (either insomnia or somnolence) and headache.[20–22] Moreover, psychiatric disturbances were described (eg hallucinations, anxiety, suicidal ideation), with a completed suicide recorded in the NightLyte study, related to the study drug by the principal investigator.[18,21,23]

In general, bitopertin did not relate to particular alterations in terms of body weight, vital signs, electrocardiogram and metabolic parameters,[18,20,22,23] even though a fatal event (cardiorespiratory arrest) was recorded in the FlashLyte study in a patient with pre-existing serious risk factors belonging to the bitopertin 10 mg group.[18]

A multiple-dose, randomized, placebo-controlled study using bitopertin 30 mg or 175 mg for 10 days assessed cardiac repolarization and other ECG parameters (eg PR, QRS, heart rate) in healthy male volunteers.[24] The primary endpoint was the change in the QT interval calculated via the Fridericia's formula (QTcF). Considering the patients completing the trial (n = 56 bitopertin 30 mg, n = 52 bitopertin 175 mg), no clinically relevant effect on the QTc interval nor other ECG parameters was detected up to 175 mg/per day. In particular, no absolute QTc interval >450 ms or change in the QTcF >60 ms were recorded from baseline.

Clinical Use of Bitopertin: Clinical Tips

Target Population

Individuals diagnosed with schizophrenia, particularly those presenting with predominant negative symptoms.

Possible Contraindications

Patients with pre-existing hematological conditions or at high risk of anemia.

AEs

Hemoglobin reduction, sleep disturbances, headache.

Medication Safety Management

Close monitoring of any AE. Regular blood tests, especially in the initial stages of treatment or during dose adjustments.

See Figure 1 for a visual summary of the clinical tips.

Concluding Remarks on Bitopertin

Despite the initial findings pertaining to the efficacy of bitopertin, subsequent studies failed to achieve significant improvements over placebo. Hence, the pharmaceutical company Roche discontinued its development for schizophrenia.[25] However, other GlyT-1 inhibitors (eg iclepertin) are still under study and may open more positive scenarios.[1]

Muscarinic Agonists (Xanomeline-Trospium Chloride, a.ka. BMS986510)

What is Xanomeline-Trospium Chloride?

Muscarinic cholinergic neurotransmission is involved in important cognitive processes, including memory, learning and sensory perception.[26] Since several lines of investigation suggest a role of muscarinic neurotransmission in the pathogenesis of schizophrenia (eg reduced number of muscarinic interneurons in the ventral striatum, reduced muscarinic receptor binding in the frontal cortex[27]), research has been focusing on muscarinic agonists as potentially effective antipsychotic and procognitive agents.[26] Xanomeline-trospium is the combination of xanomeline (agonist of central muscarinic receptors M1 and M4 and peripheral acetylcholine receptors) and trospium chloride (a pan-muscarinic receptor antagonist, with only peripheral action). The drug composition aims to maintain the central agonist action while reducing the cholinergic AEs (nausea, vomiting, diarrhea, excessive sweating and salivary hypersecretion) related to the stimulation of peripheral muscarinic receptors.[28]

Clinical Efficacy of Xanomeline-Trospium: Overview of Literature Data

The effectiveness and safety profile of xanomeline-trospium has been tested in several double-blind, randomized clinical trials with similar inclusion criteria and endpoints.

The EMERGENT 1 (phase II trial) was a 5-week study involving adult individuals with an acute exacerbation or relapse of schizophrenia.[29] The participants were randomly assigned to either twice-daily oral xanomeline-trospium (flexible dosing ranging from 50 mg/20mg to 125 mg/30 mg twice daily) or placebo. The primary endpoint was the change of the PANSS total score from baseline to week 5. The secondary endpoints included, among others, the change

