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SCHIZOPHRENIA AND OTHER PSYCHOTIC DISORDERS (AK PANDURANGI, SECTION EDITOR)

New Antipsychotic Medications in the Last Decade

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Abstract

Purpose of Review Over the last ten years, the treatment of psychosis has seen a near explosion of creative development in both novel agents and new delivery modalities. The current review summarizes these developments over the past decade (2011–2020). We performed a systematic review utilizing PubMed and PsychInfo with the aim of identifying all the RCT and related analyses in adults with psychosis (schizophrenia and mania).

Recent Findings We identified 11 significant developments: the introduction of new antipsychotics cariprazine, brexpiprazole, lumateperone, and pimavanserin; introduction of new delivery methods: subcutaneous long-acting risperidone, aripiprazole lauroxil, transdermal asenapine, and inhaled loxapine; and the introduction of new approaches such as olanzapine/samidorphan for olanzapine-associated weight gain, examination of the TAAR1 agonist SEP 363,856 as a test of concept, and the combination of Xanomeline/Trospium, an M_1 and M_4 muscarinic receptor agonist in conjunction with a peripheral anticholinergic.

Summary Last decade has seen a tremendous development in second-generation antipsychotics which provides unprecedented treatment options for clinicians in treating psychosis.

Keywords Aripiprazole lauroxil · Brexpiprazole · Cariprazine · Inhaled loxapine · Lumateperone · New antipsychotics · Pimavanserin · Olanzapine/samidorphan · SEP-363856 · Subcutaneous risperidone · Transdermal asenapine · Xanomeline/trospium

Introduction

Psychiatry has experienced a recent surge in new and innovative treatment approaches for a variety of disorders [1•]. In the area of psychosis and schizophrenia, there have been multiple new agents and formulations that have the potential of positively altering approaches to treatment. Specifically, in addition to the ability to administer medications, orally, intramuscularly (IM), and intravenously (IV), we can now administer antipsychotic medications transcutaneously and via inhalation. We have two new formulations of injectable long-acting antipsychotics (LAIs) that will achieve rapid therapeutic levels, so that concomitant oral administration is minimized. We can avoid muscular injury that is associated with IM injection of LAIs by giving medication subcutaneously. We can use new antipsychotics that have minimal metabolic, extrapyramidal, or prolactin effects and which impact multiple disorders. We now even have the first antipsychotic that has no dopaminergic activity, which provides relief to patients with Parkinson's disease and psychosis, as well as being promising for dementia-related psychosis. These developments will be reviewed in this paper.

Methods

Systematic reviews were performed following the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [2, 3]. Major introductions of new antipsychotic medications or new antipsychotic formulations in the last 10 years (2011 through 2020) were determined

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by author consensus, which produced 11 new agents or formulations. Two databases (PubMed and PsychInfo) were queried based on the topic regarding the particular agent. The goal was to include all peer-reviewed, published randomized clinical trials (RCTs); consequently, the items on the searches were screened specifically for that. We also included post hoc analyses of the RCTs and open-label studies when RCTs were not available. Each drug was searched separately, and the inclusion criteria for psychosis consisted of schizophrenia and bipolar mania but not bipolar depression, psychosis in dementia, psychosis in Parkinson's disease, and acute agitation in psychosis. Important references in key articles were also reviewed. Additional information regarding the pharmacokinetics or pharmacodynamics were not searched systematically but strategically to inform the reader. Four reviewers (MP, AS, OE, RSE) performed the study selection procedure; abstracts and title were used for screening for initial inclusion. Full-text review of the included studies was carried out, and data were extracted on study's characteristics and outcomes. All the disagreements were resolved with consensus in the presence of a senior author (RSE).

Results

There are four new antipsychotic molecules: brexpiprazole, cariprazine, lumateperone, and pimavanserin. There are four new formulations of previously available antipsychotics. These include two LAI antipsychotics (subcutaneous long-acting risperidone, aripiprazole lauroxil), one transdermal antipsychotic (asenapine), and one inhalable antipsychotic (loxapine). Additionally, the combination of an opioid antagonist samidorphan to olanzapine (OLZ/SAM) was introduced to mitigate olanzapine-induced weight gain. Finally, a novel TAAR1 agonist (SEP 363856), and a combination of procholinergics which have completed phase II trials were included.

Cariprazine searches yielded 362 potential references. There were 6 RCTs and 3 open-label studies and 5 post hoc analyses for psychosis (Table 1) and 3 RCTs,1 open-label, and 5 post hoc analyses for bipolar mania (Table 2) that met the inclusion criteria for this review. There were 48 articles on bipolar depression, but they were not included in this review on psychosis.

Brexpiprazole search yielded 348 articles; 3 clinical trials for mania in bipolar disorder (BD), 12 clinical trials in schizophrenia, and 11 post hoc analyses were included in this review (Table 3).

Lumateperone yielded 35 studies through database search and after assessing for article eligibility, a total of 5 studies that met the inclusion criteria were included (Table 4).

A total of 281 articles were identified for Pimavanserin through database search. A total of 10 studies were included on Parkinson's disease psychosis (PDP), 3 in psychosis in Alzheimer's disease, and 1 in in schizophrenia (Table 5).

OLZ/SAM combination search resulted in 30 abstracts, out of which 5 RCT and 6 open-label studies fulfilled our inclusion criteria (Table 6).

Transdermal asenapine yielded 13 articles, and 2 studies were included in the review (Table 7). Subcutaneous risperidone yielded 92 articles on database search, and 8 studies fulfilled the inclusion criteria (Table 8).

Aripiprazole lauroxil had 80 articles on both databases, and a total of 22 studies including 3 RCT's were included (Table 9).

Inhaled loxapine search yielded 94 references, 50 were duplicates, and 12 total studies were included in the review (Table 10).

SEP 36,385 had only 8 published studies, and only 1 phase II RCT was included.

Xanomeline/trospium search revealed a total of 44 references of which only 2 met the inclusion criteria in this review.

Discussion

The last decade saw a dramatic expansion of the clinical pharmacopeia for psychosis with particular emphasis on novel and unique agents. Newer antipsychotics are being developed with the aim of better efficacy in negative and cognitive symptoms in schizophrenia and BD. They also aim to mitigate the associated concerning cardio-metabolic adverse effects (AEs) with long-term treatment. There has been an introduction of (i) newer partial dopaminergic agonist, cariprazine and brexpiprazole; (ii) lumateperone (D2 antagonist) with efficacy at < 50% receptor occupancy; and (iii) pimavanserin, a $5HT_{2A}$ receptor inverse agonist with no anti-dopaminergic activity. There has been a newer approach to an existing antipsychotic: addition of samidorphan (an opioid antagonist) to olanzapine to mitigate olanzapine-induced weight gain. Additionally, concern in the treatment of long-term psychosis has been non-adherence, and thus, newer delivery methods for existing antipsychotic formulations have been introduced. The first antipsychotic patch formulation in the USA was introduced in the market with transdermal asenapine which achieves a slower and steadier plasma concentration. Another patient-friendly formulation has been subcutaneous risperidone injection which aims to avoid the muscle tissue damage along with improving long-term adherence. Adding to this list is another long-acting injectable (LAI): aripiprazole lauroxil intramuscular (IM) monthly injection formulation for better adherence and

Table 1 The characteristics of studies on cariprazine in schizophrenia

Cariprazine in Schizophrenia					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Durgam et al. 2014 [13]	6-week phase II RCT	1.5 mg 3 mg 4.5 mg	732	PANSS CGI-S EPS	Significant improvement with all the doses
Durgam et al. 2015 [11]	6-week phase III RCT	3 mg 6 mg	617	PANSS CGI-S	Improvement on both scales with all doses. Common A/E's: akathisia, insomnia, and headache
Kane et al. 2015 [14]	6-week phase III RCT	3–6 mg 6–9 mg	446	PANSS CGI-S	Improvement on all scales. Most common A/E: akathisia, EPS, tremor. Metabolic A/E minimal
Durgam et al. 2016 [20]	20-week open-label: 8-week flexible dose, 12-week fixed-dose RCT for 26–72 week	3 mg 6 mg 9 mg	264 (open-label) 200 (RCT)	Relapse prevention PANSS CGI-S	Relapse occurred in 24.8% of cariprazine patients, and time to relapse was significantly longer in comparison to placebo Long-term therapy effective for relapse prevention
Durgam et al. 2016 [12]	6-week RCT	1.5–4.5 mg 6–12 mg	392	PANSS CGI-S	Cariprazine treatment effect was not significant overall, but low dose had significant improvement in psychotic symptoms without multiplicity adjustment
Nemeth et al. 2017 [15]	26-week phase III B RCT	3 mg 4.5 mg 6 mg	460	Negative symptoms PANSS-FSNS PSP	Greater improvement in negative symptoms in comparison to risperidone at the end of 26 weeks. 54% patients reported A/E on cariprazine
Open-label studies					
Nakamura et al. 2016 [10]	28-week open-label fixed-dose	3 mg 6 mg 9 mg	38	Pharmacokinetics, safety and efficacy	Steady-state reached 1–2 weeks (cariprazine/desmethyl-cariprazine), 4 weeks (didesmethyl-cariprazine), 3 weeks for active moieties
Durgam et al. 2017 [22]	48-week open-label extension study	1.5–4.5 mg	93	Long-term safety and tolerability	50% completion rate, well-tolerated, minimal metabolic A/E. Most common A/E were akathisia, insomnia, and weight increase
Cutler et al. 2018 [23]	1-year open-label flexible dose	3–9 mg	586	Efficacy and tolerability PANSS, CGI-S SQLS-R4 CDR CTT	39% completed the study Most common A/E were akathisia, headache, insomnia, and weight gain. 10.1% experienced serious A/E
Post hoc analysis					
Nasrallah et al. 2017 [24]	Post hoc analysis	1.5–3 mg 4.5–6 mg 9 mg	679	Long-term safety and tolerability	Overall, well-tolerated, only A/E leading to discontinuation were akathisia and worsening of psychosis. A/E ≥ 10% were akathisia, insomnia, weight gain, and headache

Table 1 (continued)

Cariprazine in Schizophrenia					
Author, year	Study design	Dose	Sample size (n)	Outcome measure	Key outcome
Marder et al. 2019 [18]	Post hoc analysis	1.5 mg 3 mg 4.5 mg 6 mg	1466	Efficacy on PANSS factors and individual items	Effective in improving all five PANSS factor domains
Correll et al. 2019 [21]	Post hoc analysis	3 mg 6 mg 9 mg	200	Long-term remission PANSS	Higher remission rates Longer sustained remission Increased sustained remission ≥ 6 months
Earley et al. 2019 [19]	Post hoc analysis	1.5–6 mg	317	Efficacy on negative symptoms PANSS	Significant improvement in negative symptoms in acute schizophrenia in comparison to placebo and aripiprazole
Fleischhacker et al. 2019 [16]	Post hoc analysis	3 mg 4.5 mg 6 mg	454	Efficacy in negative symptoms PANSS	Significant improvement in negative symptoms in comparison to risperidone

BPRS, Brief Psychiatric Rating Scale; *CDSS*, Calgary Depression Scale for Schizophrenia; *PANSS*, Positive and Negative Syndrome Scale; *CGI-S*, Clinical Global Impression-Severity; *EPS*, extrapyramidal side effects; *A/E*, adverse effects; *SQLS*, schizophrenia quality of life scale; *CTT*, Color Trails test; *CDR*, Cognitive Drug Research

steadier plasma concentration. An inhaled antipsychotic formulation of loxapine has been introduced with the aim of controlling acute agitation in acute mania and schizophrenia. Finally, two very novel non-dopaminergic drugs, SEP 363,856 and procholinergic drugs xanomeline/trospium combination, have been examined in randomized phase II studies. We are presenting each agent individually to highlight each agents' unique characteristics.

Cariprazine

In 2015, cariprazine, a piperazine derivative, was approved for the acute treatment of schizophrenia and mania [4]. It is a partial agonist at the dopamine D2 and D3 and the serotonin $5HT_{1A}$ receptors. It has a tenfold higher affinity for D3 (inhibitory constant [K_i] = 0.085 nM) than D2 receptors (K_i = 0.49 nM) [5, 6]. It also binds with high potency to serotonin $5HT_{2B}$ (K_i = 0.58 nM) receptors and with moderate potency to 5HT1A (K_i = 2.6 nM) and $5HT_{2A}$ (K_i = 180 nM) receptors [5, 7, 8].

It is orally administered and reaches peak plasma concentration (T_{max}) in 3–4 h. It has two active metabolites: desmethyl-cariprazine (DCAR) metabolite (half-life 2–4 days) and didesmethyl-cariprazine (DDCAR) which has a very extended half-life (1–3 weeks) [9]. In an open-label study (n = 38) exploring pharmacokinetics of cariprazine over 28 weeks with a fixed-dose regimen (3, 6, or 9 mg). Steady-states for cariprazine and DCAR were reached in 1–2 weeks, but it took 4 weeks for DDCAR [10]. This creates a unique problem in which most short-term clinical trials are over before the drug levels have actually reached steady-state. It is mainly metabolized by CYP3A4 and to a lesser extent by the CYP2D6. It is also a weak competitive inhibitor of CYP3A4 and CYP2D6 isoenzymes. Its recommended dosage for schizophrenia is 1.5–6 mg/day. The US Food and Drug Administration (FDA) approved cariprazine for maintenance treatment of schizophrenia in adults in November 2017.

