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EVIDENCE REVIEW

- 1167 Child abuse and psychopathy: Interplay, gender differences and biological correlates
di Giacomo E, Santorelli M, Pessina R, Rucco D, Placenti V, Aliberti F, Colmegna F, Clerici M

REVIEW

- 1177 Polyamines and polyamine-metabolizing enzymes in schizophrenia: Current knowledge and concepts of therapy
Bernstein HG, Keilhoff G, Laube G, Dobrowolny H, Steiner J
- 1191 Nuclear receptors modulate inflammasomes in the pathophysiology and treatment of major depressive disorder
Wang H, Kan WJ, Feng Y, Feng L, Yang Y, Chen P, Xu JJ, Si TM, Zhang L, Wang G, Du J
- 1206 Review of barriers and interventions to promote treatment engagement for pediatric attention deficit hyperactivity disorder care
Baweja R, Soutullo CA, Waxmonsky JG

MINIREVIEWS

- 1228 Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise?
Barman R, Majumder P, Doifode T, Kablinger A
- 1239 E-technology social support programs for autistic children: Can they work?
Wall NG, Smith O, Campbell LE, Loughland C, Wallis M, Henskens F, Schall U
- 1247 Factors related to compliance with the COVID-19 health regulations among young people
Jaureguizar J, Redondo I, Galende N, Ozamiz N
- 1259 Mechanism of olfactory deficit in neurotrauma and its related affective distress: A narrative review
Logan M, Kapoor S, Peterson L, Oliveira M, Han DY
- 1267 Physical activity and mental well-being during COVID-19 pandemic
Abdelbasset WK, Nambi G, Eid MM, Elkholi SM

ORIGINAL ARTICLE**Basic Study**

- 1274 Differential aberrant connectivity of precuneus and anterior insula may underpin the diagnosis of schizophrenia and mood disorders
Aryutova K, Paunova R, Kandilarova S, Stoyanova K, Maes MH, Stoyanov D

- 1288** Validity and reliability of the Dutch version of the displaced aggression questionnaire

Smeijers D, Denson TF, Bulten EH, Brazil IA

Case Control Study

- 1301** BDNF methylation and mRNA expression in brain and blood of completed suicides in Slovenia

Ropret S, Kouter K, Zupanc T, Videtic Paska A

- 1314** Developing a nomogram for predicting the depression of senior citizens living alone while focusing on perceived social support

Byeon H

Retrospective Study

- 1328** Affect regulation in psychoanalytic treatments of patients with a borderline personality disorder-psychoanalysis and psychodynamic psychotherapy-a comparison

Steinmair D, Wong G, Frantal S, Rohm C, Löffler-Stastka H

Observational Study

- 1346** Impact of lockdown relaxation and implementation of the face-covering policy on mental health: A United Kingdom COVID-19 study

Rathod S, Pallikadavath S, Graves E, Rahman MM, Brooks A, Soomro MG, Rathod P, Phiri P

SYSTEMATIC REVIEWS

- 1366** Autism spectrum disorder and personality disorders: Comorbidity and differential diagnosis

Rinaldi C, Attanasio M, Valenti M, Mazza M, Keller R

- 1387** Psychological impact of the COVID-19 pandemic on individuals with serious mental disorders: A systematic review of the literature

Fleischmann E, Dalkner N, Fellendorf FT, Reininghaus EZ

- 1407** Psychoeducation in bipolar disorder: A systematic review

Rabelo JL, Cruz BF, Ferreira JDR, Viana BM, Barbosa IG

ABOUT COVER

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Newer antipsychotics: Brexpiprazole, cariprazine, and lumateperone: A pledge or another unkept promise?

