Review Article

Beyond Dopamine and Tablets: Investigational and Newly Approved Antipsychotics for Treating Schizophrenia

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Abstract

Objectives: To review the pharmacology, dosing/administration, efficacy, safety, and applicable costs of novel antipsychotics and formulations approved since 2018 or currently under investigation for the treatment of schizophrenia.

Methods: A PubMed search (2010 to November 2020) was conducted using the search terms schizophrenia, asenapine, evenamide, lumateperone, olanzapine, paliperidone, risperidone, roluperidone, samidorphan, ALKS 3831, HP-3070, ISM, ITI-007, LY03004, MIN-101, NW-3509, and PP6M. Additional data were obtained from references of identified articles, drug information databases, manufacturer product labeling and websites, and Clinicaltrials.gov.

Results: Two novel antipsychotic formulations have been approved (risperidone extended-release [ER] subcutaneous injection in July 2018, and asenapine transdermal patch in October 2019), with 2 risperidone ER intramuscular injections and 1 paliperidone ER intramuscular injection under investigation. One novel antipsychotic has been approved (lumateperone tosylate oral capsule in December 2019), with 3 additional drugs at least nearing phase 3 clinical trials: samidorphan (in combination with olanzapine to mitigate weight gain), roluperidone (for negative symptoms of schizophrenia), and evenamide (as an adjunctive agent for positive symptoms of schizophrenia).

Conclusions: As antipsychotic non-adherence increases risk of schizophrenia relapse, investigators have continued developing several novel molecules and non-oral formulations over the past few years that aim to solve existing efficacy gaps and minimize adverse effects. Due to the significant costs associated with these new treatments, pharmacists should be prepared to guide mental health professionals and educate patients on their efficacy, safety, and administration concerns relative to established antipsychotic treatments for schizophrenia.

Schizophrenia is a mental health disorder most often characterized by positive symptoms (such as auditory hallucinations, delusions, and disorganized speech and behavior) and negative symptoms (such as blunted affect, avolition, and anhedonia). While the lifetime prevalence is only estimated to be 0.3-0.7%, it is one of the top 15 causes of worldwide disability and increases premature mortality risk due to concurrent cardiometabolic disease.[1,2] Individuals are usually diagnosed in the second or third decade of life, leading to many years of clinical impairment and distress.

According to the 2019 American Psychiatric Association (APA) schizophrenia treatment guidelines, individuals diagnosed with schizophrenia should be started on an antipsychotic medication and continued thereafter, if observed improvements, to decrease the risk of relapse and hospitalization (evidence grade 1A).[3] Unfortunately, many individuals have poor adherence to antipsychotic medications. The National Institute of Mental Health (NIMH) sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial found that 74% of subjects (N=1061/1432) had discontinued their antipsychotic at 18 months, with 32% (N=340/1061) due to inefficacy and 20% (N=213/1061) due to intolerability.[4] Likewise, the European First Episode Schizophrenia Trial (EUFEST) of first-episode schizophrenia found that 41.6% of subjects (N=207/498) had discontinued

their antipsychotic for any cause at 12 months.[5] A meta-analysis of 1,154 total subjects from these two landmark trials found a statistically significant decrease in adherence that was associated with poorer insight, higher hostility, and increased substance use at six months.[6]

Due to the physical and psychosocial consequences of low medication adherence, research on novel antipsychotic drugs and non-oral formulations has greatly expanded over the past several years. Whereas antipsychotics to date have focused on dopamine D2 and serotonin 5-HT2A receptor antagonism, some molecules currently under investigation are exploring the glutamate system due to NMDA receptor antagonists being observed to cause psychotic symptoms.[7] Other researchers have been reformulating existing options into long-acting injectable antipsychotics (LAIAs), removing the need for daily oral administration. The APA guidelines recommend patients with a history of poor or uncertain adherence receive an LAIA (evidence grade 2B), as recent meta-analyses have found that LAIAs may reduce treatment discontinuation and hospitalization rate versus oral antipsychotics (though not necessarily relapse rates).[3,8,9] This article will review schizophrenia pharmacotherapies approved by the Food and Drug Administration (FDA) since 2018, along with molecules and formulations under investigation, using data from primary literature, governmental sources, manufacturer product labeling and websites, and Clinicaltrials.gov.