Efficacy of Cariprazine in Acute Schizophrenia

There were 4 RCTs with a similar design evaluating the efficacy and safety in acute schizophrenia [11–14] (Table 1). A 6-week phase II study compared cariprazine 1.5 mg, 3 mg, and 4.5 mg with placebo and risperidone 4 mg [13]. A total of 732 patients were enrolled and 64% completed the study. All three doses of cariprazine exhibited greater reduction in the Positive and Negative Symptom Scale (PANSS) than placebo at 6 weeks (P < 0.001). The Clinical Global Impression-Severity (CGI-S) scale also demonstrated significant improvement for all active treatments (P < 0.05). Higher doses (3 mg and 4.5 mg) appeared to have a greater response initially, but that effect was lost as steady-state levels were

Table 2 The characteristics of studies on cariprazine in bipolar disorders

Cariprazine in bipolar disorder					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Calabrese et al. 2015 [26]	3-week phase III RCT	3–6 mg 6–12 mg	497	YMRS CGI-S	Both low and high dose were more effective than placebo in acute mania and mixed episodes Most common A/E were akathisia, nausea, constipation, and tremor
Durgam et al. 2015 [27]	3-week phase II RCT	3–12 mg	118	YMRS CGI-S	Superior efficacy in acute mania and mixed episodes in comparison to placebo Most common A/E were EPS, headache, akathisia, constipation, nausea, and dyspepsia
Sachs et al. 2015 [25]	3-week phase III RCT	3–12 mg	312	YMRS CGI-S PANSS	Statistically significant remission and response on YMRS, mean change in CGI-S and PANSS, in comparison to placebo
Ketter et al. 2018 [33]	16-week open-label study	3–12 mg	402	YMRS Safety and tolerability	Well-tolerated Most common A/E were akathisia, headache, constipation, and nausea
Post hoc analysis					
Vieta et al. 2015 [28]	Post hoc analysis	3–12 mg	1037	YMRS	Statically significant improvement in mean change on all YMRS items
Earley et al. 2017 [30]	Post hoc analysis	3–6 mg 9–12 mg	1065	Safety and tolerability	Well-tolerated in mania and mixed episodes. Most common A/E were akathisia, EPS, restlessness, vomiting
Durgam et al. 2017 [32]	Post hoc analysis	1.5–12 mg	2499	CGI-S YMRS PANSS	Significant CGI-S improvement in both schizophrenia and bipolar with cariprazine in comparison to placebo
Earley et al. 2018 [31]	Post hoc analysis	3–12 mg	1037	YMRS MADRS	Significant greater remission and response in maniac symptoms in Bipolar I in comparison to placebo
McIntyre et al. 2019 [29]	Post hoc analysis	3–12 mg	1037	YMRS MADRS	Significant reduction in manic and depressive symptoms in mixed features in comparison to placebo

YMRS, Young Mania Rating Scale; *MADRS*, Montgomery–Åsberg Depression Rating Scale; *BPRS*, Brief Psychiatric Rating Scale; *CDSS*, Calgary Depression Scale for Schizophrenia; *CGI-S*, Clinical Global Impression-Severity; *EPS*, extrapyramidal side effects; *A/E*, adverse effects

reached, suggesting no dose-related differences in efficacy [13]. The risperidone group had a non-significantly larger difference in mean changes from baseline in comparison to cariprazine.

A phase III fixed-dose RCT compared cariprazine (3 mg and 6 mg) with aripiprazole 10 mg and placebo over 6 weeks. Sixty-seven percent of patients completed this study with similar retention in cariprazine and placebo and slightly better retention with aripiprazole [11]. The mean changes in PANSS and CGI-S were statistically significant for both doses of cariprazine in comparison to placebo and equivalent to aripiprazole. Another similar design phase III RCT of 6 weeks studied cariprazine 3–6 mg and 6–9 mg [14]. Both dose ranges were equivalent to each other but superior to placebo regarding changes of PANSS and CGI-S at 6 weeks. Secondary analyses again demonstrated earlier response with the higher dose range which is lost by the end of the study [14].

Durgam et al. (2016) in another proof-of-concept study [12] evaluated low-dose (1.5–4.5 mg) and high-dose (6–12 mg) cariprazine for 6 weeks in acute schizophrenia. Fifty-four percent of patients completed this study, and no

Table 3 Characteristics of studies on brexpiprazole

Study	Study design	Dose	Sample size (*N*)	Outcome measure	Key outcome
Brexpiprazole in bipolar disorder					
Vieta et al. 2021 [55]	(Studies 080 & 081) two 3-week, RCTs (Study 083) a 26-week open-label extension study	2–4 mg/day	080: 322 081: 333 083: 381	080 & 081: YMRS, CGI-BP 083: safety, YMRS, CGI-BP	080 & 081: brexpiprazole = placebo (no significant change in YMRS) in acute mania 083: patients showed gradual reduction in manic symptoms severity. Drug was safe and well-tolerated, but akathisia was a common A/E
Brexpiprazole in schizophrenia					
Van Erp et al. 2020 [52]	A functional magnetic resonance imaging (fMRI) RCT	2–4 mg/day	38	Blood oxygen-level dependent activation in the prefrontal cortex	Brexpiprazole (4 mg) treatment is associated with decreased activation of right ventrolateral prefrontal cortex during the stop-signal task suggesting improved inhibition
Girgis et al. 2020 [36]	A positron emission tomography (PET) study	1–4 mg/day	12	Dopamine and serotonin receptors occupancies	Brexpiprazole's steady-state concentration is coupled with strong dose-dependent occupancy at D2 and 5-HT2A receptors Occupancy at D3, 5-HT1A, and serotonin transporter could not be established in this study
Ishigooka et al. 2018a [42]	A 6-week RCT	1–4 mg/ day	459	PANSS	Brexpiprazole (2 mg) > placebo in Japanese patients with acute schizophrenia exacerbation
Ishigooka et al. 2018c [185]	A 2-week RCT	1, 4, and 6 mg/day	21	Pharmacokinetic safety	Brexpiprazole was safe and well-tolerated in Japanese patients with schizophrenia
Fleischhacker et al. 2017 [53]	A 52-week RCT	1–4 mg/day	202	Time to relapse	Brexpiprazole is safe and efficacious in treatment of patients with schizophrenia. Impending relapse (brexpiprazole 13.5% vs. placebo: 38.5%)
Correll et al. 2015 [40]	A 6-week phase III RCT	0.25, 2, or 4 mg/day	636	PANSS, CGI-S	Brexpiprazole at 2–4 mg dosage > placebo in patients with schizophrenia. Akathisia was the main A/E
Kane et al. 2015 [39]	A 6-week phase III RCT	1, 2, or 4 mg/day	674	PANSS, CGI-S	Brexpiprazole > placebo in patients with schizophrenia, with 4 mg/day as most effective
Ichinose et al. 2021 [49]	A flexible open- label medication switch study	1.9 ± 0.3 mg/day	37	PANSS DIEPSS safety	Brexpiprazole switch led to improvement in EPSEs, prolactin levels, and metabolic parameters. No significant change for PANSS total score and plasma homovanillic acid levels

Table 3 (continued)

Study	Study design	Dose	Sample size (*N*)	Outcome measure	Key outcome
Forbes et al. 2018 [57]	A 52-week open-label study	1–4 mg/day	1072	Safety	Brexpiprazole treatment is safe and well-tolerated by the patients with schizophrenia. Most common A/Es are insomnia, weight gain, headache, and agitation
Ishigooka et al. 2018b [43]	A 52-week open-label study	1–4 mg/ day	282	PANSS, Safety	Brexpiprazole is safe and efficacious in Japanese patients with acute schizophrenia exacerbation. TEAEs ≥ 10% were nasopharyngitis (23.1%) and worsening of schizophrenia (22.4%)
Malla et al. 2016 [47]	A 16-week phase, open-label study	1–4 mg/day	49	PANSS, PSP	Brexpiprazole could be efficacious in early-episode schizophrenia
Citrome et al. 2016 [58]	A 6-week phase III, open-label study	Brexpiprazole: 1–4 mg/day	97	PANSS, cognitive testing, safety	Brexpiprazole and aripiprazole showed comparable results in terms of safety and efficacy. Akathisia occurred less with brexpiprazole
Ishigooka et al. 2021 [186]	Post hoc analysis	2–4 mg/day	186	Metabolic parameters	Switching patients with schizophrenia to brexpiprazole is safe and effective. Risk of metabolic abnormalities is minimal
Inada et al. 2020 [187]	Post hoc analysis	2–4 mg/day	208	PANSS, safety	Long-term brexpiprazole was safe and effective elderly patients with schizophrenia
Meade et al. 2020 [45]	Post hoc analysis	2–4 mg/day	1405	PANSS, safety	Brexpiprazole > placebo in patients with schizophrenia. Safety and effectiveness were sustained in the extension, 52-week follow-up period
Ishigooka et al. 2020 [46]	Post hoc analysis	1–4 mg/day	200	PANSS Discontinuation rates	There was no substantial change in PANSS at week 8 post-switching. Discontinuation rate was 4.9% switching from aripiprazole versus 25.4% switching from other antipsychotics. Cautious consideration and tapering are needed when switching from olanzapine
Marder et al. 2020 [44]	Post hoc analysis	2–4 mg/day	468	PANSS, safety	Separation from placebo for brexpiprazole was shown by sensitivity analysis. Potential confounding of efficacy ratings in patients with quetiapine XR A/E's

Table 3 (continued)

Study	Study design	Dose	Sample size (*N*)	Outcome measure	Key outcome
Citrome et al. 2019 [51]	Post hoc analysis	1–4 mg/day	Short: 1094 Long: 346	PANSS excited component (EC)	Brexpiprazole > placebo in the management of agitated and hostile schizophrenic patients; improvement was maintained over 58 weeks
Correll et al. 2019 [50]	Post hoc analysis	1–4 mg/day	404	PANSS, discontinuation rates	Cross-titration while switching safely and effectively from primary antipsychotic treatment to brexpiprazole takes mostly 22–33 days
Ivkovic et al. 2019 [61]	Post hoc analysis	Short-term 0.25–4 mg/day Long–term 2–4 mg/dl	Short: 1774 Long: 1240	Prolactin changes	Low incidence of prolactin-related TEAEs was observed after treatment with brexpiprazole; 1.8% short-term and 1.7% in long-term studies
Weiss et al. 2018 [188]	Post hoc analysis	2–4 mg/day	724	Metabolic parameters	The effect on body weight of brexpiprazole = aripiprazole when compared as monotherapy for schizophrenia and as adjunctive treatment in unipolar depression
Newcomer et al. 2018 [59]	Post hoc analysis	2–4 mg/day	Short: 1730 Long: 696	Metabolic parameters	Mean weight gain in brexpiprazole-treated group (1.2 kg) > with placebo (0.2 kg)
Marder et al. 2017 [41]	Post hoc analysis	2–4 mg/ day	Short: 311 Long: 201	PANSS	Brexpiprazole > placebo in patients with schizophrenia in acute and long-term treatment

RCT, randomized controlled trial; *YMRS*, Young Mania Rating Scale; *CGI-BP*, Clinical Global Impression-bipolar version; *PANSS*, Positive and Negative Syndrome Scale; *DIEPSS*, Drug-Induced Extrapyramidal Symptoms Scale; *TEAEs*, Treatment-Emergent Adverse Events; *PSP*, Personal and Social Performance; *CGI-S*, Clinical Global Impression-Severity; *A/E*, adverse effects

Table 4 The characteristics of studies on lumateperone in schizophrenia

Lumateperone in schizophrenia					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Correll et al. 2020 [71]	4-week phase III RCT, placebo-controlled	42 mg 28 mg	450	PANSS CGI-S CDSS A/E	42 mg lumateperone had significant improvement in PANSS score; improvement with 28 mg was not significant in comparison to placebo Both 42 mg and 28 mg had significant improvement in CGI-S scores & PANSS positive subscale Somnolence most common A/E with lumateperone, No EPS
Lieberman et al. 2016 [70]	4-week phase II RCT, placebo- and active-controlled trial	60 mg* 120 mg	335	BPRS PANSS CDSS A/E	60 mg ITI-007 reduced positive symptoms significantly, but negative symptoms were not significantly reduced 120 mg showed no statistical improvement in symptoms No significant A/E noted
Vancouver et al. 2018 [73]	4-week phase III RCT	14 mg 42 mg	696	PANSS	No significant difference for either dose of lumateperone in comparison to placebo on PANSS score
Correll et al. 2021 [76]	6 weeks open-label switch study	42 mg	301	A/E PANSS	45.5% experienced adverse effects Most common A/E were somnolence, headache, and dry mouth. EPS were rare PANSS score remained stable in comparison to previous antipsychotics
Kane et al. 2021 [75]	Pooled post hoc analysis	42 mg	1073	Safety and tolerability	TEAE with lumateperone (0.5%) were similar to placebo (0.5%) and less than risperidone (4.7%) TEAE ≥5%- somnolence/sedation, dry mouth

PANSS, Positive and Negative Syndrome Scale; *BPRS*, Brief Psychiatric Rating Scale; *CDSS*, Calgary Depression Scale for Schizophrenia; *CGI-S*, Clinical Global Impression-Severity; *EPS*, extrapyramidal side effects; *A/E*, adverse effects

*60 mg lumateperone tosylate = 42 mg of lumateperone

difference was detected between both doses of cariprazine and placebo on PANSS and CGI-S. However, low-dose cariprazine had significantly greater improvement in PANSS total and PANSS negative score in comparison to placebo without multiplicity adjustments.