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Abstract

Antipsychotic agents are used for various indications in the treatment of psychiatric disorders. Despite their proven roles in multiple conditions, the treatment-emergent side effects of antipsychotic medications, such as metabolic side effects, are often the limiting factor for their long-term and short-term uses. Moreover, antipsychotic medications are often criticized for being less effective in treating different disabling symptoms such as negative symptoms of schizophrenia. As a result, the search for safer and more efficacious antipsychotic agents is ongoing. Newer antipsychotic agents are gaining attention related to emerging efficacy and tolerability data in treating neuropsychiatric conditions. In this review, we attempt to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of second-generation antipsychotics, namely brexpiprazole, cariprazine, and lumateperone. We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications, keeping broad inclusion criteria. There were no restrictions on the age of the study population or the year of publication. We also cross-referenced articles and references to capture all existing studies. Our review of the current literature indicates that all three antipsychotic agents appear to be promising based on their short-term studies, while long-term studies remain limited. There is also a need for a head to head comparison between the newer antipsychotics with the other antipsychotic agents to ascertain if the newer agents are any better than the others.

Key Words: Antipsychotic agent; Brexpiprazole; Cariprazine; Lumateperone; Psychopharmacology; Schizophrenia

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Core Tip: In this review article we attempted to appraise the scientific literature on three newer antipsychotics such as brexpiprazole, cariprazine and lumateperone and presented their safety and efficacy data. Our aim was to investigate the status of these antipsychotic agents in treating various psychiatric disorders.

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INTRODUCTION

Antipsychotics have revolutionized the treatment of psychiatric disorders in the last few decades[1]. Despite advances in psychopharmacology, the quest for more effective and safer antipsychotic medications is not yet over. Schizophrenia remains one of the most chronic, debilitating psychiatric disorders whose optimal treatment approach is still a matter of research. In a global burden of disease study involving more than 30000 respondents from four European countries, schizophrenia was found to have the highest functional burden across hundreds of physical and mental health issues[2]. Second-generation antipsychotics (SGAs) are commonly used to treat schizophrenia and other conditions, including bipolar disorder[3-5]. Despite their proven efficacy, existing antipsychotic medications are limited by treatment-emergent side effects and their ability to address a limited collection of symptoms of schizophrenia such as delusions, hallucinations, disorganized thoughts, and bizarre behavior[6]. The lack of efficacy of medications to treat negative symptoms of schizophrenia, poor quality of life, and medication non-adherence remain a challenge[7,8]. Clozapine, which was introduced in 1971, remains the most efficacious antipsychotic medication despite potentially dangerous side effects[9]. This review aims to appraise the scientific data on psychopharmacology, safety profile, and efficacy of the newer additions to the list of SGAs, including brexpiprazole, cariprazine, and lumateperone.

LITERATURE SEARCH

We conducted a selective review utilizing PubMed, clinicaltrials.gov, and Cochrane databases to gather appropriate publications. The search was carried out between December 2020 to January 2021, keeping broad inclusion criteria to ensure the incorporation of relevant articles. There were no restrictions on the age of the study population or the year of publication. The authors cross-referenced articles and references to capture all existing studies. Authors PM, RB, and TD performed the literature search with author AK as a consultant. PM, RB, and TD wrote the initial draft and AK provided feedback and elaboration on the manuscript. All authors approved the final version.

BREXPIRAZOLE

Brexpiprazole, a novel serotonin-dopamine activity modulator, a partial agonist of the dopamine D2 receptors and is structurally similar to its predecessor, aripiprazole. Brexpiprazole is also a partial agonist at serotonin 1A (5-HT1A) receptors and a potent antagonist at 5-HT2A, α 1B, and α 2C adrenergic receptors[10]. This newer antipsychotic has less intrinsic agonist activity at the D2 receptor compared to aripiprazole and, as a result, may be less activating (as manifested by agitation and restlessness) than aripiprazole[11]. Antagonism of 5-HT2A and α 1B receptors and agonism of 5-HT1A receptors decrease side effects related to D2 receptor blockade in the striatum including akathisia and other extrapyramidal side effects (EPS) due to an increased

release of dopamine downstream[11,12]. Compared to aripiprazole, brexpiprazole has increased potency at these three receptors, namely, 5-HT_{2A}, 5-HT_{1A}, and α 1B leading to fewer potential treatment-emergent movement effects. Brexpiprazole also has lower antihistamine activity at the H₁ receptor, and as a result, may be associated with less sedation and weight gain than aripiprazole[11]. Brexpiprazole has no apparent anticholinergic side-effects given its minimal activity and affinity for the muscarinic acetylcholine receptors[12]. CYP3A4 and CYP2D6 primarily metabolize brexpiprazole to DM-3411, an inactive metabolite; has about 95% bioavailability after oral administration, and achieves peak plasma concentration 4 h after administration, and a steady-state concentration is reached within 10-12 d of daily administration[13].