Novel Formulations

Long-Acting Injectable Antipsychotics

In July 2018, Indivior announced the FDA approval of a once-monthly, long-acting subcutaneous risperidone injection (Perseris™) for schizophrenia in adults.[10] This product is the first subcutaneous LAIA formulation available on the US market. Subcutaneous injections use a shorter and wider needle than intramuscular injections, which patients have been shown to prefer due to ease of administration.[11] Perseris™ is intended for patients who tolerate an oral risperidone dose of 3 or 4 mg/day, corresponding to a dose of 90 or 120 mg once monthly into the abdomen. It does not require oral risperidone overlap upon initiation like the existing intramuscular risperidone LAI (Risperdal Consta®), nor a loading dose like other available LAIAs.[12] The average wholesale price (AWP) of each subcutaneous injection ranges from $2,154.60 (90 mg) to $2,872.80 (120 mg), which is approximately 1.6-1.8 times the monthly cost of intramuscular risperidone LAI and 2.7 times the monthly cost of comparable oral risperidone tablet dosing.[13]

Nasser et al. conducted a phase 3, randomized, double-blind, placebo-controlled trial regarding the efficacy and safety of 90-mg and 120-mg doses of Perseris™.[14] Included subjects had a schizophrenia diagnosis according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), had a schizophrenia exacerbation within the past 8 weeks, and would benefit from hospitalization. The primary endpoint was change in the total Positive and Negative Syndrome Scale (PANSS) score from baseline to day 56. A statistically significant least-squares mean difference (LSMD) was observed versus placebo for both 90 mg (-6.148, 95% CI [-9.982 to -2.314]; P = 0.0004) and 120 mg (-7.237, 95% CI [-11.045 to -3.429]; P < 0.0001). The most common adverse effects were headache, injection site pain, and weight gain. There were also notable increases in mean prolactin levels for both the 90-mg and 120-mg doses compared to placebo, though this finding is consistent with other risperidone formulations.

Andorn et al. conducted a phase 3, open-label, outpatient trial including 92 rollover patients from the Nasser et al. study and 408 new patients clinically stable on Perseris™ 120 mg once monthly.[15] The primary objective was to assess long-term safety and tolerability over 52 weeks, with long-term effectiveness being a secondary objective. The most common adverse effect reported was injection site pain (13%), though more than 80% of subjects reported no injection site reactions. Weight increase was observed in 12.8% of subjects, with such increases stabilizing after the first 3 months. The mean change in total PANSS score was -0.4 for new patients and ranged from -10.9 to -20.2 for rollover patients. This long-term study demonstrates that extended-release subcutaneous risperidone remains well-tolerated and effective over a 1-year period.

Additional intramuscular risperidone LAIs avoiding oral overlap and loading doses are under investigation. In May 2019, the FDA accepted a new drug application (NDA) from Luye Pharma for a microsphere formulation known as LY03004 or Rykindo®. Proposed dosing from the manufacturer is 12.5-50 mg once every two weeks.[16] In November 2020, ROVI announced filing an NDA with the FDA for Doria® (Risperidone ISM®), an *in situ* microimplant suggested to have greater stability and easier administration than existing LAIAs.[17] Investigators of this formulation recently conducted a phase 3, randomized, double-blind, placebo-controlled trial of 437 subjects experiencing acute psychosis with schizophrenia. Subjects were randomized 1:1:1 once every 4 weeks to Risperidone ISM® 75 mg, Risperidone ISM® 100 mg, or placebo, with a primary endpoint of change in the total PANSS score from baseline to day 85. A statistically significant LSMD was found versus placebo for both the 75-mg dose (-13, 95% CI [-17.3 to -8.8]; P < 0.0001) and 100-mg dose (-13.3, 95% CI [-17.6 to -8.9]; P < 0.0001). The most common adverse effects—of hyperprolactinemia (5.6-8.9%), akathisia (3.5-7.5%), and headache (3.4-6.3%)—versus placebo were comparable to those found with other risperidone formulations.[18]