in the PANSS positive symptom subscore, negative symptom subscore and Marder negative symptom subscore. Considering the individuals completing the trial, those belonging to the xanomeline-trospium group (n = 72) presented a reduction of 17.4 points at the PANSS total score versus 5.9 points of those receiving placebo (n = 73, $p < 0.001$). Moreover, xanomeline-trospium was superior to placebo in reducing positive, negative and Marder PANSS subscores ($p < 0.001$).[29] Post-hoc analyses of data from EMERGENT 1[30,31] provide more specific information on the clinical efficacy of xanomeline-trospium on the modified intent-to-treat population, defined as all randomized patients who received at least 1 dose of study medication. Considering the lowest widely accepted threshold for response of ≥20% reduction of PANSS total score, 59% of xanomeline-trospium patients (49 out of 83) met the response rate at week 5. Increasing the threshold (up to ≥50%), the proportion of responding patients progressively decreased, but remained significantly higher than the proportion of placebo patients. The time course of response was significantly higher in the xanomeline-trospium patients up to 30% threshold by week 2 ($p < 0.01$). Moreover, the xanomeline-trospium group presented greater change throughout the entire trial in the Marder 5-factor model (positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility, and anxiety/depression) of the PANSS.[31] Another analysis, considering only patients with some extent of cognitive impairment associated with schizophrenia (CIAS), showed that the xanomeline-trospium group presented greater improvement in cognitive performance, both relative to baseline and compared to placebo ($p < 0.01$), even after removal of outliers. The strength of association between PANSS total score and scores at the cognitive battery was small, indicating that xanomeline-trospium's effect on cognition could be relatively independent from its antipsychotic activity.[30] The efficacy of xanomeline-trospium in reducing both positive and negative symptoms has been confirmed in subsequent phase III trials (with similar inclusion criteria, study procedures and endpoints), namely EMERGENT 2[32] and EMERGENT 3,[33] demonstrating the drug's superiority compared to placebo. In particular, both EMERGENT 2 and 3 studies reported that around 50% of xanomeline-trospium patients presented a ≥30% improvement in PANSS total score compared to placebo (less than 30% of subjects).[32,33] However, apart from its general antipsychotic action, the most promising xanomeline-trospium's characteristic could lie in its effect on specific symptom domains. In fact, a post-hoc analysis of 1, 2 and 3 EMERGENT trials, focusing on a subgroup of patients with prominent negative symptoms at baseline, reported xanomeline-trospium's superiority compared to placebo in improving negative symptoms ($p < 0.001$), even after controlling for changes in positive symptoms, disorganization, hostility and depression/anxiety. Although the clinical value of these findings needs further investigation, they open up promising scenarios, indicating xanomeline-trospium as a drug with a (possible) profile of efficacy on negative symptoms of schizophrenia.[34]

Safety Profile of Xanomeline-Trospium

In a 9-day, double-blind, placebo-controlled Phase I trial, trospium contained in xanomeline-trospium was reported as being effective in mitigating five a priori selected xanomeline-related cholinergic AEs, namely: nausea, vomiting, diarrhea, excessive sweating and salivary hypersecretion.[28] More specifically, xanomeline-trospium led to a reduction of the 5 AEs by 46% and each individual AE by ≥29% compared to xanomeline alone.[28] EMERGENT 1 findings indicate that xanomeline-trospium relates to AEs (54% of cases; 43% in the placebo group), most frequently constipation and nausea (17%), along with dry mouth (9%). Negligible weight gain (3% xanomeline-trospium versus 4% placebo) was reported, along with an increase in resting heart rate and some cases of akathisia (3%), in the xanomeline-trospium group. The majority of AEs (including akathisia) decreased by the end of the trial.[29] A post-hoc analysis of EMERGENT 1[35] confirmed that most of the procholinergic and anticholinergic xanomeline-trospium-related AEs were mild, rapidly-occurring and transient. Sedation was not commonly reported (n = 7/89 xanomeline-trospium; 6/90 placebo). No clinically relevant changes in weight, metabolic parameters (cholesterol, triglycerides, and glucose) or vital signs (blood pressure, heart rate) were detected, except for an initial trend of increased heart rate in xanomeline-trospium chloride group, decreasing over the course of the trial.[35] The findings from EMERGENT 2 trial indicate that xanomeline-trospium chloride might primarily lead to mild gastrointestinal AEs. Extrapyramidal motor symptoms or akathisia in the xanomeline-trospium chloride group were infrequent, shared similar rates with the placebo group, and did not require neurological treatment nor changes in the antipsychotic dosing regimen.[32] Xanomeline-trospium chloride was confirmed

as being an overall well-tolerated drug in EMERGENT trial 3, confirming the already reported safety profile: mostly gastrointestinal, mild-moderate and generally transient AEs.[33]

Clinical Use of Xanomeline-Trospium Chloride: Clinical Tips

Target Population

Persons with schizophrenia, with negative and/or cognitive symptoms.

AEs

Constipation, nausea, dry mouth.