Improvement in negative symptoms has been examined in both secondary analyses and primary negative symptom studies. Nemeth et al. prospectively studied its role in negative symptoms in a 26-week RCT that compared cariprazine 4.5 mg with risperidone 4 mg in 460 adult patients [15]. This study did not have a placebo arm and required PANSS factor score for negative symptoms (FSNS) to be ≥ 24 (moderate negative symptoms). This study had extensive exclusion criteria that included acute exacerbation or hospital admission in the last 6 months, PANSS positive factor score > 19, moderate-to-severe depression, clozapine in the last 12 months, parkinsonian symptoms, clinical instability during prospective lead-in period, or treatment with anticholinergic/antidepressant. The completion rate was 77%, and the mean daily dose of cariprazine was 4.2 mg, and risperidone was 3.8 mg. Response rate of PANSS-FSNS (defined as ≥ 20% improvement) at week 26 was 69% for cariprazine and 58% for risperidone (odds ratio [OR] 2.08; $P = 0.0022$; number needed to treat [NNT] = 9) [15]. This improvement was accounted for by changes in the N1–N5 items (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking) without any changes in N6 (lack of spontaneity/flow of conversation)

Table 5 The characteristics of studies on oral pimavanserin in schizophrenia, Parkinson's disease psychosis, and psychosis in Alzheimer's disease

Oral pimavanserin					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Schizophrenia					
Meltzer et al. 2012 [90]	6-week RCT	20 mg	423	Efficacy of combination therapy with risperidone, haloperidol	Subtherapeutic risperidone 2 mg dose, when combined with pimavanserin, displayed comparative efficiency to risperidone 6 mg with fewer motor and metabolic A/E Pimavanserin did not potentiate the efficacy of haloperidol
Parkinson's disease psychosis (PDP)					
Cummings et al. 2014 [85]	6-week phase III RCT	40 mg	199	SAPS-PD Safety/tolerability	Pimavanserin may benefit PDP for whom few other options exist
Meltzer et al. 2010 [84]	4-week phase II RCT	20 mg 40 mg 60 mg	60	SAPS-PD CGI-S UPDRS	Pimavanserin was found to be tolerable and efficacious by some, but not all measures for treatment of PDP
Ancoli-Israel et al. 2011 [189]	13-day RCT	1 mg 2.5 mg 5 mg 20 mg	45	SWS Attention vigilance	Significantly increased SWS in treatment group compared to placebo
Vanover et al. 2007 [82]	14-day RCT escalating dose study	20–300 mg	25	PK Tolerability and Safety	Pimavanserin exhibited dose-proportionate PK Median time of peak plasma was 6 h. Half-life was between 53 and 58. ACP-103 was well-tolerated overall, and A/E were generally mild in nature
Isaacson et al. 2021 [88]	4- week open-label extension study	34 mg*	459	SAPS-PD H + D scales CGI-I	Both the treatment group and the placebo group of the previous trials reported durability of efficacy and improvement respectively
Ballard et al. 2020 [89]	Median 454 days Open-label extension study	34 mg*	459	Safety and tolerability	Overall a favorable benefit/risk profile. At least 1 A/E occurred in 85.4%. Serious AE occurred in 41% of patients and an AE leading to study termination in 29%. 13.3% patients died over a span of 11 years
Nordstrom et al. 2008 [83]	Open-label study	1–100 mg	4	PET analysis (Cortical NMSP) PK Safety and tolerability	Cortical NMSP binding was dose-dependent and fitted well to the law of mass action, indicating passage of the blood brain barrier. The drug was well-tolerated in all 4 subjects
Vanover et al. 2007 [81]	Open-label study	20–100 mg	8	Bioavailability	Immediate release tablets were 99.7% bioequivalent to the solution Food doesn't alter the bioavailability
Espay et al. 2018 [86]	Post hoc analysis	34 mg*	199	SAPS-PD CGI-I Tolerability	Larger improvement in group with low baseline cognition. Participants taking concomitant cognitive-enhancing medication showed a larger numerical SAPS-PD effect
Ballard et al. 2015 [190]	Post hoc analysis	40 mg	459	Safety UPDRS-II+III	Significant increase in the mortality rate for participants taking concurrent antipsychotics compared to the group not taking antipsychotic medications. They were also more likely to experience overall serious A/E

Table 5 (continued)

Oral pimavanserin					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Psychosis in Alzheimer's disease					
Ballard et al. 2018 [98]	6-week phase II RCT	34 mg*	181	NPI-NH psychosis change Safety	Pimavanserin showed efficacy at 6 weeks with acceptable tolerability profile and without negative effect on cognition Follow-up at 12 weeks did not show significant advantage vs placebo
Ballard et al. 2020 [99]	Post hoc analysis	34 mg*	181	NPI-NH domain C CMAI-SF	Non-significant improvement in agitation in psychotic responders
Ballard et al. 2019 [191]	Post hoc analysis	34 mg*	181	NPI-NH psychosis	Overall exhibited efficacy for the NPI-NH psychosis in AD at week 6 without negative cognitive effects in participants with more severe psychosis at baseline

SAPS-PD, Scale for the Assessment of Positive Symptoms for Parkinson's Disease Psychosis; *CGI-S*, Clinical Global Impression-Severity; *UPDRS*, Unified Parkinson's Disease Rating Scale; *PDP*, Parkinson's disease psychosis; *A/E*, adverse events; *SWS*. slow sleep wave; *PK*, pharmacokinetics; *SAPS-H; + D*, Scale for the Assessment of Positive Hallucinations + Delusions; *CGI-I*, Clinical Global Impression-Improvement; *NMSP*, N-methylspiperone; *NPI-NH*, Neuropsychiatric Inventory Nursing Home version; *CMAI-SF*, Cohen-Mansfield Agitation Inventory-Short Form

*34 mg pimavanserin = 40 mg pimavanserin tartrate

or N7 (stereotyped thinking) [16]. Modeling of this data revealed that patients gain 1/3 of 1 month of quality life after 1 year of treatment with cariprazine versus risperidone (0.029 of a quality-adjusted life year [QALY]) [17].

Several post hoc analyses evaluated pooled data from the above 3 acute studies [11, 13, 14]. Marder et al. showed a significant difference in PANSS total score, negative symptoms, and disorganized thought score ($P < 0.001$) at 6 weeks for all cariprazine doses versus placebo in the 3 fixed-dose studies combined [18]. Early et al. [19] pooled the data from two trials [11, 13] and found that change in PANSS-FSNS at 6 weeks from baseline showed significant difference for cariprazine versus placebo (1.5–3 mg, $P = 0.179$; 4.5–6 mg, $P = 0.0002$) and cariprazine 4.5–6 mg versus aripiprazole ($P = 0.0197$). Response in negative symptoms was significantly higher for cariprazine (54.3–69.7%) in comparison to placebo (35.4%).

Long-Term Safety/Relapse Prevention of Cariprazine

A long-term randomized withdrawal study [20] was conducted over 97 weeks. Initial phase was a 20-week open-label treatment with 8 weeks of flexible dose phase followed by 12-week fixed-dose stabilization phase. Out of 265 patients that completed the open-label treatment, 200 patients were randomized to cariprazine (3, 6, or 9 mg) or placebo for up to 72 weeks. Primary efficacy outcome was time to first relapse which was defined as worsening of symptom scores, psychiatric hospitalization, suicidal risk, or aggressive/violent behavior. Kaplan–Meier analysis showed time to relapse was significantly longer for cariprazine than placebo. By study end, 24.8% of cariprazine patients had relapsed compared to 47.5% patients on placebo (hazard ratio [HR] 0.45, 95% CI 0.28–0.73) for a NNT of five [20]. If the data are viewed from the perspective of maintaining remission, defined as a score of ≤ 3 on the 8 positive symptom items of the PANSS, 60.5% cariprazine treated and 34.9% placebo-treated maintained remission ($P = 0.0012$). During the double-blind phase, the time to loss of remission was longer for cariprazine vs. placebo (HR = 0.51). Around 40% of cariprazine patients met symptomatic remission criteria at all visits for ≥ 6 consecutive months vs. 21.2% of the placebo group. Also, 41.6% cariprazine patients sustained remission (including meeting criteria for remission) for any ≥ 6 consecutive months [21].

Safety and Tolerability of Cariprazine

Common AEs during short-term studies were akathisia, tremor, restlessness, Parkinsonism, sedation, and gastrointestinal disturbance [11–14].

Long-term studies looking at safety and tolerability included a 48-week open-label extension study [22]

Table 6 The characteristics of studies on olanzapine + samidorphan

Olanzapine and samidorphan (OLZ/SAM)					
Author, year	Study design	Dose OLZ/SAM	Sample size (*n*)	Outcome measure	Key outcome
Sun et al. 2020 [108]	Phase I RCT	10/10 20/20 mg 30/30 mg	100	Heart rate ECG–QTc	No significant QTc effect noticed
Potkin et al. 2020 [111]	4-week, phase III RCT ENLIGHTEN-1	10/10 mg to 20/10 mg	401	PANSS CGI-S	Significant improvements in PANSS and CGI-S with both OLZ /SAM and OLZ
Correll et al. 2020 [112]	24-week phase III randomized study ENLIGHTEN-2	OLZ/SAM: 10/10 mg 20/10 mg OLZ:10–20 mg	561	Weight gain	Weight gain was significantly less in OLZ/SAM in comparison to OLZ
Martin et al. 2019 [110]	12-week phase II RCT	5–20/0 mg 5–20/5 mg 5–20/10 mg 5–20/20 mg	347	Weight gain	37% lower weight gain with OLZ/SAM compared to OLZ/placebo
Silverman et al. 2018 [109]	3-week phase I RCT	10/5 mg	106	Weight gain in healthy volunteers	Weight gain for OLZ/SAM was less as compared to OLZ ($P = 0.02$)
Kahn et al. 2021 [113]	52-week open-label extension study ENLIGHTEN-2 EXT	10/10 mg 15/10 mg 20/10 mg	265	Long-term safety and tolerability	Weight, waist circumference, metabolic parameters, and PANSS/CGI-S remained stable on OLZ/SAM
Yagoda et al. 2020 [114]	52-week open-label extension study of ENLIGHTEN-1	10/10 mg 15/10 mg 20/10 mg	281	Long-term safety and durability	Weight gain and somnolence were most common A/E Mean weight gain was 1.86 kg
Sun et al. 2019 [106]	Phase I open-label crossover study	10/10 mg	36	Effect of food on PK	No effect of food on PK of OLZ/SAM
Sun et al. 2019 [105]	Phase I open-label	10/10 mg	48	Bioequivalence of OLZ/SAM compared to OLZ	OLZ/SAM doesn't affect PK and bioavailability of OLZ
Sun et al. 2019 [107]	6-week phase I open-label	5/10 mg	41	Effect of hepatic and renal impairment on PK	Generally, well-tolerated in hepatic and renal impairment
Sun et al. 2018 [104]	2-week, phase I randomized open-label study	10/10 mg 20/10 mg	42	Plasma concentration PK Safety	Steady-state for OLZ took 3–4 days and SAM took 5 days Different levels of OLZ had no impact on pharmacokinetic profile of SAM. SAM was well-tolerated

PANSS, Positive and Negative Syndrome Scale; *CGI-S*, Clinical Global Impression-Severity; *ECG*, electrocardiogram; *PK*. pharmacokinetics; *A/E.* adverse effects

Table 7 The characteristics of studies on transdermal asenapine

Transdermal asenapine					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Suzuki et al. 2021 [119]	Three phase I open-label studies	I.1.9 mg/24 h II.3.8 mg/24 h III 1.9 mg/24 h 3.8 mg/24 h 5.7 mg/24 h 7.6 mg/24 h	I. 18 II.40 III.24	I. Pharmacokinetics (PK) II. Bioavailability with different patch sites, potential ethnic differences III.PK with multiple doses	1. Asenapine concentration increased gradually over 12 h, and steady-state was reached within 72 h 2. PK was dose proportional, not affected by ethnicity or administration site 3. Similar AUC with lower troughs and peak in comparison to sublingual asenapine
Citrome et al. 2020 [122]	6-week phase 3 RCT	3.8 mg/24 h 7.6 mg/24 h	607	PANSS CGI-S TEAE	LSMD for PANSS were −4.8 for 7.6 mg (P = 0.003) and −6.6 for 3.8 mg ($p < 0.001$) Systemic safety profile similar to sublingual asenapine

PANSS, Positive and Negative Syndrome Scale; *CGI-S*, Clinical Global Impression-Severity; TEAE, Treatment-Emergent Side Effects

which recruited patients with response ($n = 93$; CGI-S ≤ 3 and reduction of PANSS ≥ 20%) in a previous RCT [13]. Patients received flexible dose cariprazine (1.5–4.5 mg) for 48 weeks. Approximately half completed the study and 70% of them were on 4.5 mg by the end of study. Most common AEs were akathisia (14%), insomnia (14%), and weight gain (12%). The mean weight gained was 1.9 kg at the end of the study, but a large fraction gained ≥ 7% of their body weight ($n = 31$, 33.3%). A smaller fraction ($n = 7$, 7.5%) had weight decrease of ≥ 7%. Weight increase was most likely to occur in patients who started the study in the normal or underweight category [22].

A second open-label study [23] evaluated cariprazine 3–9 mg for long-term safety and tolerability in schizophrenia for 1 year. A total of 586 patients were recruited, out of which 235 were new and 351 were recruited from two phase III studies [11, 14]. Less than 39% of patients completed the year of the study, and the frequency of dosing prescribed was 6 mg (50.9%), 9 mg (25.3%), and 3 mg (22.9%). Most common AEs (> 10%) were akathisia, headache, insomnia, and weight gain. Discontinuation rate due to AEs was 12.5% and 10.1% experienced serious AEs. There was a 1.5 kg increase in the mean body weight, and ≥ 7% increase in body weight occurred in about 26% patients, whereas cardio-metabolic AEs were minimal.

Nasrallah et al. [24] pooled data from both open-label 48-week studies [22, 23] to report long-term safety and tolerability. Less than half of the patients (40.1%) completed the study. The most common AEs causing discontinuation were akathisia and worsening of psychosis/schizophrenia. AEs reported in > 10% patients were akathisia, insomnia, weight gain, and headache. The mean cholesterol and prolactin levels decreased versus baseline. The mean body weight gain was 1.58 kg, and ≥ 7% weight gain occurred in 27% of patients [24].

Efficacy of Cariprazine in Manic and Mixed Episodes

There have been 3 short-term (3-week) phase II/III RCT [25–27] (Table 3) which have evaluated cariprazine at 3–12 mg for acute manic or mixed episodes in BD type I (BD-I). Two studies [25, 27] had flexible cariprazine dosage of 3–12 mg/day, while a third study [26] used two arms of cariprazine dosage ranges of 3–6 mg and 6–12 mg. All three studies used the Young Mania Rating Scale (YMRS) as their primary outcome and CGI-S as their secondary outcome for analysis. The mean baseline YMRS scores in all three studies ranged from 30 to 33.