Risperidone's active metabolite is currently available on the US market as 2 paliperidone LAIs: Invega Sustenna® (once monthly) and Invega Trinza® (once every 3 months, the longest duration of current FDA-approved LAIAs). Patients must be effectively treated for 4 months with Invega Sustenna® before moving to Invega Trinza®.[19,20] In November 2017, Janssen began a phase 3, randomized, double-blind, active-controlled, non-inferiority trial comparing time to relapse on investigational paliperidone palmitate 6-month formulation (PP6M) versus Invega Trinza®. While no results have been posted, the primary study completion date was in May 2020.[21]

Transdermal Patch

In October 2019, Noven Pharmaceuticals' Secuado® (HP-3070, asenapine) became the first FDA-approved transdermal antipsychotic formulation.[22]

It is applied to the abdomen, upper arm, upper back, or hip and is dosed 3.8-7.6 mg once daily. Asenapine was already available in a sublingual tablet formulation (Saphris®), though Secuado® aims to overcome its notable adverse effects (e.g. dysgeusia and oral hypoesthesia) and administration concerns (e.g. twice-daily dosing and avoiding food/drinks within 10 minutes).[23] The AWP for a package of 30 patches, regardless of strength, is $1,440, which appears to be similar to the monthly cost of sublingual asenapine.[24]

In a phase 3, randomized, double-blind, placebo-controlled trial of transdermal asenapine, 617 subjects experiencing an acute schizophrenia exacerbation were randomized 1:1:1 to 3.8 mg, 7.6 mg, or placebo.[25] The primary endpoint was change in the total PANSS score from baseline to day 42. A statistically significant LSMD was observed versus placebo for both 3.8 mg (-6.6, 95% CI [-9.81 to -3.40]; P < 0.001) and 7.6 mg (-4.8, 95% CI [-8.06 to -1.64]; P = 0.003). The most common adverse effects were headache, extrapyramidal symptoms (EPS, notably akathisia), weight gain, and application site reaction, a similar profile to sublingual asenapine except for site reactions.[25]

Novel Molecules

Lumateperone tosylate (Caplyta™)

In December 2019, Intra-Cellular Therapies announced the FDA approval of lumateperone tosylate (ITI-007, Caplyta™) for the treatment of schizophrenia in adults.[26] The approved dosing is 42 mg by mouth once daily (active free base equivalent to 60 mg of available tosylate salt). Though primarily acting as a D2 and 5-HT2A antagonist, lumateperone also exerts indirect glutamate receptor activation, presynaptic D2 partial agonism, and a larger difference between D2 and 5-HT2A affinity; the latter two features might suggest a lower propensity for EPS.[27] The monthly AWP of lumateperone 42-mg capsules is $1,584, which is approximately 3-7 times the cost of usual dosing of oral risperidone tablets.[13,28]

Lieberman et al. conducted a phase 2, randomized, double-blind, placebo- and active-controlled trial of 335 subjects experiencing acute psychosis with schizophrenia.[29] These subjects were randomized 1:1:1:1 to lumateperone 42 mg or 84 mg, risperidone 4 mg, or placebo, with a primary endpoint of change in the total PANSS score from baseline to day 28. A statistically significant LSMD was observed versus placebo for both lumateperone 42 mg (-5.8, effect size 0.42; P = 0.017) and risperidone, but not for lumateperone 84 mg (-0.9, effect size 0.7; P = 0.44); the study was not powered to directly compare lumateperone with risperidone. Somnolence was the most common adverse effect of lumateperone (17% for 42 mg and 32.5% for 84 mg), which the investigators concluded was a hindrance of the 84-mg dose's efficacy. While akathisia occurred in 7% of subjects receiving risperidone, akathisia rates for lumateperone 42 mg (1.2%) and 84 mg (2.4%) did not differ from placebo (2.3%). No significant difference in other EPS types or metabolic parameters were found between lumateperone and placebo.[29]