Safety and efficacy data of brexpiprazole in schizophrenia research

On July 10, 2015, the United States Food and Drug Administration (FDA) approved brexpiprazole for the maintenance treatment of schizophrenia and as an adjunct treatment to antidepressants for the treatment of major depressive disorder (MDD) in adults[14]. However, brexpiprazole continues to be examined in clinical trials for possible use in attention deficit hyperactivity disorder, autism, conduct disorder, oppositional defiant disorder, Bipolar disorder, and agitation in Alzheimer's disease [15,16].

VECTOR[17] and BEACON[18] trials are the two major studies establishing the efficacy of brexpiprazole in schizophrenia treatment. These two, 6-wk, phase 3, randomized, placebo-controlled clinical trials used fixed doses of brexpiprazole *vs* placebo in patients with acute schizophrenia. Brexpiprazole demonstrated statistically significant improvement in the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions-Severity (CGI-S) in both studies. In the VECTOR trial, Correll *et al*[19] demonstrated a statistically significant reduction in PANSS scores with both 2 and 4 mg brexpiprazole compared to placebo[19]. On the other hand, in the BEACON trial, Kane *et al*[20] found a statistically significant decrease in PANSS scores with the 4 mg brexpiprazole dose group only, not with 1 or 2 mg doses, compared to placebo[20]. However, both VECTOR and BEACON trials lacked active comparators and were short term trials. Few studies have established the long-term efficacy of brexpiprazole as maintenance therapy for schizophrenia. In a phase 3, randomized, double-blind, placebo-controlled trial, Fleischacker *et al*[21] demonstrated that patients taking brexpiprazole had significantly longer time to impending relapse and a lower rate of relapse (13.5% *vs* 38.5%) as compared to placebo[21,22]. ZENITH trial [23], a 52-wk, open-label brexpiprazole study, reported that the PANSS total score improved on average by 12.2 points in patients receiving brexpiprazole. There was an improvement in mean CGI-S score of 0.6 and Personal and Social Performance scale total score of 7.7 points in patients taking brexpiprazole[24]. A recent randomized, double-blind, functional magnetic resonance imaging (fMRI) study[25] evaluating the effects of brexpiprazole on brain regions that control impulsive behavior in patients with stable schizophrenia reported that this medication decreased right ventrolateral prefrontal cortex (VLPFC) activation and decreased stop-signal reaction time (SSRT). The stop-signal task was a task associated with inhibition/control of impulsivity. Thus, this study concluded that brexpiprazole might be exerting benefits on inhibition-related brain activation and behavior in patients with schizophrenia[26]. Brexpiprazole was well-tolerated in schizophrenia trials with akathisia, headache, somnolence, tremor, weight gain as commonly reported side effects[13].

Safety and efficacy data of brexpiprazole in MDD research

PYXIS[27] and POLARIS[28] phase 3 trials led to the FDA approval of brexpiprazole as an adjunctive treatment for MDD. Both of these studies were six weeks, randomized, double-blind, and placebo-controlled, and evaluated the efficacy of brexpiprazole as an adjunctive treatment in MDD by comparing changes in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. The participants were adult patients with MDD with an inadequate response to 1-3 previous antidepressant trials. Both studies had an 8-wk single-blind prospective treatment phase where subjects received a standard antidepressant; those with inadequate responses were included in the study. In the POLARIS trial, 3 mg brexpiprazole demonstrated a statistically significant improvement in MADRS score as compared to placebo. However, brexpiprazole 1 mg did not reach statistical significance[29]. Similarly, the PYXIS trial, which used 2 mg brexpiprazole dosing, also reported a reduced mean MADRS total score compared to placebo corroborating its efficacy as an adjuvant treatment in MDD[30].