One study was phase II [25] and included a total of 235 patients: 118 on cariprazine flexible dosing of 3–12 mg/day. There was a significant reduction in YMRS from baseline at the endpoint with a least squared mean difference (LSMD) of −6.1 ($P < 0.0001$) compared to placebo. Significantly higher percentage of patients on cariprazine achieved response ($P < 0.0001$) and remission ($P < 0.002$) on YMRS in comparison to placebo.

Sachs et al. conducted a phase III study on 310 participants [25]: 158 randomized to cariprazine flexible dose of 3–12 mg/day [25]. YMRS scores were statistically different at the end of study with LSMD of −4.3 for cariprazine

Table 8 The characteristics of studies on subcutaneous risperidone

Subcutaneous risperidone					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Ivaturi et al. 2017 [132]	8-week phase III RCT	90 mg 120 mg	354	Efficacy, safety, and tolerability PANSS CGI-S	CYP2D6 poor/intermediate metabolizers and lower rates of active moiety
Nasser et al. 2016 [131]	8-week phase III RCT	90 mg 120 mg	354	PANSS CGI-S	Significant improvement in PANSS and CGI-S Most common A/E were somnolence, weight gain, and akathisia
Isitt et al. 2016 [133]	8-week phase III RCT	90 mg 120 mg	354	HRQoL-EuroQol SWN-S MSQ POM	120 mg showed statistically significant improvement in health status (EQ-5D-5L VAS), SWN-S, MSQ, and POM in comparison to placebo
Andorn et al. 2019 [134]	52-week, phase III open-label study	367	500	PANSS CGI-S A/E	PANSS and CGI remained stable over 12 months 73.4% reported ≥1 A/E
Dhanda et al. 2019 [135]	52-week phase III single-arm open-label	120 mg	482	HRQoL-EuroQol SWN-S MSQ POM	HRQoL and SWN-S remained stable. Increase in medicine satisfaction and preference of medicine seen at the end of study
Dammerman et al. 2018 [192]	1. 3-month open-label fixed-dose phase I for RI 2. 6-month open-label dose ranging phase I for RI	375 mg 480 mg 720 mg 960 mg	23	PK PANSS CGI-S CGI-I	In both studies, RI reached therapeutic concentration in 2 days and remained relatively stable. Patients maintained their stable status and no major side effect noticed
Laffont et al. 2014 [129]	Phase IIA, open-label, multiple ascending dose	60 mg 90 mg 120 mg	45	PK	Steady-state plasma concentration reached after second or third injection BMI was a significant factor affecting absorption
Gomeni et al. 2013 [128]	1. Phase I/IIA open-label	60 mg 90 mg 120 mg	90	PK	Initial peak followed by delayed delivery BMI affected absorption Prolactin concentration described by Emax model

PANSS, Positive and Negative Syndrome Scale; *BPRS*, Brief Psychiatric Rating Scale; *CDSS*, Calgary Depression Scale for Schizophrenia; *CGI-S*, Clinical Global Impression-Severity; *CGI-I*, Clinical Global Improvement; *EPS*, extrapyramidal side effects; *A/E*, adverse effects; *PK*, Pharmacokinetics; *HRQoL*, health-related quality of life; *SWN-S*. Subjective Wellbeing Under Neuroleptics; *MSQ*, Medication Satisfaction Questionnaire; *POM*. preference of medicine; *BMI*, basal metabolic rate

Table 9 The characteristics of studies on aripiprazole lauroxil

Aripiprazole lauroxil					
Author, year	Study design	Dose	Sample size (*N*)	Outcome measure	Key outcome
Weiden et al. 2020b [151]	A 25-week phase IIIb RCT	AL 1,064 mg q8wk or paliperidone palmitate (PP) 156 mg q4wk	200	PANSS	AL was safe and effective in outpatient continuation treatment
Hard et al. 2019 [146]	A phase I, randomized, open-label study	AL NCD (NanoCrystal Dispersion)	47	PK Safety	Deltoid injection is comparable to gluteal injection for the administration of ALNCD
Hard et al. 2018 [203]	A 6-month, phase I RCT	ALNCD 662 mg AL 441 or 882 mg, 15, or 30 mg oral aripiprazole	161	PK Safety	A 1-day initiation AL regimen (single injection of ALNCD + single oral dose of aripiprazole) = current 21-day initiation regimen
Meltzer et al. 2015 [147]	A 12-week RCT	AL 441 or 882 mg q4wk	623	PANSS, CGI-I	In acute schizophrenia patients, both doses were tolerated and resulted in a rapid, significant improvement in symptoms that were sustained for the study duration
Weiden et al. 2020a [155]	A 44-week, phase I, open-label study	AL 1064 mg q8wk, AL 882 mg q6wk, or AL 441 mg q4wk	104	PK Safety	All 3 AL regimens achieved clinically effective and well-tolerated plasma aripiprazole concentrations and were similarly safe to oral aripiprazole
Miller et al. 2019 [193]	A 6-month open-label study	AL 441, 662, or 882 mg q4wk or 882 mg q6wk	51	All-cause and medication-related discontinuation	Switching from PP to AL was effective, safe, and well-tolerated
Nasrallah et al. 2019 [194]	A 52-week, phase III safety study	AL 441 or 882 mg q4wk	478	Safety A/E	During the 1-year follow-up, AL was safe and well-tolerated
Nasrallah et al. 2017 [152]	A 52-week, open-label extension study	AL 441 or 882 mg q4wk	478	Metabolic parameters	Long-term AL was consistent with oral aripiprazole. Results showed small reduction in prolactin levels and minor changes in metabolic parameters regardless of dose
Risinger et al. 2017 [154]	A 48-week, phase-1, open-label study	AL 441 mg q4wk, AL 882 mg q6wk, or AL 1064 mg q8wk	139	PK, Safety	Concentrations of AL 1064 mg q8wk, like 882 mg q6wk, were above lower doses of AL during the dose interval. Safety was consistent with other therapeutic doses of AL
Hard et al. 2017 [143]	A phase I open-label study	AL 441 mg q4wk, AL 882 mg q6wk, or AL 1064 mg q8wk	140	PK	AL 1064 mg q8wk achieved concentrations within the therapeutic range similar to 441 mg and 882 mg q4wk
Turncliff et al. 2014 [145]	A phase I randomized, open-label, study	AL 221 or 441 mg single dose	46	PK Safety	AL 441 mg deltoid or gluteal injections were safe and well-tolerated. Deltoid injections had more injection site reactions but had slightly higher mean exposure to the drug
McEvoy et al. 2021 [195]	Post hoc analysis	AL 441 mg or 882 mg q4wk	291	HRQoL	Over 124 weeks of follow-up, stable patients with schizophrenia reported continuing improvement in mental HRQoL
Lauriello et al. 2020 [196]	Post hoc analysis	AL 441 or 882 mg q4wk	478	Safety	Long-term safety (follow-up of up to 3.5 years) was consistent. AL continued to be safe and clinically effective

Table 9 (continued)

Aripiprazole lauroxil					
Author, year	Study design	Dose	Sample size (*N*)	Outcome measure	Key outcome
Citrome et al. 2019 [197]	Post hoc analysis	AL 441 or 882 mg q4wk	623	NNT NNH	Pooled doses analysis compared with placebo produced NNT of 6 and NNH of 14. AL is effective and well-tolerated
Correll et al. 2019 [198]	Post hoc analysis	AL 441 or 882 mg q4wk	623	PANSS, PSP	AL resulted in improved social functioning as measured by PANSS Prosocial and PSP scores
Weiden et al. 2019 [199]	Post hoc analysis	AL 882 mg	190	Retention rate	Switching to AL from oral antipsychotics had completion rate in outpatients
McEvoy et al. 2017 [200]	Post hoc analysis	AL 441 or 882 mg q4wk	181	Retention time to discontinuation	Effectiveness of AL continued over the 1-year follow-up period and was associated with low discontinuation rate
Citrome et al. 2018 [201]	Post hoc analysis	AL 441 or 882 mg q4wk	596	PANSS CGI-S	This supportive efficacy analysis shows that 441 and 882 mg q4wk are effective in acute schizophrenia patients
Potkin et al. 2017 [148]	Post hoc analysis	AL 441 or 882 mg q4wk	309	PANSS Responder rates	AL 441 mg and 882 mg were effective (more responders with 882 mg) in a subgroup of acute schizophrenia patients with severe psychosis
Targum et al. 2017 [149]	Post hoc analysis	AL 441 or 882 mg q4wk	622	PANSS	This age stratification analysis showed that AL is effective in all age groups of schizophrenia patients regardless of gender
Nasrallah et al. 2016 [202]	Post hoc analysis	AL 441 or 882 mg q4wk	622	Metabolic parameters	AL was associated with slight increase in weight and a slight decrease in prolactin. No significant change to serum lipid, lipoprotein, plasma glucose, or HbA1c
Citrome et al. 2016 [150]	Post hoc analysis	AL 441 or 882 mg q4wk	623	PANSS Hostility, PANSS excited component, PSP	AL reduces hostility and agitation symptoms in schizophrenia patients

AL, aripiprazole lauroxil; *HRQoL*, health-related quality of life; *PANSS*, Positive and Negative Syndrome Scale; *NNT*, number needed to treat; *NNH*, number needed to harm; *PSP*, Personal and Social Performance; *CGI-S*, Clinical Global Impression-Severity; *CGI-I*. Clinical Global Impression-Improvement; *PK*, pharmacokinetics; *A/E*, adverse effects

Table 10 The characteristics of studies on inhaled loxapine

Inhaled loxapine					
Author, year	Study design	Dose	Sample size (*n*)	Outcome measure	Key outcome
Cassella et al. 2015 [174]	Phase I RCT	10 mg	60	QTc	Two doses of 10 mg inhaled loxapine 2 h apart did not cause threshold QTc prolongation and were well-tolerated
Gross et al. 2014 [176]	4-month phase II RCT	10 mg	105	Spirometry	Inhaled loxapine resulted in more airway A/E and changes in PFT function than placebo. These effects were more common in asthmatics than COPD patients
Spyker et al. 2014 [173]	Phase I RCT	10 mg	48	QTc	Inhaled loxapine did not increase QT intervals
Kwentus et al. 2012 [169]	Phase III RCT	5 mg 10 mg	315	PANSS-EC	Significant reduction in agitation in both doses of inhaled loxapine against placebo
Allen et al. 2011 [167]	Phase II RCT	5 mg 10 mg	129	PANSS-EC	Significant difference in efficacy for treating psychotic agitation against placebo
Lesem et al. 2011 [168]	Phase III RCT	5 mg 10 mg	344	PANSS-EC	Inhaled loxapine provided rapid, well-tolerated acute treatment for agitation in people with schizophrenia
Spyker et al. 2010 [164]	Phase I RCT, dose escalation	0.625–10 mg	50	PK Safety	90% confidence interval dose proportional loxapine AUC across doses with *T*max median at 2 min. A/E were mild. With the most common events being dizziness, somnolence and bad taste
Gil et al. 2018 [172]	6-month phase IV, single-arm, open-label	10 mg	500	SAE AESI CGI-I	10 patients completed with no reported SAE or AESI. 60% reported significant improvement, 10% improved
San et al. 2018 [170]	22-month phase III, randomized open-label	10 mg	359	CGI time to response	Significantly shorter CGI-I response time in inhaled loxapine compared to IM aripiprazole group
Selim et al. 2017 [166]	Open-label phase I multiple dose	2.5 mg, 5 mg, 10 mg	30	PK Safety	Inhaled loxapine showed very rapid absorption with peak concentrations in 2 to 5 min. While 97% experienced A/E, none were serious
Spyker et al. 2015 [175]	Open-label followed by RCT phase IV	Lorazepam 1 mg IM + loxapine 10 mg	22	Pharmacodynamics Safety	No difference of concomitant use of inhaled loxapine with lorazepam in its effect on respiration rate or pulse oximetry than either alone. No respiratory A/E were recorded
Takahashi et al. 2014 [165]	Single-dose open-label	10 mg	35	PK VAS Safety	Loxapine exposure, sedation profiles, and VAS scores were similar for both smokers and nonsmokers

SAE, serious adverse events; *AESI*, adverse events of special interest; *CGI-I*, Clinical Global Impressions-Improvement; *PK*, pharmacokinetics; *PANSS-EC*, Positive and Negative Syndrome Scale–Excited Component; *PFT*, pulmonary function tests; *AUC*, area under the curve

vs. placebo ($P = 0.0004$). Statistically significant difference was noticed with cariprazine vs. placebo on YMRS response (58.9% vs. 44.1%; $P = 0.0097$), remission (51.9% vs. 34.9%; $P = 0.0025$), mean CGI-S score ($P = 0.003$), and total PANSS score ($P = 0.004$) [25].

The third pivotal phase III trial was performed by Calabrese and colleagues [26] and recruited 497 patients, out of which 167 were randomized to cariprazine 3–6 mg, 169 to cariprazine 6–12 mg, and 161 to placebo. Both doses of cariprazine showed statistically significant change in LSMD score at the end of 3 weeks (−6.1 for 3–6 mg, −5.9 for 6–12 mg); even the changes on single items of YMRS were significant. Secondary analysis found significant changes to CGI-S scores for cariprazine compared to placebo (LSMD −0.6 for 3–6 mg; −0.6 for 6–12 mg; $P < 0.001$ for both). In addition, both doses of cariprazine had significant response and remission rates, corresponding to NNT of 5 and 7, respectively [26].