Medication Safety Management

Close monitoring of any AEs, particularly during treatment initiation. Instruct the patients on the possible disturbances and encourage them to report any complaint. Monitor possible initial heart rate changes.

See Figure 1 for a visual summary of the clinical tips.

Concluding Remarks on Xanomeline-Trospium

Xanomeline-trospium chloride has shown a promising antipsychotic action, with an overall favorable tolerability and safety profile. In September 2024, the Karuna/Bristol Myers Squibb's drug was approved by FDA for the treatment of schizophrenia.[36]

Serotonin Receptor Antagonists/Inverse Agonists (Pimavanserin, a.k.a. ACP 103)

What is Pimavanserin?

Pimavanserin, already approved for the treatment of Parkinson's disease psychosis, is a selective 5-hydroxytryptamine $(5\text{-HT})_{2A}$ inverse agonist and antagonist with negligible activity on 5-HT_{2C} and no action on adrenergic, dopaminergic, histaminergic and muscarinic receptors.[1] 5-HT2A are usually excitatory receptors, located not only on serotoninergic but also glutamatergic, GABAergic, cholinergic and dopaminergic neurons.[37] The concept behind this drug is that, attenuating 5-HT_{2A} receptors activity, the dopaminergic transmission in the prefrontal cortex normalizes. Such an effect would result in reduced positive and negative symptoms while minimizing the AEs typical of dopaminergic blockade, such as ataxia and hyperprolactinemia.[1]

Clinical Efficacy of Pimavanserin: Overview of Literature Data

A phase II randomized, double-blind, 6-week trial[37] investigated the effect of pimavanserin (20 mg/day) in add-on to a suboptimal dose of risperidone or haloperidol, compared to the reference dose of risperidone 6 mg. Adults with a recent exacerbation of schizophrenia were enrolled and assigned to one of five treatment arms (including risperidone/haloperidol suboptimal dose+placebo, risperidone reference dose+placebo, risperidone/haloperidol suboptimal dose+pimavanserin). The primary endpoint was the change in PANSS total score, while secondary outcome measures included changes in PANSS subscores and CGI severity. Considering the risperidone groups, 69 patients were randomized to risperidone 2 mg+pimavanserin, 76 to risperidone 6 mg+placebo and 77 to risperidone 2 mg+placebo. The combination of risperidone 2 mg and pimavanserin resulted in greater improvements in PANSS total score and subscales, at all visits from day 8, compared to risperidone 2 mg+placebo. At day 43 (endpoint), the risperidone 2 mg+pimavanserin group showed a 23-point reduction of the PANSS total score, versus 16.3-point reduction in the risperidone 2 mg+placebo group ($p = 0.007$). Significant improvements in negative symptoms ($p = 0.018$) and general psychopathology ($p = 0.006$) were also detected at the end point. PANSS changes ≥20% were greater at week 2 in risperidone 2 mg+pimavanserin compared to risperidone 2 mg+placebo ($p = 0.002$). Considering the reference dose (risperidone 6 mg), no differences were recorded in terms of outcome measures, indicating that co-therapy with pimavanserin showed similar antipsychotic efficacy. However, pimavanserin might present a more rapid onset of action, as suggested by PANSS changes (risperidone 2 mg+pimavanserin: 15 days; risperidone 6 mg+placebo: 29 days) at a threshold ≥20%. Considering the haloperidol group, co-therapy with pimavanserin did not add any clinical value.[37]

The ENHANCE study, a phase III randomized, double-blind, placebo-controlled, 6-week trial, investigated the efficacy of adjunctive pimavanserin (20 mg/day, flexible dosing up to 34 mg/day) for the treatment of schizophrenia in patients with inadequate response to current antipsychotic treatment in European and North American sites.[38] Adult patients previously stabilized on an adequate dose of antipsychotics (for at least 8 weeks) were enrolled. Similarly to other clinical trials, the primary endpoint was the change in PANSS total score. Secondary outcome measures included scales assessing sleepiness, personal and social performance, and depression. The participants were randomized to pimavanserin (n = 198) or placebo (n = 198). Despite a trend of greater changes in PANSS total score, the difference between groups was not statistically significant. However, pimavanserin showed greater efficacy in reducing negative symptoms compared to placebo, particularly at European study sites, as per PANSS negative symptoms subscale (LS mean difference at week 6 of −2.9 versus 1.9, 95% CI: −1.9,-0.2) and PANSS Marder negative symptom factor score (LS mean difference at week 6 of −3.4 versus −2.2, 95% CI: −2.2,-0.4). The scores at the scales for depression and performance showed similar changes in pimavanserin versus placebo. The sleepiness scale favored pimavanserin starting from week 4 up to week 6 (LS mean difference at week 6 of −0.3 versus −0.2, 95% CI: −0.6,-0.0). Study completion rates were similar in both groups (88% pimavanserin patients versus 96% placebo patients).