Data from short- and long-term trials of brexpiprazole as a treatment adjunct in MDD reported minimal changes in prolactin levels, low rates of post-baseline prolactin elevation, low rates of prolactin-related side effects, and a moderate improvement in

sexual functioning[31]. Akathisia, headache, somnolence, tremor, and weight gain were reported as common side effects[13].

CARIPRAZINE

Cariprazine is a SGA approved by the United States FDA in 2015 for the maintenance treatment of schizophrenia[32]. While most atypical antipsychotics are D2 antagonists, cariprazine is a dopamine D3/D2 receptor partial agonist with a 10-fold higher affinity for D3 receptors than D2 receptors[33,34]. Cariprazine differs from two other dopamine receptor partial agonists, aripiprazole and brexpiprazole, by its distinct receptor-binding characteristics not only at dopamine D2/D3 receptors but also at serotonin 5HT1A, 5HT2B, 5HT2A, 5HT2C, and histamine H1 receptors[35]. Structurally, cariprazine is an antagonist at the dopamine D3 receptor but functionally acts as a partial agonist with 70% intrinsic agonism[34]. Dopamine D3 receptors in the prefrontal cortex regulate cognition, mood, and negative symptoms and are also distributed in other brain regions, including the nucleus accumbens that controls reward and motivation. Cariprazine, as an antagonist of the dopamine D3 autoreceptors, is hypothesized to play a role in motivation, depression, and reward by increasing dopamine release in the prefrontal cortex[36].

The pharmacokinetic characteristics of cariprazine are also distinct from other antipsychotics. Cariprazine is highly plasma protein bound, time to peak concentration is 3-6 h[37] and it is primarily metabolized by CYP 3A4, and by CYP 2D6, to a lesser extent. It has two major active metabolites, desmethyl cariprazine, and didesmethyl cariprazine. Didesmethyl-cariprazine (DDCAR) has a long half-life of 1-3 wk[38]. A longer half-life might protect against the rapid onset of relapse following non-adherence in patients with schizophrenia.

Safety and efficacy data of cariprazine in schizophrenia research

Among the four major randomized, placebo-controlled pivotal trials, one trial of cariprazine in the treatment of schizophrenia failed as the placebo response was much higher than the cariprazine group[39]. In the other three trials, all tested cariprazine dosages of 1.5, 3, 4.5, 6, 3-6, and 6-9 mg/d, were superior to placebo in reducing the PANSS and CGI-S scores[40-42]. A significant improvement in the hostility item of the PANSS was observed in these three studies. In two meta-analyses, both higher and lower dosages of cariprazine demonstrated superior efficacy as compared to placebo in acute schizophrenia[43,44].

Safety data collected from these four trials reported a lower discontinuation rate in the patients who received cariprazine 1.5-6 mg/d compared to patients on placebo [35]. Pooled data on adverse effects noted a higher likelihood of weight gain, hypertension, akathisia, and EPS that led the FDA to recommend the lower dose range of 1.5 to 6 mg/d in schizophrenia[45,46]. In the pooled data, mean changes in metabolic parameters and hypotension were no different from the placebo group; there were also no differences in syncope, prolactin level, or $Q_{tc} > 500$ ms[46,47]. As per the product label, the most common side effects are EPS and akathisia[45]. In a study among 586 patients with schizophrenia[48], the most common adverse effect was akathisia (16%), followed by headache, insomnia, and weight gain. However, the discontinuation rate from akathisia was $< 1\%$ in comparison to 12.5 % from all other adverse events. Among the D2 partial agonist antipsychotics, the risk of weight gain and somnolence is much lower with cariprazine, but akathisia is higher than with aripiprazole and brexpiprazole[47]. In placebo-controlled studies, observed relapse rates were much higher in the placebo group than the patients on cariprazine 47.5% *vs* 24.8%[49]. Because of longer half-life, relapse at 4 wk following discontinuation of cariprazine was 2-7 times lower than in other relapse prevention studies[50].