There are 4 post hoc analyses evaluating effects of cariprazine in BD-I [28–31] and one study for both schizophrenia and BD-I [32]. McIntyre et al. pooled data from all three BD-I studies [25–27] to examine response of patients with mixed features, which was operationalized as 3 depressive symptoms (DS) on the Montgomery–Åsberg Depression Rating Scale (MADRS) with a score ≥ 3, or 2 depressive symptoms with a score ≥ 2 and a total MADRS score ≥ 10 [29]. Cariprazine significantly improved mean YMRS scores in comparison to placebo. The depressive symptom scores also improved. Cariprazine was significantly better than placebo on response in ≥ 2 DS (47% vs. 37%, $P = 0.05$), MADRS ≥ 10 (57% vs. 31%, $P < 0.0001$), and for remission in ≥ 2 DS (39% vs. 27%, $P = 0.05$), and MADRS ≥ 10 (44% vs. 23%, $P < 0.0001$) [29].

Vieta et al. [28] pooled data from the same above 3 studies to study the effects of cariprazine across symptoms of mania. Mean change on YMRS scale using mixed-effect model repeated measure (MMRM) showed significant improvement for cariprazine in all 11 YMRS items in comparison to placebo ($P < 0.0001$) and 4 YMRS "core" symptoms (irritability, speech, content, and disruptive–aggressive behavior) ($P < 0.0001$). Also significant for cariprazine was the number of patients with moderate or worse symptoms shifting to mild or no symptoms on all 11 YMRS items ($P < 0.0001$) [28].

Early and colleagues pooled data for the same three BD-I RCTs and found that rates for remission (YMRS ≤ 12 or ≤ 8) and response (≥ 50% decrease in score) were significantly greater for cariprazine groups on all measures ($P < 0.01$). Estimated NNT for each measure was ≤ 10 [31].

Safety and Tolerability of Cariprazine in Bipolar Mania

A phase III open-label study assessed safety and tolerability of cariprazine flexible dose of 3–12 mg/day over 16 weeks [33]. A total of 33% completed the trial with adverse events (A/E) seen in 16%, and the most common A/E were akathisia (4.7%) and depression (1.5%). Early et al. examined tolerability of cariprazine in data pooled from all three pivotal acute mania studies [30]. AEs noted in cariprazine group occurring in > 5% of patients receiving cariprazine were akathisia, Parkinsonism, restlessness, and vomiting. Fasting blood glucose increased similarly with lower and higher doses of cariprazine (3–6 mg = 6.6 mg/dL; 9–12 mg = 7.2 mg/dL) at a level greater than with placebo (1.7 mg/dL) [30].

Summary of Cariprazine Data

Cariprazine is a partial agonist at D2 and D3 with low intrinsic activity (24–30% of dopamine) [8]. It has demonstrated efficacy in bipolar mania and for psychosis in schizophrenia. There is a possible concern of akathisia in comparison to placebo. It has a wide dose range, but there is confusion regarding effective doses since many of the studies end right around the time that all active moieties are reaching steady-state. Similarly, in the schizophrenia studies, there is an impression that higher doses are more effective because they appear to be effective earlier. However, it is likely that this impression is erroneous since the efficacy of lower dose arms nearly always matches higher doses at the end of the studies.

Brexpiprazole

Brexpiprazole was approved by the US FDA in 2015 for the treatment of schizophrenia and as an adjunct for the treatment of unipolar depression [34]. It is a partial agonist with high affinity at dopamine D2 ($K_i = 0.30$ nM/L), and 5-HT_{1A} (0.12 nM/L), and an antagonist at 5-HT_{2A} (0.47 nM/L) receptors [35, 36]. The intrinsic activity at D2 is lower than aripiprazole which gives it a slightly different clinical profile [37].

The recommended dose for brexpiprazole in schizophrenia is 2 to 4 mg/day. It has a 95% oral bioavailability and reaches steady-state concentrations within 10 to 12 days. Brexpiprazole is primarily metabolized in the liver by the CYP3A4 and CYP2D6 isoenzymes with no active major metabolites [38].

Efficacy of Brexpiprazole in Schizophrenia

Brexpiprazole's efficacy in the treatment of acute schizophrenia was demonstrated by two 6-week, phase III, randomized, placebo-controlled trials [39, 40]. Kane et al. (2015) randomized 674 adults suffering from an exacerbation of psychotic symptoms into four groups 1, 2, or 4 mg

brexpiprazole or placebo (2:3:3:3). Results showed that only brexpiprazole 4 mg led to a statistically significant change in the primary efficacy endpoint which was a change in total PANSS from baseline to the end of week 6 (−6.47; $P=0.0022$), as well as improvements in CGI-S scores (−0.38; $P=0.0015$) [39].

In a similar study design, Correll et al. randomized 636 patients into 0.25, 2, or 4 mg/day brexpiprazole or placebo (1:2:2:2), with the same primary endpoint for efficacy assessment [40]. Both 2 and 4 mg brexpiprazole successfully separated from the placebo group, showing equivalent statistically significant improvements in total PANSS score of (−8.72; $P=0.0001$ for 4 mg and −7.64; $P=0.0006$ for 2 mg) [40].

Several subsequent studies and post hoc analyses confirmed the efficacy of brexpiprazole in schizophrenia, both acutely and in the long-term [41–46]. A 16-week phase III, open-label study found brexpiprazole to be effective in improving psychotic symptoms and social functioning in patients with early-episode schizophrenia [47]. Early intervention for patients following the first episode of psychosis is paramount and is evidenced to provide patients with more favorable outcomes regarding the neurobiological and social functioning aspects of the illness [48].

One antipsychotic-switching study reported statistically significant improvements in Parkinsonism, prolactin levels, and metabolic parameters when patients were switched to brexpiprazole [49]. A post hoc analysis found that cross-titration in most patients (72%) to switch safely and effectively from primary antipsychotic treatment to brexpiprazole takes between 22 and 33 days [50].

Brexpiprazole was also found to reduce agitation and hostility as assessed by (PANSS) Excited Component (EC), and PANSS hostility item (P7), respectively [51]. Moreover, a functional magnetic resonance imaging (fMRI) study reported that brexpiprazole (4 mg) treatment is associated with decreased blood oxygen-level dependent (BOLD) activation of the right ventrolateral prefrontal cortex (VLPFC) during the stop-signal task ($P=0.0053$) suggesting improved inhibition and impulsivity control [52].

One relapse prevention study found that time to impending relapse (exacerbation of psychosis) was longer in the brexpiprazole group compared to placebo ($P<0.0001$). Interestingly, 38.5% of patients on placebo met the criteria for impending relapse versus only 13.5% of patients on brexpiprazole [53].

Brexpiprazole in Manic Episodes of Bipolar Disorder

Antipsychotics have demonstrated their efficacy in the management of acute mania in BD-I. Recent guidelines recommend antipsychotics as first-line monotherapy treatments [54]. Two 3-week, RCTs (study 080 N = 322, study 081 $n=333$) were conducted across multiple sites in the USA and Europe to investigate the efficacy of brexpiprazole (2–4 mg/day) in patients with an acute manic episode with or without mixed features. The primary endpoint to measure efficacy in both studies was the mean change in YMRS total score from baseline to end of week 3. Results did not show a statistically significant difference in YMRS total score change between the brexpiprazole treatment group and the placebo group [55].

Similar negative findings were reported in a previous similar study for aripiprazole and were attributed to a high placebo response rate that with subsequent analyses were found to be influenced by symptom severity at baseline and the geographical region of the study population [56]. On a similar note, a post hoc analysis of studies 080 and 081 found that baseline level of insight was a statistically significant modifier for the mean change in YMRS score ($P=0.0013$). Patients with impaired or no insight (95.1% of European patients versus 36.8% of US patients) reported better clinical improvement to their manic symptoms with brexpiprazole treatment than those with excellent insight [55].

A 26-week open-label, extension trial (study 083 $n=381$) assessing the safety and tolerability of long-term brexpiprazole treatment found gradual numeric improvement in YMRS and Clinical Global Impression-bipolar version (CGI-BP) severity of illness scores at the end of the treatment duration.

Safety and Tolerability of Brexpiprazole

Both pivotal efficacy trials, mentioned before, had a high completion rate and reported brexpiprazole to be safe and well-tolerated with incidence rates of treatment-emergent AEs and discontinuation due to AEs higher in the placebo group than brexpiprazole-treated groups [39, 40]. Three long-term (52-week) studies were conducted to investigate the safety of brexpiprazole as a maintenance treatment [43, 53, 57]. The most common AEs were insomnia, headaches, nasopharyngitis, akathisia, and weight gain [38].

A 6-week phase III, open-label study comparing brexpiprazole (1–4 mg/day) to aripiprazole (10, 15, 20 mg/day) reported that the incidence of akathisia was lower with brexpiprazole (9.4%) than with aripiprazole (21.2%) [58].

Metabolic AEs are a major concern for atypical antipsychotics. A pooled post hoc analysis found that the mean increase in weight from baseline was 1.2 ± SD 3.4 kg for brexpiprazole-treated patients compared to 0.2 ± 2.7 kg with placebo in the short-term study population[59]. While in the long-term study, the mean increase with brexpiprazole from baseline was 2.0 ± 5.9 kg at week 26 and 3.2 ± 7.6 kg at week 58 [59]. Comparing brexpiprazole to other antipsychotics, a study reported that both brexpiprazole and aripiprazole have

similar effects on weight gain with the mean weight increase being 2.1 and 3.0 kg, respectively (Weiss et al., 2018). In a meta-analysis, lurasidone resulted in less weight gain than brexpiprazole as well as better outcomes for other metabolic parameters such as total cholesterol and low-density lipoprotein cholesterol (LDL) levels [60].

Another common AE of antipsychotics is hyperprolactinemia due to dopamine blockade. Brexpiprazole appears to cause minimal changes to prolactin levels, with the incidence of prolactin-related AEs around 1.8% as reported in a pooled post hoc analysis [61]. In addition, a recent network meta-analysis also found no significant increase in prolactin levels in brexpiprazole-treated patients ($n = 1070$) with acute schizophrenia when compared with placebo (mean difference = 0.95, credible interval [CrI] = −3.64 to 5.62) [62].

Summary of Brexpiprazole

Brexpiprazole is like aripiprazole in its mechanism of action with partial agonism at D2 and $5HT_{1A}$ receptors and antagonism at $5HT_{2A}$ receptor. However, it has less D2 receptor intrinsic activity and equally potent action at $5HT_{1A}$, $5HT_{2A}$, and α_{1B} receptors causing lesser AE and EPS. It has shown efficacy in acute schizophrenia but not acute mania. It has lesser weight gain and minimal hyperprolactinemia in comparison to aripiprazole.

Lumateperone

Lumateperone (ITI-007) was approved by the FDA in December 2019 for the treatment of schizophrenia in adults [63]. It has several unique features among antipsychotic medications. It is a *postsynaptic D2 full antagonist* that achieves maximal antipsychotic effect at only 39% receptor occupancy [64], but it acts as a *partial agonist at the presynaptic D2 receptor* [65]. The presynaptic D2 receptor is coded for by the same gene as the postsynaptic D2 and is missing 29 amino acids from the third cytoplasmic loop; for this reason, the presynaptic D2 is known as the short form, and the postsynaptic receptor is the long form [66, 67]. The different structure usually results in diverging affinities of the two receptor forms with most antipsychotic drugs, but lumateperone is the only known agent that has a different function at the two receptors. Additionally, lumateperone is a serotonin transporter (SERT) inhibitor with antagonist activity at serotonin 5-HT_{2A} receptors with affinity that is 60-fold higher than D2. It is also a D1 receptor agonist and will indirectly increase phosphorylation of the glutamatergic N-methyl-d-aspartate (NMDA) GluN2B receptor [68, 69]. Lumateperone appears to have a therapeutic window so that 84 mg daily was not effective [70] and 28 mg daily was not effective [71]. Its recommended dosage is 42 mg orally with food, but the effect of food is minimal — a high-fat meal increases the total amount of drug absorbed by only 9%, but it slows absorption so that T_{max} is delayed from 1 h, at fasted state, to 2 h with food, and the maximal concentration (C_{max}) is reduced by 33%. It reaches a steady-state within 5 days [63]. The terminal half-life is approximately 18 h, and it is mainly excreted in urine (58%) and feces (29%) [63].

Efficacy of Lumateperone in Acute Schizophrenia

Two phase II/III RCT studies and one open-label study have been published and are included (Table 4). A third study was not published but is discussed briefly.

A phase III trial recruited 450 patients aged 18–60 years. They were randomized to lumateperone 42 mg, 28 mg, or placebo, once daily for 4 weeks. The LSMD compared to placebo for reduction in total PANSS score at 28 day was −4.2 (95% CI, −7.8 to −0.6; effect size = −0.3; multiplicity-adjusted $P = 00.04$). The LSMD for lumateperone 28 mg vs. placebo was −2.6 (95% CI, −6.2 to 1.1; effect size −0.2; multiplicity-adjusted $P = 0.18$) [71]. For the 42 mg dose, there were significant improvements in the PANSS subscales for positive symptoms, general psychopathology, and psychosocial functions but not for negative symptoms. A second phase III trial that was only published in abstract format randomized 696 patients to lumateperone 14 mg or 42 mg, risperidone 4 mg, and placebo. There was a large placebo response effect as frequently happens with an RCT that has an active comparator and multiple arms [72], and neither lumateperone arm separated from placebo [73].

The other published study was a phase II multicenter RCT that recruited patients aged 18–55 years with acute exacerbation of schizophrenic psychosis for 4 weeks. Eighty-four patients were randomized to lumateperone 42 and 84 mg each, 82 to risperidone, and 85 to placebo. At day 28, least squared mean change from baseline in total PANSS score was −13.2 (lumateperone 42 mg), −8.3 (lumateperone 84 mg), −13.4 (risperidone), and −7.4 in placebo. Both lumateperone 42 mg ($P = 0.017$) and risperidone 4 mg ($P = 0.013$) were significantly better than placebo, but lumateperone 84 mg was indistinguishable from placebo. Only the positive symptoms and general psychopathology PANSS subscales improved significantly with lumateperone 42 mg and risperidone, whereas none of the treatments showed improvement in negative symptoms [70].