Correll et al. then conducted a phase 3, randomized, double-blind, placebo-controlled trial of 449 subjects experiencing acute psychosis with schizophrenia.[30] These subjects were randomized 1:1:1 to lumateperone 28 mg, lumateperone 42 mg, or placebo, with a primary endpoint of change in the total PANSS score from baseline to day 28. A statistically significant LSMD was again observed versus placebo for the 42-mg dose (-4.2, 95% CI [-7.8 to -0.6]; P = 0.02) but not the lower 28-mg dose (-2.6, 95% CI [-6.2 to 1.1]; P = 0.16). Somnolence was once more the most common adverse effect (11.3% for 28 mg and 17.3% for 42 mg), with no significant increases in EPS or metabolic abnormalities compared to placebo.[30] An additional phase 3 trial did not find statistically significant improvements in total PANSS score after 6 weeks on lumateperone 14 mg or 42 mg versus placebo (unlike an active risperidone comparator), though detailed study results have not been published.[31]

Olanzapine/Samidorphan (OLZ/SAM, ALKS 3831)

OLZ/SAM (ALKS 3831) is a combination product under investigation by Alkermes to optimize tolerability of the FDA-approved antipsychotic olanzapine, which is associated with a higher risk of metabolic abnormalities comparable to clozapine. Unlike clozapine, however, olanzapine's utilization is not limited by a Risk Evaluation and Mitigation Strategy (REMS) program, leading to more ubiquitous utilization.[3] These metabolic abnormalities are believed to be associated with activity at 5-HT2C, histamine-1, and muscarinic-3 receptors, as well as due to increased leptin levels.[32] Preclinical evidence suggests modulating the opioid system may improve feeding behavior and metabolism as reduction in weight gain has been reported in genetically engineered mice with mu-opioid receptors removed despite no differences in caloric intake from wild-type mice.[33] Samidorphan is an investigational mu-opioid receptor antagonist, not binding to any receptors suspected to be responsible for olanzapine's efficacy.[34] In a phase 1 trial of healthy volunteers, weight gain was significantly lower in those treated with OLZ/SAM than those treated with olanzapine alone.[35]

ENLIGHTEN-1 was a phase 3, randomized, double-blind, placebo- and active-controlled trial of 401 subjects experiencing an acute schizophrenia exacerbation.[36] Subjects were randomized 1:1:1 to OLZ/SAM (10-20 mg/10 mg), olanzapine (10-20 mg), or placebo, with a primary endpoint of change in the total PANSS score from baseline to day 28. Metabolic monitoring was performed at baseline, day 28, and a safety follow-up visit on day 43. A statistically significant LSMD in the primary outcome was observed versus placebo for both olanzapine (-5.3 ± 1.8; P = 0.004) and OLZ/SAM (-6.4 ± 1.8; P < 0.001). Mean changes in weight from baseline to day 28 for olanzapine, OLZ/SAM, and placebo were 2.38 ± 3.65 kg, 3.02 ± 3.56 kg, and 0.24 ± 2.76 kg, respectively, suggesting that samidorphan did not mitigate weight gain. However, the investigators emphasized that the study was primarily powered to assess efficacy. No differences in other adverse effects (e.g. somnolence, dry mouth, headache) were found between the active groups.[36] An open-label, 52-week extension of ENLIGHTEN-1 was conducted in 277 subjects, with all maintained on or switched to OLZ/SAM (10-20 mg/10 mg). Metabolic changes appeared to stabilize in the 183 study completers by week 52, with a mean weight increase of 1.86 ± 6.69 kg, fasting LDL cholesterol of 5.7 ± 28.8 mg/dL, and fasting glucose of 6.0 ± 14.4 mg/dL.[37]

ENLIGHTEN-2 was a phase 3, double-blind, randomized trial designed to assess the safety of OLZ/SAM in 550 subjects with stable schizophrenia, randomized 1:1 to either OLZ/SAM (10-20 mg/10 mg) or olanzapine (10-20 mg).[38] The co-primary endpoints were percent change from baseline in body weight and proportion of patients with >10% weight gain at week 24. Statistically significantly lower weight changes were observed with OLZ/SAM versus olanzapine, both in terms of percent change (4.21% vs. 6.59%; P = 0.003) and proportion with >10% gain (17.8% vs. 29.8%; P = 0.003). An open-label, 52-week extension of ENLIGHTEN-2 demonstrated that weight and other metabolic parameters in 265 subjects remained stable over long-term treatment, showing its promise as a novel therapeutic.[38] The FDA accepted an NDA for OLZ/SAM in January 2020, with the Psychopharmacologic Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee jointly voting in its favor in October 2020.[39,40] While the target NDA action date was in November 2020, the FDA has since requested resolution of identified concerns with the tablet coating process before OLZ/SAM may be approved.[41]