Safety and efficacy data of cariprazine in mood & anxiety disorders research

Cariprazine is also approved in the United States for mania and mixed episodes related to bipolar mood disorder type I in adults[51]. In bipolar mania, more cariprazine treated patients had improved CGI-S scores than patients on placebo; that is, more cariprazine-treated patients shifted from the severely ill to the mildly ill or better category as compared to the placebo-treated patients (55% *vs* 36%, odds ratio = 2.1)[51]. Post hoc analyses of three randomized, double-blind, placebo-controlled clinical studies showed that a significantly higher proportion of patients with cariprazine achieved response and remission in bipolar mania on all evaluated measures when compared with the placebo-treated group[52]. Most importantly,

improvement in manic symptoms did not precipitate depressive symptoms. Subsequent research on the role of cariprazine in bipolar I depression and MDD are being studied.

In animal studies, cariprazine has demonstrated antidepressant-like activity and has reduced anhedonia-like behavior[53], comparable to aripiprazole and the tricyclic antidepressant imipramine[54]. In the same study by Duric *et al*[54], the anxiolytic-like action of cariprazine has also been elicited in mice. Theoretically, cariprazine may improve depressive symptoms because of its unique D3 preferring dopamine D3/D2 receptor partial agonism along with serotonin 5HT1A receptor partial agonism. However, in a randomized, double-blind, placebo-controlled phase 3 trial, cariprazine did not show significant benefit as an augmenting agent in MDD, though it was well-tolerated with no significant differences in side effects compared to placebo[55].

On the contrary, in a study by Earley *et al*[56], cariprazine at 1.5-3 mg/d was safe and effective in reducing the depressive symptoms in bipolar I depression[56]. In a recent placebo-controlled study, cariprazine 1.5 mg/d significantly reduced depressive symptoms but not cariprazine 3 mg/d[57]. Clearly, the efficacy of cariprazine in bipolar I depression is not yet fully established.

Additional studies of cariprazine

In a case series described by Sanders and Miller[58], three cases of type I bipolar mood disorder with co-morbid substance abuse elicited an abrupt decrease in craving and use of the substances concomitant with improved mood symptoms after initiating cariprazine with their existing medication regimen. Findings in animal studies demonstrate that cariprazine improves cognition, improves pro-social behavior, and decreases the rewarding effect of cocaine[59]. Interestingly, cariprazine can resensitize resistant cancer cells to mitoxantrone by modulating ABCG2 (breast cancer resistance protein) and *via* several other distinct mechanisms[60].

LUMATEPERONE

Lumateperone[7], received United States FDA approval to treat schizophrenia in adults in December 2019[61]. Lumateperone possesses unique pharmacologic actions on the serotonin, glutamine, and dopamine systems. It is a presynaptic partial agonist and postsynaptic antagonist at D₂ receptors, an antagonist at serotonin 5-HT_{2A} receptors, and a glutamate modulator[7,8,62]. The presynaptic partial agonism and postsynaptic antagonism at dopamine D₂ receptors allow a lowered presynaptic release of dopamine and postsynaptic blockade of dopamine, leading to a more efficient reduction of dopaminergic signaling than other antipsychotic medications [63]. At the same time, it has negligible binding potential to other receptors such as histaminic or muscarinic receptors, which are associated with sedation, cognitive and metabolic side-effects[63]. One of the critical components of lumateperone is the 60-fold separation between its affinity for 5-HT_{2A} receptors and D₂ receptors. At a lower dose, lumateperone antagonizes the 5-HT_{2A} receptor and promotes sleep and reduces aggression, but at a higher dose, antipsychotic and antidepressant effects emerge[63, 64]. It also indirectly modulates the glutamatergic phosphoprotein associated with D1-dependent augmentation of N-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) activity *via* the mammalian target of the rapamycin (mTOR) pathway, which could contribute to a potent and rapid antidepressant action[65]. Additional actions such as serotonin transporter inhibition and stimulation of phosphorylation of glutamatergic NMDA GluN_{2B} receptors[8] are unique to lumateperone. The steady-state concentration is reached in approximately five days and is metabolized by several enzymes, including but not limited to uridine 5'- diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2[66]. The half-life of lumateperone and its metabolites ranges from 13 to 21 h which allows a once a day dosing regimen[8].