The two positive studies were combined in a pooled analysis which found that the combined LSMD versus placebo was −4.76 ($P < 0.001$), which was similar to risperidone 4 mg (LSMD = −4.97; $P = 0.014$). Only two PANSS subscales improved versus placebo, the positive subscale (LSMD = −1.71, $P < 0.001$) and the general psychopathology subscale (LSMD = −2.04, $P = 0.009$) [74].

Safety and Tolerability of Lumateperone in Schizophrenia

A pooled analysis of the 1,073 patients recruited in all three RCTs examined AEs. Only somnolence (24.1%) and dry mouth (5.9%) occurred in lumateperone-treated patients at a rate that exceeds 5% and occurs twice the rate of placebo. Discontinuation due to AEs, a measure of their severity, occurred in 0.5% of participants, a rate identical to placebo (0.5%) and much lower than the 4.7% seen with risperidone [75].

In an open-label switch study on safety and tolerability of lumateperone 42 mg, 301 patients with stable schizophrenia were switched from current antipsychotic to lumateperone 42 mg once daily for 6 weeks and then switched back to previous or another antipsychotic for 2 weeks. PANSS scores remained stable on lumateperone in comparison to baseline scores on another antipsychotic. A total of 71.2% completed the study, among which 45.5% had some AE. AEs exceeding 5% were somnolence (6.6%), headache (5.3%), and dry mouth (5.3%). Significant decrease in total cholesterol, low-density lipoprotein, body weight, and prolactin were noted on lumateperone. Parkinsonism was rare (1%) [76]. The reduction in these parameters was seen when patients were switched to lumateperone from risperidone (28.6%), quetiapine (19.9%), aripiprazole (14.0%), and olanzapine (12.3%) [76].

Summary of Lumateperone Data

Lumateperone is a unique antipsychotic with < 50% receptor occupancy that appears to have similar efficacy to risperidone in reducing psychosis in acute schizophrenia but with dramatically fewer AEs. The drug has a therapeutic window, and doses higher or lower than the recommended 42 mg per day are ineffective.

Pimavanserin

Pimavanserin is a novel antipsychotic medication that has very high affinity to the 5-HT_{2A} receptor ($K_i = 0.087$ nM) and significant affinity at the 5-HT_{2C} receptor ($K_i = 0.44$ nM) where it functions as an inverse agonist [77, 78]. An inverse agonist reduces a receptor's activity to below what an antagonist can achieve because it removes any constituent, or spontaneous, activity of that receptor [79]. Pimavanserin does not demonstrate clinically significant affinity to dopaminergic, histaminergic, muscarinic, or adrenergic receptors, which makes it appropriate for use in Parkinson's disease psychosis (PDP) [77]. In 2016, pimavanserin received FDA approval for the treatment of hallucinations and delusions associated with PDP [80]; also, there is emerging evidence for its use in the treatment of dementia-related psychosis.

Pimavanserin is slowly absorbed after an oral dose, reaching C_{max} after about 6 h (T_{max}) without a significant effect of food [81], but with a reduction of C_{max} by about 9%, and an increase in bioavailability as measured by the total absorbed drug (area under the curve) of 8% [82]. It is over 90% protein bound (91.2–96.8%). It has a half-life of 53–58 h but has an active demethylated metabolite with a half-life of approximately 200 h [82]. It is predominantly metabolized by CYP 3A4 and CYP 3A5. The recommended dose is 34 mg once daily, but maximal 5-HT_{2A} receptor occupancy is achieved by 20 mg of pimavanserin tartrate (equivalent to 17 mg of pimavanserin) without any increase with increasing doses [83].

It is important to note that many of the original studies were performed with dosing based on the weight of pimavanserin tartrate, but the final clinical dosing is based on the weight of pimavanserin. Ten mg of pimavanserin tartrate is equivalent to 8.5 mg of pimavanserin (or 40 mg of pimavanserin tartrate is equivalent to 34 mg of pimavanserin).

Efficacy of Pimavanserin in PDP

The initial exploration of efficacy was done with a phase II study that randomized only 60 patients to pimavanserin or placebo for 4 weeks [84]. Hallucinations and delusions as measured by the Scale for the Assessment of Positive Symptoms (SAPS) global ratings improved significantly ($P = 0.02$) with a large effect size (0.66). However, total SAPS did not reach statistical significance because of the small sample size ($P = 0.09$) [84].

The pivotal phase III trial [85] randomized 199, 40 years or older PDP patients into a 6-week double-blind, placebo-controlled study. Patients were started on 40 mg per day pimavanserin or placebo. Primary outcome utilized a modified SAPS for Parkinson's disease (SAPS-PD). At study end, psychosis improvement on the SAPS-PD was 37% versus 14% with placebo ($P = 0.006$). Additionally, there were benefits in the SAPS-H + D scales and on the separate hallucinations and delusions domain. Furthermore, more patients in the treatment group had a greater than 20% reduction in SAPS-PD scores. Improvements were also displayed in CGI-S and CGI-Improvement (CGI-I). Ten patients in the treatment group did not finish the study compared with four in the placebo group, 6 citing psychosis [85]. At least 2 additional phase III studies have not been published.

One post hoc analysis of the above study [85] assessed the efficacy of pimavanserin when patients were stratified by baseline cognition and use of cognitive-enhancing medications [86]. Patients were stratified as cognitively impaired (21–24) MMSE vs. unimpaired (MMSE ≥ 25). In cognitively impaired (− 6.62 versus placebo − 0.91, $P = 0.002$), cognitively unimpaired (− 5.50 versus placebo − 3.23, $P = 0.046$), those receiving cognitively protective medications (− 6.04

versus placebo − 2.18, P = 0.012), and not (− 5.66 versus placebo − 3.15, $P = 0.041$) benefited from pimavanserin [86]. However, the conclusion in the paper that pimavanserin has an effect on cognition and may be enhanced with concomitant cognitive protecting medications is not supported by the data presented. Further studies are needed.

Two open-label extension studies are published. One of these [87] described 171 patients who had previously been in a 6-week blinded, placebo-controlled study. However, these very same patients are included in a larger analysis that included patients from three 6-week, blinded, placebo-controlled studies (NCT01174004, NCT00658567, and NCT00477672) of which only one has been published (NCT01174004) by Cummings et al. [85]. Only the other larger analysis is included in this review [88]. This analysis assessed 459 patients who had previously completed one of three 6-week, similar design RCTs. SAPS-PD change from the baseline of the open-label extension to its end in 4 weeks, with pimavanserin 34 mg, was − 1.8 ± SD 5.5. Patients receiving placebo during the Core studies had greater improvements (SAPS-PD − 2.9 ± SD 5.6) during the open-label extension. For participants treated with pimavanserin 8.5 or 17 mg during the Core studies, further improvement was observed during the extension with pimavanserin 34 mg. The final mean change from the Core study baseline for SAPS-PD score was similar among prior pimavanserin 34 mg and prior placebo-treated participants (− 7.1 vs. − 7.0).

Safety and Tolerability of Pimavanserin in PDP

An open-label extension study was carried over 11 years on 459 patients with a median follow-up of 454 days of treatment [89]. The average age of the participants was 71.2 years. Eighty-five percent of patients had at least 1 AE, majority being mild to moderate with falls, urinary tract infections (UTIs), and hallucinations being the most commonly found. Serious AE occurred in 41% of patients, and discontinuation occurred in 29%; 12.9% of patients died [89]. Considering the nature of the patients treated, mortality rates suggested no increased risk following long-term treatment with a favorable benefit/risk profile.

In the one published phase III study, AEs occurring at ≥ 5% of patients were seen in 11% of the treatment group and 4% of the placebo group [85]. Discontinuation due to AE occurred in ten patients on pimavanserin compared to four patients on placebo, and psychosis was the major reason. Overall, pimavanserin was well-tolerated with no significant safety concerns or worsening of motor functions. In the major analysis of the 4-week open-label extensions, AEs were reported by 215 (46.8%) patients. The most common AEs were fall (5.9%), hallucination (3.7%), UTIs (2.8%), insomnia (2.4%), and peripheral edema (2.2%) [88].

Efficacy of Pimavanserin in Schizophrenia

In another study, 423 non-first episode patients with schizophrenia and a recent exacerbation of psychotic symptoms were randomized into a 6-week trial that aims at testing the effectiveness and safety of combining pimavanserin with suboptimal doses of risperidone and haloperidol [90]. Patients received either risperidone 6 mg plus placebo (RIS6PBO) risperidone 2 mg plus placebo (RIS2PBO), risperidone 2 mg plus 20 mg pimavanserin (RIS2PIM), haloperidol 2 mg plus pimavanserin 20 mg (HAL2PIM), or haloperidol 2 mg plus placebo (HAL2PBO). Primary outcome would use changes in PANSS assessment. Statistically significant change in PANSS total score between the RIS2PBO and the RIS2PIM groups was reported ($P < 0.0001$), achieving a mean of 23-point (27.4%) mean reduction in the RIS2PIM group compared to 16.3 (18.6%) in RIS2PBO. Discontinuation in the RIS2PBO group was also significantly higher citing lack of efficacy (50% vs. 17.9% $P = 0.05$). Decrease in PANSS total score from baseline in the RIS6PBO, HAL-2PIM, and HAL2PIM showed no significant change from the RIS2PIM group. AEs were similar among all treatment groups, most frequently reported being headache, sedation, nausea, and agitation. The study, therefore, concludes that using pimavanserin in combination with risperidone 2 mg would have efficacy comparable to RIS6PBO at 6 weeks with higher efficacy on day 15. Unfortunately, the lack of a pimavanserin-only group limits the conclusions.

Efficacy and safety of Pimavanserin in Alzheimer's Disease

Several second-generation antipsychotics have been studied in dementia-related psychosis [91]. Unfortunately, the significantly increased risk for death when elders with dementia and psychosis when exposed to a second-generation agent [92] or a first-generation agent [93] resulted in the US FDA creating a class-wide warning for all antipsychotic use in elders with dementia and psychosis [94]. The FDA acknowledged that pimavanserin is different from other antipsychotic agents but felt that the risk remained significant [95] and included pimavanserin in the class-wide warning [96]. Nonetheless, the fact that pimavanserin's target population is frequently older has suggested that it may be reasonable to consider in dementia-related psychosis. The US FDA granted pimavanserin breakthrough therapy designation for dementia-related psychosis in 2017 [97].

A phase II study randomized 178 patients to pimavanserin 34 mg or placebo for 6 and 12 weeks [98]. Psychosis was measured using the Neuropsychiatric Inventory Nursing Home version (NPI-NH) psychosis score. At week 6, the mean change in the NPI-NH psychosis score was − 3·76 ± SE 0.65 for pimavanserin and − 1·93 ± 0·63 for placebo (mean difference − 1·84, 95% CI − 3·64, − 0·04, $P = 0.045$), but the effect was lost by 12 weeks [98].

A secondary report on this study examined whether there was a greater reduction in agitation and aggression (NPI-NH domain C (agitation/aggression) and Cohen-Mansfield Agitation Inventory-Short Form [CMAI-SF]) in patients who responded to pimavanserin [99]. It found that those who had > 50% response in psychotic symptoms showed a significant improvement in agitation on both scales: NPI-NH domain C (week 6, LSMD = −3.64, $t = -4.69$, $P < 0.0001$) and the CMAI-SF (week 6, LSMD = −3.71, t = −2.01, $P = 0.048$) [99].

Summary of Pimavanserin

Pimavanserin is a unique antipsychotic that functions mainly as an inverse agonist of $5HT_{2a}$ receptor while also exhibiting significant affinity at the $5HT_{2c}$ receptor. It is the only antipsychotic without any anti-dopamine effect, allowing it to be utilized for the treatment of PDP. It appears to be moderately effective without significant AEs and without worsening of Parkinson's disease. However, 2 of the 3 major phase III studies have not yet been published despite approval some 8 years ago. While the FDA included pimavanserin in the class-wide warning for the use of antipsychotics in dementia-related psychosis, it also acknowledged that pimavanserin is different and has granted it breakthrough designation for dementia-related psychosis. Ongoing studies on the utility of pimavanserin use in dementia-related psychosis look promising.

Olanzapine and Samidorphan Combination (OLZ/SAM)

Among the antipsychotic medications, olanzapine appears to be associated with a higher likelihood of weight gain and undesirable metabolic abnormalities [100, 101]. This has resulted in recommendations that olanzapine be a second-line agent despite its documented efficacy in the treatment of psychosis [101]. Samidorphan is an opioid antagonist which has been combined with olanzapine to combat olanzapine-induced weight gain. It is a μ-opioid receptor antagonist and partial agonist with low intrinsic activity at k- and ∂-opioid receptors [102]. Opioid antagonists can cause weight loss, opening the way to use samidorphan as a tool to mitigate weight gain and obesity [103]. The combination of OLZ/SAM recently got FDA approval in June 2021 for acute and maintenance treatment of schizophrenia and BD-I. This combination (OLZ/SAM) is intended to have antipsychotic effect of olanzapine while mitigating associated weight gain due to olanzapine.

The included studies are summarized in Table 6. When OLZ/SAM are coadministered, steady-state for olanzapine is reached in 3–4 days, but samidorphan took 5 days [104]. Coadministration of the two agents causes a slight increase in olanzapine levels compared to olanzapine alone, but there was no impact on samidorphan pharmacokinetics [104, 105]. Similarly, there was no impact of food regarding the pharmacokinetics of the combination agent [106]. In healthy subjects, OLZ/SAM had no impact on the liver or kidney, but in subjects with renal impairment, there was 33% (OLZ) and 56% (SAM) reduction in clearance as compared to healthy controls [107]. In hepatic impairment, plasma concentration time curve for OLZ had a 1.67-fold increase in AUC, and SAM had a 1.52-fold increase in AUC compared to healthy subjects [107]. To examine the effect of OLZ/SAM on the electrocardiogram (ECG), doses were escalated from 10/10, 20/20 to 30/30 mg over 2 weeks. No clinically significant derangements in ECG parameters, including QT_c interval, were observed up to olanzapine plasma level of 110 ng/ml and samidorphan level of 160 ng/ml [108].