In light of the promising perspective of pimavanserin as specifically effective on negative symptoms, the ADVANCE, a Phase II, randomized, double-blind, placebo-controlled, 26-week trial, investigated the efficacy of adjunctive pimavanserin (20 mg/day, flexible dosing 10–34 mg until week 8) compared to placebo in adults with schizophrenia and predominant negative symptoms while on optimized background antipsychotic therapy.[39] The primary efficacy measure was the change in the negative symptom assessment (NSA-16) from baseline to week 26 and secondary measures included personal and social performance along with the proportion of responders in terms of NSA-16. Overall, 201 patients were randomized to pimavanserin, versus 202 to placebo. Pimavanserin was superior to placebo when considering the primary endpoint. Regarding the secondary measures, while the performance scale scores were similar between groups, the proportion of patients with at least 20% improvement at the NSA-16 at week 26 was higher in the pimavanserin group [53% (93/174 patients) versus 49% (84/173 patients), p = 0.30].

A post-hoc analysis of the ADVANCE study highlighted how higher pimavanserin exposure related to greater probability of changes in terms of negative symptoms, performance and CGI, without higher risk of AEs. In this regard, the dosage regimen of pimavanserin 34 mg/day could be of reference for clinical efficacy and tolerability.[40]

Safety Profile of Pimavanserin

A randomized, double-blind, placebo-controlled study specifically focused on the tolerability of pimavanserin after single and multiple oral administrations of increasing doses in healthy young males. The findings highlight that pimavanserin is well tolerated at single doses from 20 to 300 mg, while a once-daily dose of 100 mg was the maximum tolerated dose. Nausea and vomiting were dose-related (following daily administration of 150 mg), as opposed to mild postural dizziness. No meaningful changes were observed for laboratory data, vital signs and 12-lead ECG.[41] In the already reported study investigating pimavanserin as adjunctive therapy to haloperidol/risperidone, the most commonly detected pimavanserin-related AEs were somnolence and nausea. Moreover, the risperidone 2 mg+pimavanserin group showed significantly fewer motor and metabolic side effects[37] than risperidone 6 mg. In the ENHANCE study, the rates of AEs were similar in the pimavanserin (39.9%) and placebo (36.4%) group, with somnolence and headache being among the frequent ones in the pimavanserin group. The 2.5% (n = 5) of pimavanserin patients discontinued treatment due to clinically significant AEs (palpitations, psychogenic visual disorder, suicidal ideation, hallucinations, worsening of psychotic symptoms). Irrelevant changes in terms of laboratory tests, vital signs and body weight were reported. No patient showed elevations >500 ms in the QTc and the changes at the measures of motor symptoms were minimal.[38] The ADVANCE study similarly indicated somnolence and headache as the most common AEs, detected with similar rates (around 5%) in both the pimavanserin and placebo groups. Most of the AEs were mild-moderate. No relevant changes were recorded in terms of laboratory tests and vital signs. The favorable safety profile in terms of motor symptoms was confirmed.[39]

A post-hoc analysis focused on the effects of adjunctive pimavanserin and current antipsychotic treatment on QT interval prolongation in patients from ENHANCE, ADVANCE and study 035 (a 52-week, open-label extension study of

patients from ENHANCE and ADVANCE). No clinically meaningful changes in ECG were reported as well as no cases of QTc values >500 postbaseline. Overall, pimavanserin 34 mg can increase the QT interval of 5–8 ms, without causing further effects as adjunctive treatment with any of the 3 commonly used antipsychotics (risperidone, olanzapine, and aripiprazole). However, clinicians must always use caution, since combining pimavanserin with other antipsychotics could compound the cardiological effects of such drugs.[42]

Clinical Use of Pimavanserin: Clinical Tips

Target Population

Patients with schizophrenia and predominant negative symptoms with suboptimal response to current treatment (add-on therapy).