Safety and efficacy data of lumateperone in schizophrenia research

Three industry-sponsored placebo-controlled trials among patients with an acute exacerbation of schizophrenia have investigated the role of lumateperone in the treatment of schizophrenia[67-70]. Correll *et al*[71], in a four-week-long, three-armed placebo-controlled, randomized phase 3 clinical trial[71], involving 450 patients aged 18-60, with acute exacerbation of schizophrenia, demonstrated that 42 mg of lumateperone (equivalent to 60 mg of lumateperone tosylate), brought significant improve-

ment as compared to placebo from baseline to day 28 on the PANSS total score and the CGI-S[71]. There was no statistically significant difference between 28 mg of lumateperone (equivalent to 40 mg of lumateperone tosylate), as compared to placebo. A previous phase 2 multi-site randomized, double-blind, placebo-controlled, and active-controlled trial (risperidone) involving 335 acutely psychotic patients with schizophrenia also demonstrated antipsychotic efficacy at 42 mg (equivalent to 60 mg of lumateperone tosylate), but not at the 84 mg dose (equivalent to 120 mg of lumateperone tosylate)[72]. A subgroup analysis revealed that the forty-two mg also significantly reduced the total PANSS and the Calgary Depression Scale for Schizophrenia (CDSS) score with an effect size much larger than risperidone (effects sizes for PANSS and CDSS approximated 1 for lumateperone, and 0.60 and -0.48, respectively for risperidone). The improvement in negative symptoms with lumateperone 42 mg did not reach statistical significance. The authors concluded that the lack of a significant difference was due to relatively low negative symptoms at baseline[72]. In another phase 3 randomized clinical trial[73], involving 696 subjects, 60 mg, and 20 mg lumateperone tosylate were compared with risperidone 4 mg and placebo for six weeks, but lumateperone (at either dose) was not significantly different from the placebo on the primary endpoint in the intent-to-treat population[74]. Such results may be related to an unusually high placebo response rate at specific sites, which affected the overall results. In a position emission tomography study[75] in patients with schizophrenia, the mean peak dorsal striatal D2 receptor blockade was 39% attained after an hour of taking 60 mg lumateperone tosylate. Higher D2 receptor occupancy is associated with a higher risk of EPS and hyperprolactinemia, indicating lumateperone may be associated with less risk of EPS and hyperprolactinemia[76].

All studies indicate a favorable side-effect profile of lumateperone. Lumateperone was also favorable to risperidone in terms of safety and tolerability, including a lower risk of hyperprolactinemia, hyperglycemia, hyperlipidemia, and weight gain. The most commonly reported adverse effects with lumateperone are mild sedation and somnolence. The most common side effect reported by Correll *et al*[71] was sedation (9.3%-12.7%), followed by fatigue (4.7%-5.3%), and constipation (4%-6.7%) among lumateperone-treated patients. In the same study, two patients discontinued treatment due to severe, treatment-emergent adverse effects: One developed orthostatic hypotension and the other one developed convulsions with preexisting risk factors. There was no increase in suicidal ideation or behavioral or EPS[71]. In the other trial, by Lieberman *et al*[72], no severe adverse reaction occurred in the lumateperone group[72]. In the same study, two patients discontinued treatment in the lumateperone group- one for dryness of mouth and another for worsening schizophrenia whereas, three patients stopped treatment in the risperidone group due to akathisia and increased creatine phosphokinase level; 17% developed somnolence. There was no difference in the median weight gain between lumateperone and placebo groups; interestingly, the median weight gain was less than the patients on risperidone experienced (2.5 kg *vs* 1 kg), and no EPS were reported[72]. In an open-label safety switching trial, 301 patients with stable symptoms of schizophrenia were switched from previous antipsychotic medication to a daily dose of 60 mg lumateperone tosylate for six weeks and then switched back to the previous or another antipsychotic and reassessed after two additional weeks[77]. The study demonstrated a statistically significant improvement in total cholesterol, low-density lipoprotein cholesterol, body weight, and prolactin with switching to lumateperone. The progress was reversed as the treatment was changed back to the previous antipsychotic medication[77]. The most commonly reported side effects were mild to moderate and comprised of somnolence (6.6%), headache (5.3%), and dry mouth (5.3%), EPA (1.0%) [77]. Part 2 of the open-label study[78], is currently evaluating the safety and efficacy of switching to 60 mg lumateperone from the previous antipsychotic medication. In another study, one hundred seven patients experienced a mean reduction of 1.82 kg weight by day 175 and 3.16 kg by day 350. Almost 24% had at least 7% weight loss. The most common side effects were somnolence (20%), dryness of the mouth (7%), headache (7%), diarrhea (7%), and EPS (0.8%). The rate of somnolence decreased with night administration[79].