Efficacy of OLZ/SAM in Prevention of Weight Gain

A proof-of-concept phase I RCT was performed by Silverman et al.[109]. The study randomized 106 healthy male volunteers to olanzapine alone, OLZ/SAM, samidorphan alone, and placebo in a 2:2:1:1 ratio [109]. The mean body weight change at 3 weeks was + 2.2 ± SD 1.4 kg for OLZ/SAM and + 3.1 ± 1.9 kg for olanzapine alone ($P = 0.02$). No significant weight gain was noticed in the samidorphan or placebo groups [109].

An early phase II RCT was conducted over 12 weeks. All patients were started on open-label flexible dose olanzapine (5–20 mg) and were randomized to blinded samidorphan at 5 mg ($n = 80$, 10 mg ($n = 86$), 20 mg ($n = 68$), or placebo ($n = 75$) [110]. At study end, the mean percent change in body weight was 37% lower in OLZ/SAM groups compared to OLZ/placebo. The risk of gaining ≥ 10% of baseline body weight was 2.7 times higher in OLZ/placebo group compared to all the combined OLZ/SAM groups ($P = 0.023$). The least square mean percent change in body weight was greater for patients not receiving samidorphan (4.1%, OLZ/placebo) than those receiving any samidorphan dose of the OLZ/SAM combination (2.6% for combined OLZ/SAM, 2.8% for 5 mg, 2.1% for 10 mg, and 2.9% for 20 mg) [110].

The pivotal phase III 4-week RCT (ENLIGHTEN-1) randomized 401 patients to OLZ/SAM, olanzapine alone, or placebo in 1:1:1 ratio [111]. OLZ/SAM combination led to significant improvements in total PANSS (LSMD versus placebo − 6.4 ± SE 1.8; $P < 0.001$) and CGI-S (LSMD versus placebo − 0.38 ± 0.12; $P = 0.002$); this efficacy was similar to olanzapine alone (PANSS LSMD versus placebo − 5.3 ± 1.84; $P = 0.004$; CGI-S LSMD versus placebo − 0.44 ± 0.12, $P < 0.001$).

ENLIGHTEN-2 was a longer term (24-week) that compared weight gain with OLZ/SAM versus olanzapine alone [112]. Among the 538 patients who received at least one dose, the LSMD versus olanzapine alone was − 2.38% ($P = 0.003$). Patients gaining ≥ 10% and ≥ 7% of their baseline weight were twice as likely to be in the olanzapine only arm (29.8% and 42.7%, respectively) than in the OLZ/SAM arm (17.8% and 27.5%; OR = 0.50 for both 10% and 7%).

Safety and Tolerability of OLZ/SAM in the Prevention of Weight Gain

In ENLIGHTEN-1, the 4 weeks of the pivotal trial, AEs occurred in 54.5% in OLZ/SAM, 54.9% in olanzapine only arm, and 44.8% in the placebo arm [111]. In ENLIGHTEN-2, the most common AEs for OLZ/SAM and olanzapine alone were weight gain (24.8% vs. 36.2%), somnolence (21.2% vs. 18.1%), dry mouth (12.8% vs. 8.0%), and increased appetite (10.9% vs. 12.3%, respectively) [112].

Both ENLIGHTEN studies had 52-week open-label safety extensions to assess safety and tolerability. The ENLIGHTEN-2-EXT enrolled 265 patients that completed the 24-week study [113]. Sixty-three percent of the patients completed the 52 weeks and maintained stable PANSS and CGI-S scores. The mean change at 52 weeks from baseline for weight was − 0.03 ± SD 6.17 kg, and waist circumference was − 0.35 ± 6.12 cm. The most common AEs were weight loss (8.7%), headache (6.8%), and weight gain (6%); metabolic parameters remained stable overall [113].

In the ENLIGHTEN 1–EXT, 183 of 281 patients completed the 52 weeks (66%), and almost 50% had some AE, with most common being weight gain and somnolence [114]. The mean weight gained was 1.86 kg, which stabilized by week 6 with minimal changes after that. Twenty-eight percent of patients experienced an increase of one body mass index (BMI) point (i.e., gained ≥ 7% of their baseline weight), but 12% lost one BMI point (i.e., losing ≥ 7% of baseline weight) [114]. There were no changes in other metabolic parameters, total PANSS, or CGI-S [114].

Summary of OLZ/SAM

OLZ/SAM combination intends to maintain the antipsychotic effect of olanzapine and mitigate its associated weight gain by the addition of opioid antagonist.

Transdermal Asenapine

Asenapine is a tertiary amine that belongs to dibenzo-oxepino pyrrole group [115]. It is rapidly metabolized in the liver by direct glucuronidation (via UGT1A4) and oxidation (predominantly CYP1A2 and to a lesser degree CYP3A4 and CYP2D6) [116] with 95% liver first-pass metabolism of 95% of oral dose [117]. Initially, a sublingual preparation was developed to bypass hepatic metabolism and has 35% bioavailability [115, 117]. A new transdermal asenapine was approved by the FDA in October 2019 for schizophrenia and is the only transdermal antipsychotic available in the USA [118]. Sublingual asenapine is very rapidly absorbed, but the transdermal approached is much slower (T_{max} ~ 16 h, t1/2 = 30 h) and is associated with steadier, sustained delivery (C_{max} ~ 1.72 ng/mL) [115, 119] that is unaffected by food or drink [120]. The peak to trough ratio of sublingual asenapine is quite high (> 3) because of the rapid initial absorption, but this ratio is only 1:1 for the transdermal route [115]. Three different patch doses are available, 3.8, 5.7, and 7.6 mg/24 h, which are equivalent to 10, 15, and 20 mg sublingual daily. The patch can be applied on the abdomen, upper back, hips, or arms [121].

Efficacy and Safety of Transdermal Asenapine in Acute Schizophrenia

A single 6-week phase III RCT led to the US FDA approval. Patients were randomized to 7.6 mg/24 h ($n = 204$), 3.8 mg/24 h ($n = 204$), or placebo ($n = 206$). The majority of the population was white (76%) and male (60%). Discontinuation rates were 22.5% in 7.6 mg, 18.6% in 3.8 mg, and 21.4% in placebo group. There was a significant improvement in total PANSS (LSMD vs. placebo − 4.8 for 7.6 mg/24 h [$P = 0.003$], − 6.6 for 3.8 mg/24 h [$P < 0.0001$]) [122]. Transdermal asenapine was well-tolerated, and among all published studies, the most frequent AEs were somnolence (11.9%), application site erythema (7.4–15.2%), dizziness (4.7%), headache, insomnia, and fatigue (3%) [119, 122]. Application site irritation was more common for active patches (14.2% for 7.6 mg, 15.2% for 3.8 mg) than placebo (4.4%); however, it did not lead to discontinuation [122] (Table 7).

Summary of Transdermal Asenapine

Transdermal asenapine has a steady delivery and 1:1 peak to trough ratio in comparison to the much higher ratio of the sublingual preparation. Efficacy and overall AE load appear very similar.

Subcutaneous Long-Acting Risperidone Injection

An alternate route of administering a LAI antipsychotic was approved by the US FDA in July 2018. Risperidone is now available as a subcutaneous sustained release formulation to be given every 4 weeks for the treatment of schizophrenia in adults [123]. This subcutaneous LAI places risperidone into a delivery system of a biodegradable poly (dl-lactide-co-glycolide) dissolved

in N-methyl-2-pyrrolidone, a water-miscible, biocompatible solvent. This system is patented as the Atrigel® delivery system and has been used clinically previously for the LAI of buprenorphine, Sublocade® [124]. Risperidone itself is available as an intramuscular (IM) LAI in a polylactide and polylactide-co-glycolide polymers microsphere formulation [125, 126]. One of the main advantages of a subcutaneous injection is that it avoids the muscle tissue damage that can result from IM injections [127].

The risperidone LAI was formulated to match the oral 3 mg (90 mg injection) and 4 mg (120 mg injection) daily and provide 60–80% D2 receptor occupancy with much fewer fluctuations in comparison to oral risperidone [128, 129]. After a single subcutaneous injection, there is rapid absorption of risperidone with an initial peak at 4 h, which is sufficient to provide adequate D2 receptor occupancy (around 6 ng/mL) [128–130]. Over the subsequent 11 days, there is a slow increase in the combined levels of risperidone + paliperidone until the peak is reached (around 18 ng/mL for 90 mg and 32 ng/mL for 120 mg). Steady-state is achieved after only two subcutaneous doses [128–130]. In a post hoc analysis of the pivotal RCT [131], Ivaturi et al. [132] found that there was a significant relationship between plasma levels of risperidone and paliperidone and change in symptoms, so that half of the maximum placebo-subtracted decrease in PANSS of 5.4% could be achieved at total active moiety plasma concentration of 4.6 ng/mL.

Efficacy of Subcutaneous Long-Acting Risperidone Injection in Schizophrenia

The pivotal phase III clinical trial randomized 354 acutely psychotic inpatients with schizophrenia, aged 18–55 years to receive 90 or 120 mg of subcutaneous risperidone or subcutaneous placebo on day 1 and day 29 [131] (Table 8). Both were superior to placebo, and the placebo-subtracted difference of total PANSS scores was − 6.148 ($P = 0.0004$) and − 7.237 ($P < 0.0001$) for 90 mg and 120 mg groups, respectively [131]. This was associated with significant improvement in health-related quality of life (HRQoL, measured using EuroQol EQ-5D-5L) [133]. Similarly, physical functioning, social integration, and subjective wellbeing (measured with Subjective Wellbeing Under Neuroleptic treatment-Short version, SWN-S) also improved [133]. Patients reported a greater level of overall satisfaction with the medication in comparison to placebo or previous medicine [133].

A 52-week phase III open-label study enrolled 408 stable new patients and 92 rollover participants from the Nasser RCT[131]. All received 13 monthly subcutaneous injections of 120 mg [134]. PANSS scores continued to improve in patient's rollover from RCT and remained stable in new participants. HRQoL remained stable throughout (EQ-5D-5L index 0.83 baseline to 0.86 end), as did subjective wellbeing (SWN-S, 89 at baseline and 90 at end) [135]. Satisfaction with the subcutaneous injection increased from week 4 to the end of study [135].

Safety and Tolerability of Subcutaneous Long-Acting Risperidone Injection

The most common AEs in the acute psychosis study were injection site pain, constipation, sedation/somnolence, weight gain, and pain in extremity [131]. In the 52-week safety study, 73.4% patients reported at least one AE; the most common being injection site pain (13%) and weight increase (12.8%). No changes were noticed in vitals, laboratory, or ECG values [134].

Summary of Subcutaneous Long-Acting Risperidone

Subcutaneous sustained release preparation of risperidone is given 4 weekly and avoids muscle tissue damage caused by IM preparation.

Aripiprazole Lauroxil

Aripiprazole lauroxil is a LAI antipsychotic that was approved in October 2015 by the US FDA for the treatment of patients with schizophrenia [136]. Aripiprazole lauroxil is a prodrug of the well-established atypical antipsychotic aripiprazole that acts as a partial agonist at dopamine D2 and serotonin 5-HT_{1A} receptors and antagonist at 5-HT_{2A} receptors [137].

LAIs have emerged in recent years to be a valuable and effective option for long-term treatment yet remain underutilized. They markedly help with medication adherence, thus reducing relapse and are designed to provide patients with a steady concentration of the medication for the treatment interval [138, 139]. Aripiprazole lauroxil is administered via deltoid or gluteal intramuscular (IM) injections. It was originally approved as 441 mg monthly and 882 mg monthly regimens. Additional regimens were later developed and approved as 662 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months [140], as well as a 1-day delayed release NanoCrystal® formulation of 675 mg that forgoes the need for oral medication overlap (called Initio®) [141].

Aripiprazole lauroxil is a crystalline preparation of the active moiety, (aripiprazole), a connector molecule (which breaks down into formaldehyde), and a fatty acid (lauric or dodecanoic acid), to reduce the solubility of aripiprazole and prolong its life in muscle. After injection, aripiprazole lauroxil is cleaved into N-lauroyloxymethyl aripiprazole and lauric acid. The former is chemically hydrolyzed into methanol and aripiprazole [142, 143]. In addition to altering the solubility of aripiprazole, the delivery system also slows absorption through the size of the aripiprazole lauroxil crystals [144]. To create the Initio®, the researchers

simply scaled down the size of the injected crystals, thereby expanding the surface area available for dissolution, enzymatic breakdown, and hydrolysis [144].

The slow biotransformation and prolonged dissolution of aripiprazole lauroxil and subsequent absorption of aripiprazole after an IM injection are the reason that maximal concentrations are achieved after ~ 41 days (T_{max}) [143]. There are slight differences in T_{max} as a function of injection site location. With aripiprazole lauroxil, T_{max} is about 11.8 faster with deltoid injections (median 44.1 vs. 50.0 days) [145]. The difference is even bigger with the NanoCrystal® Initio® formulation, median T_{max} occurring after 17.0 days with deltoid versus 25.5 days with gluteal injection (34% faster) [146]. Consequently, without Initio®, oral aripiprazole supplementation for 3 weeks is necessary with the first injection but not if Initio® is coadministered [144].

Efficacy of Aripiprazole Lauroxil in Schizophrenia

In the pivotal trial investigating the efficacy of aripiprazole lauroxil, 623 acutely psychotic patients with schizophrenia were randomized to receive 441 mg or 882 mg of aripiprazole lauroxil or placebo once monthly. Both active arms achieved significantly greater improvement on total PANSS score ($P < 0.001$) and CGI-I score at day 85 ($P < 0.001$). In this study, there was an oral overlap for the first 3 weeks. However, clinical improvements were evident by the beginning of the second week [147].