AEs

Somnolence and headache.

Medication Safety Management

Close monitoring for any AEs. Special attention to QT interval prolongation (particularly when combined with QT-prolonging APs). Schedule regular cardiologic check-ups and investigate any pre-existing risk factor.

See Figure 1 for a visual summary of the clinical tips.

Concluding Remarks on Pimavanserin

Due to the mixed results pertaining to the antipsychotic efficacy of pimavanserin, the company Acadia discontinued its development in March 2024.[43] Minerva Pharmaceuticals is currently investigating another similar compound, namely roluperidone, but the FDA rejected its approval and required additional data supporting the effectiveness and safety of the compound.[44]

Trace Amine-Associated Receptor 1 Agonists (Ulotaront, a.k.a. SEP-363856)

What is Ulotaront?

Ulotaront is a TAAR1 and 5-HT1A receptor agonist.

Despite being a non-D2-receptor-binding AP, it can have a broad effect on several neurotransmitters, with potentially fewer AEs typically associated with anti-dopaminergic compounds. Indeed, TAARs are G protein-coupled receptors that exert modulatory activity on dopaminergic, serotonergic, and glutamatergic circuits. These receptors are located in brain areas implicated in the pathogenesis of schizophrenia, such as ventral tegmental area and prefrontal cortex.[1]

Clinical Efficacy of Ulotaront: Overview of Literature Data

The first contribution regarding ulotaront was a 4-week randomized, double-blind, placebo controlled trial[45] involving adults with schizophrenia experiencing an acute exacerbation. After a washout period for psychotropic medications, the participants were randomly assigned to receive ulotaront (flexible dose of 50 or 75 mg/day) or placebo. Ninety-four ulotaront and 99 placebo patients completed the trial. Efficacy measures included PANSS, CGI, brief negative symptom scale and Montgomery-Åsberg Depression Rating Scale. The mean change in the PANSS total score was significantly higher in the ulotaront group versus placebo (−17.2 points versus −9.7, $p = 0.001$). Similarly, all the other endpoints (negative symptoms, CGI, depressive symptoms) showed a greater improvement in the ulotaront group (eg LS mean change of CGI from baseline at week 4: ulotaront −1.0 versus placebo −0.5; 95% CI: −0.7 to −0.2).

This research was followed by a 26-week, open-label extension study.[46] Of the participants completing the study, 51 continued to receive ulotaront (already assigned in the double-blind trial) and 54 switched from placebo to ulotaront. Overall, ulotaront treatment was associated with sustained improvement (PANSS positive, negative, general psychopathology, depressive symptoms). Similarly, double-blind placebo patients showed improvement in the outcome measures when receiving ulotaront.

Safety Profile of Ulotaront

Overall, the findings from the double-blind study[45] indicate a similar incidence of AEs among patients taking ulotaront and those receiving placebo. Safety assessments included, among others, weight, laboratory tests, 12-lead electrocardiography,

sleep quality and evaluation of extrapyramidal symptoms. Minimal changes in prolactin levels were recorded in the ulotaront group, along with negligible weight gain (0.3 kg). No clinically significant electrocardiographic abnormalities were registered, and the incidence of extrapyramidal symptoms was similar between ulotaront and placebo groups (3.3% and 3.2%, respectively). Treatment with ulotaront was associated with an improvement in sleep quality compared to placebo. However, two serious adverse events (worsening of schizophrenia and fatal acute cardiovascular insufficiency in a patient with risk factors) were recorded in the ulotaront group. Worsening of schizophrenia and headache were among the most frequently recorded AEs in the extension study (incidence >10%).[46] Suicidal ideation (with one case of aborted attempt) was detected in 3 patients. No clinically relevant changes in terms of prolactin and weight were recorded in the ulotaront group. Considering the vital signs, 8 (5.2%) and 4 (2.6%) presented orthostatic hypotension and orthostatic tachycardia, respectively. No patient showed a QTcF interval ≥480 msec. One patient had an increase in QtcF interval by ≥60 msec.

A Phase I, randomized, single-dose, crossover study[47] specifically investigated the effects of ulotaront (highest practical dose: 150 mg) on electrocardiogram intervals in adults with schizophrenia. The study considered QTcF, heart rate, QTc, PR and QRS intervals. Considering the patients receiving the first dose of ulotaront (n = 60), treatment with ulotaront had no clinically meaningful effects on heart rate, PR interval, QRS duration and QTcF and QTc. Nausea and somnolence were among the most frequently recorded AES. One patient (1.6%) experienced hypotension.