Roluperidone (MIN-101)

Currently available antipsychotic medications have shown efficacy evidence for positive symptoms of schizophrenia, though they have mixed to no evidence in relieving negative symptoms and

mood alterations.[3] Roluperidone (MIN-101) is under investigation by Minerva Neurosciences as the first drug for treating negative symptoms of schizophrenia through its antagonism of both sigma-2 and 5-HT2A receptors; it has no direct affinity for dopamine receptors.[42]

Davidson et al. conducted a phase 2, randomized, double-blind, placebo-controlled trial of 244 subjects with controlled schizophrenia except for >3 months of negative symptoms according to the PANSS.[43] Subjects were randomized 1:1:1 to roluperidone 32 mg, roluperidone 64 mg, or placebo, with a primary endpoint of change in the PANSS negative symptom pentagonal structure factor score from baseline to week 12. No other psychiatric medications were allowed during the study except for as-needed options to treat agitation or insomnia. Compared to the placebo group's least squares mean change from baseline (-1.53 ± 0.47), statistically significant differences were observed for both the 32-mg (-3.07 ± 0.49; P = 0.024) and 64-mg (-3.5 ± 0.48; P = 0.004) groups; a post hoc analysis found a poor correlation between these changes and Calgary Depression Scale for Schizophrenia (CDSS) total scores (r = 0.26). No significant improvement of PANSS positive symptom scores were observed in any groups at week 12. The most common adverse effect was headache, with no significant changes in EPS, vital signs, or metabolic parameters.[43] Minerva Neurosciences reportedly met with the FDA in November 2020 to solicit recommendations regarding the NDA process.[44] A 12-week, phase 3 trial of roluperidone for negative symptoms in schizophrenia is ongoing, with an estimated study completion date of April 2021.[45]

Evenamide (NW-3509)

As discussed previously, FDA-approved antipsychotic medications have acted primarily through D2 and 5-HT2A antagonism.[3] Newron Pharmaceuticals has begun investigating evenamide (NW-3509) as the first adjunctive therapy for treating positive symptoms of schizophrenia. Evenamide is a voltage-gated sodium channel blocker, indirectly modulating glutamate release that is hypothesized to be dysfunctional in schizophrenia.[46]

While quantitative data is limited, evenamide has been studied in a proof-of-mechanism, randomized, double-blind, placebo-controlled study of 89 subjects with uncontrolled schizophrenia despite receiving previously effective risperidone (>2 mg/day) or aripiprazole (>10 mg/day).[47] Subjects were randomized 1.3:1 to evenamide (15-25 mg twice daily) or placebo as an add-on to their existing antipsychotic medication, with statistically significant improvements versus placebo in the PANSS positive symptom score at week 4 according to an available abstract. Common adverse effects included somnolence, insomnia, and headache.[47] The FDA delayed further progression of evenamide's clinical trials in May 2019, citing safety concerns in rat and dog models. Plans for short-term exploratory studies in humans were discussed in November 2020 by the FDA and Newron Pharmaceuticals, now aiming to have initial results in early 2021 to allow for phase 3 trials later this year.[46,48]

Conclusion

As antipsychotic non-adherence increases risk of schizophrenia relapse, investigators have continued developing novel formulations beyond the oral administration route over the past few years. Additionally, mechanisms of action beyond dopaminergic and serotonergic receptor antagonism continue to be explored through novel antipsychotic molecules to solve efficacy gaps (e.g. negative symptoms of schizophrenia) and minimize adverse effects (e.g. EPS, weight gain). Due to the significant costs associated with these new treatments, pharmacists should be prepared to guide mental health professionals and educate patients on their efficacy, safety, and administration concerns relative to established antipsychotic treatments for schizophrenia.

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