The most severely psychotic patients in this study were able to achieve a sustained therapeutic effect, with those randomized to the higher dose achieving a greater improvement [148]. An examination of the effect of age and gender revealed no difference in response [149]. In another post hoc analysis, significant improvement was seen in the PANSS hostility item (P7), PANSS excited component (PANSS-EC), and the Personal and Social Performance (PSP) scales disturbing and aggressive behavior domain [150].

The Initio® formulation of aripiprazole lauroxil studied patients with acute exacerbation of schizophrenia in a 25-week phase IIIb double-blind trial comparing aripiprazole lauroxil (started with one oral 30 mg dose, Initio® 675 mg, and LAI aripiprazole lauroxil 1064 mg on day 8) and paliperidone palmitate (started on day 1 with 234 mg and 156 mg on day 8). Aripiprazole lauroxil 1064 mg was given on day 8, so that the patients would receive the same schedule of shots and the blind remain intact. The outcome as assessed by total PANSS total score was equivalent with the two treatments. The most common AEs were pain at injection site, akathisia, and increase weight in both groups [151].

Safety of Aripiprazole Lauroxil in Schizophrenia

In the pivotal trial, the AEs that were > 5% were injection site reactions, akathisia, insomnia, headache, and anxiety [147]. Injection site pain mild intensity is the most common AE with a higher incidence in deltoid versus gluteal injections [145]. The incidence of akathisia in the aripiprazole lauroxil treatment groups was more than double the placebo group (over 11% versus 4.3%). The majority of akathisia episodes occurred in the early phase of the study before the second injection when the active aripiprazole lauroxil treatment patients were also taking oral aripiprazole [147]. Aripiprazole lauroxil is similar to oral aripiprazole with a slight increase in weight and a slight decrease in prolactin levels. There was no significant change to serum lipid parameters, lipoprotein plasma glucose, or glycosylated hemoglobin (Hb_{A1c}) as reported by a post hoc analysis [147]. A 52-week open-label extension study in outpatients reported the similar metabolic changes as a result of long-term aripiprazole lauroxil to oral aripiprazole treatment [152]. Similar pharmacokinetics [153] and AE profiles are seen with higher dose (1064 mg) and longer dosing intervals (1064 mg administered every 8 weeks and 882 mg every 6 weeks) [154, 155].

Summary of Aripiprazole Lauroxil

Aripiprazole lauroxil is a LAI preparation of aripiprazole to improve medication adherence and reduce relapse rates.

Inhaled Loxapine

Agitation can be defined as abnormal and excessive motor and verbal activity [156]. Agitation is associated with aggression which could result in patient and staff injury; therefore, it should be considered a medical and psychiatric emergency. Loxapine is a medium potency dibenzoxazepine antipsychotic medication that is structurally similar to clozapine [157]. It displays postsynaptic antagonistic activity at the D2 receptor, dissociating at an intermediate rate, as well as acting as an antagonist at the serotonin 5-HT_{2A} receptor. It is considered a first-generation antipsychotic because it was created and used at a time prior to the understanding of the difference between first- and second-generation antipsychotics and is best classified as a second-generation antipsychotic [158]. It has been used as an oral preparation for over 40 years, and an intramuscular formulation had been previously approved for the control of acute agitation in schizophrenia [159–161]. Inhaled loxapine powder had been approved by the FDA in 2012 for the use in agitation control in schizophrenia and mania patients [162].

Inhaled loxapine is delivered through a handheld, single-use, breath-activated device, designed to quickly administer the aerosolized drug into the alveoli, leading to rapid systemic effect [163]. This is patented as the Staccato® system. Plasma concentration showed median T_{max} values of 2 min, declining to half C_{max} with a median of 10 min and

a terminal $t_{1/2}$ of 6.19 ± SD 1.65 h [164]. It has been shown that loxapine C_{max} was similar in smokers and nonsmokers with a geometric mean ratio of 99% [165] following a single dose of 10 mg inhaled loxapine in a mixed population, suggesting no need for dose adjustment in smokers. Similar pharmacokinetics were seen in children and adolescents (aged 10–11 years, $n=5$; aged 12–17 years, $n=25$) [166].

Efficacy of Inhaled Loxapine in Agitation

A phase II and 2 phase III studies with similar designs examined the efficacy of inhaled loxapine for the treatment of agitation associated with BD and schizophrenia (Table 10). All three studies measured the change from baseline on the PANSS-EC. The studies also recorded the CGI-I scale and time to rescue medication (IM lorazepam).

In the phase 2 study, 129 agitated patients with either schizophrenia or bipolar 1 disorder received either 5 mg, 10 mg, or placebo [167]. PANSS-EC was reduced significantly in both groups compared to placebo ($P=0.088$ and 0.002, respectively) after 2 h. The 10 mg group separated from placebo earlier (20 min) than the 5 mg group.

One phase III, the study examined schizophrenia ($n=344$) [168], and another examined acute mania ($n=314$) [169]. Agitated patients were randomized to receive inhaled loxapine 5 mg, 10 mg, or placebo. PANSS-EC scores for loxapine separated significantly from placebo in the first assessment at 10 min in both schizophrenia (5 mg, $P=0.0003$; 10 mg, $P<0.001$) and bipolar mania ($P<0.0001$ for both). Similar separations were seen for the primary outcome measure at 2 h (schizophrenia 5 mg, $P=0.0004$; 10 mg, $P<0.0001$; mania $P<0.0001$ for both 5 and 10 mg). In the schizophrenia study, the need for rescue intramuscular (IM) lorazepam was 6%, 5%, and 15% for those receiving 5 mg, 10 mg, and placebo, respectively [168]. The need for rescue IM lorazepam in the mania study was 9%, 9%, and 21% in the 5 mg, 10 mg, and placebo groups, respectively [169].

A more recent study compared the efficiency of inhaled loxapine 10 mg to IM aripiprazole 9.75 mg in an open-label, assessor-blind randomized study with primary efficacy point being time to response on the CGI-I score [170]. A total of 357 acutely agitated patients with either schizophrenia or bipolar I disorder received either inhaled loxapine or IM aripiprazole. Patients received a maximum of two doses of the drug with the second dose being at least 2 h following the first. Patients with schizophrenia responded faster to loxapine than aripiprazole (50 min vs. 60 min, $P=0.0025$), with a similar trend for bipolar patients (30 min vs. 50 min, $P=0.06$) [170]. A larger fraction of patients responded within 10 min (loxapine 14%; aripiprazole 3.9%; $P=0.0009$) [170].

In a prospective naturalistic study, 61 patients received inhaled loxapine and 29 received treatment as usual (TAU) [171]. The time to outcome for patients receiving inhaled loxapine was 21 ± SD 21 min compared to 121 ± 206 min for TAU ($P=0.014$); at outcome, 89% of patients treated with loxapine experienced resolution of symptoms, compared to 69% of TAU ($\chi^2=17.4$, $P<0.0001$). Ten percent of loxapine patients had no change in symptoms and 1% had worsening symptoms versus 14% experienced no change in symptoms ($z=0.5$, ns) and 17% worsening of symptoms in the TAU group ($z=6153.9$, $P<0.0001$).

There is an ongoing phase IV, open-label, study in Europe, with no data as of yet, where inhaled loxapine is available outside the hospital setting in which 500 patients with schizophrenia or BD will self-administer loxapine in the event of an agitation episode. Endpoint will be the incidence of AEs, respiratory AEs, and serious AEs [172].

Safety and Tolerability of Inhaled Loxapine

In phase II and III studies, inhaled loxapine at doses up to 10 mg is well-tolerated. Most frequently reported AEs were bad taste, dose-related dizziness, and somnolence. Most were mild to moderate in intensity and resolved spontaneously [167–169]. In the child and adolescent study, nearly all patients (97%) reported at least 1 AE [166]. Most were mild/moderate in intensity. Most frequently occurring AEs were sedation (90%) and dysgeusia (70%). There were no respiratory or serious AEs in any of the pivotal studies [166–169]. There were no clinically meaningful trends in mean changes from baseline for clinical chemistry, hematology, urine analysis, vital signs, or ECG findings. No QT_c interval prolongation of > 450 ms occurred at any time [173]. This is in line with a safety study which found that neither 5 nor 10 mg of inhaled loxapine cause QT_c prolongation ($n=60$) [174].

In phase I safety studies, concomitant administration of inhaled loxapine with IM lorazepam 1 mg in healthy volunteers showed no effect on respiration rate or pulse oximetry versus either drug alone [175].

The label warning against administering inhaled loxapine to individuals with asthma or chronic obstructive pulmonary disease (COPD) is based on safety studies in which bronchospasm occurred in 53.8% of subjects with asthma after inhaled loxapine and 19.2% of those with COPD. The same group of individuals experienced bronchospasm 11.5% and 11.1%, respectively, when receiving inhaled placebo [176]. All subjects responded to rescue bronchodilator within 1 h, and no treatment-related serious AEs occurred.

Summary of Inhaled Loxapine

Loxapine is a medium potency dibenzoxazepine, which is similar to clozapine structurally. An inhalable preparation is approved for use in acute agitation in schizophrenia and mania and has a much faster onset of action. It is delivered

through a breath-activated device called the Staccato® system. The maximum serum levels are achieved in 2 min with control of agitation within 10 min. While this mode of delivery provides benefits, the nature of its self-administration poses challenges and requires a certain degree of patient cooperation. The most common side effects were bad taste, dose-related dizziness, and somnolence. Inhaled loxapine should be avoided in patients with asthma and COPD due to the possibility of bronchospasm.

New Antipsychotics Under Study

SEP-363856

SEP-363856 is a novel potential antipsychotic that is in phase III trials. We include it in this review due to its unique mechanism of action with agonistic activity at trace amine-associated receptor 1 (TAAR1) and $5HT_{1A}$ and has *no* activity with any dopamine receptor [177]. Preclinical studies suggest that TAAR1 receptors have a role in modulating dopaminergic circuit, specifically inhibiting neurons in ventral tegmental area and attenuating ketamine-induced increased dopamine synthesis in striatum [178].

A single placebo-controlled, 4-week RCT randomized 245 patients with acute exacerbation of schizophrenia, to flexibly dosed SEP-363856 (50 or 75 mg daily) or placebo [179] (Table 9). The mean age of the population was 30.3 years, 80% were white, and most (63%) were male. The changes on total PANSS at week 4 were − 17.2 vs. − 9.7, in SEP363856 and placebo, respectively (LSMD vs. placebo − 4.3, $P = 0.001$). AEs included GI symptoms and somnolence, and one sudden cardiac death occurred in SEP 363,856 group. The incidence of EPS was similar in both the groups ~ 3%; also similar were other cardio-metabolic markers. This study was followed by a 26-week open-label extension study which enrolled 156 patients [179]. The mean change in PANSS at the end of 26 weeks in 77 patients that were on SEP363856 in the RCT and continued in this study was − 17.1 ± SE 12.4, whereas patients that switched from placebo to active drug had a mean change of − 27.9 ± 16.4 [179].

Xanomeline/Trospium Combination

Procholinergic interventions appear to be effective in animal models of schizophrenia [180], and xanomeline, a selective M_1 and M_4 muscarinic receptor agonist, has efficacy in animal models of the illness [181]. However, an early placebo-controlled exploratory study of 20 patients was negative for positive symptoms but promising for cognitive benefits [182]. More recently, xanomeline combined with the peripheral muscarinic antagonist, trospium, an approved treatment for overactive bladder [183], has garnered attention. When the two agents are coadministered, trospium blocks peripheral muscarinic receptors allowing xanomeline to enter into the central nervous system and increasing activity of M1 and M4. In a blinded, placebo-controlled 5-week phase II RCT of the xanomeline 125 mg/trospium 30 mg ($n = 90$) vs. placebo ($n = 92$), there was a significant reduction in the total PANSS score by − 17.4 points compared to − 5.9 points for placebo (LSMD, − 11.6 points; 95% CI − 16.1 to − 7.1; $P < 0.001$) [184]. Both cholinergic and anticholinergic AEs, such as constipation, nausea, dry mouth, dyspepsia, and vomiting, were more common in the active arm [184]. There are now ongoing phase III trials.

Conclusion

This extensive review has evaluated the latest clinical advances in antipsychotics in psychosis. We have elaborated and differentiated the various mechanisms of action along with synthesizing the existing evidence on the efficacy, safety, and tolerability of newer antipsychotics in acute and chronic psychosis. The advances in the past decade have been tremendous from (i) introduction of newer antipsychotics (cariprazine, brexpiprazole) with fewer AE, (ii) mechanism of action with < 50% receptor binding (lumateperone), (iii) agents that do not block dopamine (pimavanserin), and (iv) a new combination of olanzapine/samidorphan to mitigate weight gain. In addition, newer formulations of existing antipsychotics have seen the introduction of (v) first patch (transdermal asenapine), (vi) first inhaled loxapine, (vii) subcutaneous long-acting risperidone injections, (viii) IM aripiprazole lauroxil LAI, and (ix) newer research molecules SEP 363,856 and xanomeline/trospium with an antipsychotic action without dopaminergic blockade.

These agents expand the armamentarium and the routes of administration available to clinicians. The data on newer antipsychotics do not support additional benefits on negative symptoms or cognitive dysfunction but do have a similar effect on acute psychotic symptoms with fewer AEs.

Author Contribution PRISMA mandates that multiple individuals review the same material, and all coauthors served as alternate reviewers. Each author was responsible for the primary review of several agents. Additionally, Mehak Pahwa and Rif S. El Mallakh were instrumental in the overall organization, Ahmad Sleem and Omar H. Elsayed for the organization of the tables, and Mehak Pahwa and Megan Elizabeth Good for writing the final discussion. Dr. El Mallakh was responsible for all aspects of the review.

Compliance with Ethical Standards

Conflict of Interest Dr. El Mallakh is a speaker for Eisai, Indivior, Intra-Cellular Therapies, Janssen, Lundbeck, Noven, Otsuka, Sunovion, and Teva. None of the other authors have any potential conflicts of interest to declare.

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