Clinical Use of Ulotaront: Clinical Tips

Target Population

Patients with schizophrenia. Potential use in case of sleep disturbances.

AEs

Worsening of schizophrenia, headache. Special attention toward suicidal ideation.

Medication Safety Management

Close monitoring of any AE. Exclude the presence of pre-existing suicidal thoughts and focus on the early detection of emerging ones. Schedule regular mental health evaluations and encourage the patients and their support network to promptly address any concern.

See Figure 1 for a visual summary of the clinical tips.

Concluding Remarks on Ulotaront

Despite the initial findings on the effectiveness of ulotaront, topline results from phase III DIAMOND 1 and DIAMOND 2 trials (2023) showed no superiority over placebo. However, Sumitomo Pharma and Otsuka Pharmaceuticals decided to further analyze their data and discuss them with the FDA, believing that the higher than expected placebo response might have masked the therapeutic effect of ulotaront.[48]

Discussion

The therapeutic options for schizophrenia are still insufficient and fail to meet the symptom domains (negative and cognitive symptoms) severely impacting the patients' social functioning and quality of life.[7,49,50] Indeed, despite treatment, many patients present residual symptoms and do not reach a satisfactory life fulfillment.[51,52] In addition, drug-related AEs include, and are not limited to, the following: extrapyramidal symptoms, cardiological disturbances, hyperprolactinemia, metabolic alterations, sexual dysfunction, weight gain and excessive sedation. As a result, many patients show poor adherence to their medication, which in turn leads to higher rates of relapse and hospitalization.[53] In light of this, research should strive to identify new, better-tolerated drugs, with clinical efficacy on burdening symptom domains.

The findings of our review indicate that research on the treatment of schizophrenia is gaining momentum, while finally focusing on the development of APs with innovative mechanisms of action.

However, it is crucial to remain cautious about over-optimism, as many compounds have failed to deliver the expected results. In fact, of the pharmacological agents reviewed here, only xanomeline-trospium chloride was recently approved by the FDA for the treatment of schizophrenia, making it the first drug with a new mechanism of action since the 1950s,[36] while the development of the other compounds either produced mixed results or was halted.

Nevertheless, several agents belonging to the pharmacological classes reviewed here (targeting serotoninergic, muscarinic, TAAR1 and GlyT-1 receptors) are still being tested, such as iclepertin, and there is hope that additional data may present new therapeutic opportunities.[54] Indeed, it would be a mistake to simply dismiss a pharmacological class based on a single compound, since small molecular peculiarities can make a difference. For example, trospium (contained in xanomeline-trospium chloride), gave new impetus to the clinical development of muscarinic drugs, which had previously been limited by cholinergic AEs.[28] In addition, the compounds failing to achieve the expected goals might find clinical application in other psychiatric conditions. For instance, pimavanserin and ulotaront are currently under investigation for the treatment of major depression.[55,56]

In general, a balanced approach is recommended when dealing with new APs, whether under investigation or approved. In the latter case, while valuing the patients' health and quality of life as the main goal, clinicians should also engage in considerations pertaining to the cost–benefit ratio (eg long-term savings through reduced hospitalization), as innovative medicines always imply considerable costs.[57]

This review has some limitations. First of all, it only considered a limited number of pharmacological classes, narrowing the analysis on a pre-selected representative per class. A wider focus on other compounds (eg milsaperidone and brilaroxazine) might have offered a complete overview of the therapeutic options being forwarded for the treatment of schizophrenia. However, the aim of our review was to focus on the most renowned non-dopaminergic pharmacological agents, with a particular emphasis on those at a late stage of development. Our paper adds to previous reviews on new APs,[1,9,14] covering in detail the efficacy, safety and progress status of bitopertin, xanomeline-trospium chloride, pimavanserin and ulotaront. Moreover, it provides practical advice for clinicians, which we hope will be useful, although not a substitute for clinical judgment and scientific evidence.

Conclusions

The introduction of new APs offers new hope for the treatment of schizophrenia. However, it is essential to maintain a critical and balanced approach. Indeed, clinicians are prompted to carefully evaluate emerging evidence while taking into account both clinical needs and available economic resources.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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