Summary of comparisons between newer FDA approved antipsychotics and the other SGAs

Although there is a lack of head-to-head comparisons among the newer antipsychotic medications, there is some evidence showing possible differences. In three 26-wk randomized clinical trials in Europe, higher efficacy of cariprazine over risperidone for negative symptoms has been established[40,80,81]. In a recent retrospective chart

Table 1 Characteristics and indications of brexpiprazole, cariprazine, and lumateperone

| Name | Characteristics | Dose | Common adverse reactions | FDA indications |
|---------------|---|---|---|--|
| Brexpiprazole | Partial agonist of dopamine D2 receptor, a partial agonist of serotonin 1A (5-HT _{1A}) receptors, and a potent antagonist at 5-HT _{2A} , α 1B, and α 2C adrenergic receptors | 2-4 mg/d for schizophrenia; 2 mg/d for MDD | Akathisia, headache, somnolence, tremor, and weight gain | Maintenance treatment of schizophrenia Adjunctive treatment for major depressive disorder in adults |
| Cariprazine | Dopamine D3/D2 receptor partial agonist with 10-fold higher affinity for D3 receptors than D2 receptors, antagonism at serotonin 5HT _{2A} , 5HT _{2B} with moderate to high binding affinity | 1.5 mg/d-6 mg/d for schizophrenia; 3-6 mg/d for bipolar mania | Akathisia, EPS, headaches, weight gain, headache, insomnia, and extrapyramidal side effects | Maintenance treatment of schizophrenia. Mania and mixed episodes related to bipolar mood disorder type I in adults |
| Lumateperone | Presynaptic partial agonist and postsynaptic antagonist at D ₂ receptors, an antagonist at serotonin 5-HT _{2A} receptors, and a glutamate modulator | 42 mg for schizophrenia | Sedation, somnolence, headache, dryness of mouth, extrapyramidal side effects | Schizophrenia in adults |

FDA: Food and Drug Administration; MDD: Major depressive disorder; EPS: Extrapyramidal side effects.

review, the metabolic parameters of patients treated with brexpiprazole, lurasidone, asenapine, cariprazine, or iloperidone were assessed at six weeks, 12 wk, and up to 12 mo. Olanzapine was used as a comparator. Although all the newer antipsychotics had significantly favorable metabolic characteristics compared to olanzapine, the risk of weight gain and increased body mass index was more with brexpiprazole and iloperidone among the newer antipsychotics. In contrast, a minimal increase in weight was reported with cariprazine and asenapine[64]. Among the three dopamine partial agonists (aripiprazole, brexpiprazole, and cariprazine), patients on aripiprazole had the most significant reduction of PANSS scores in schizophrenia, cariprazine had the most potent effects on Young Mania Rating Scale scores in mania, and brexpiprazole significantly reduced the MADRS score as an adjunctive treatment of MDD[35]. However, a recent systematic review and network meta-analysis concluded that there was no difference in the safety and efficacy between aripiprazole and brexpiprazole in the treatment of schizophrenia[82].

CONCLUSION

Brexpiprazole, cariprazine, and lumateperone have demonstrated efficacy in treating schizophrenia in the short term. Longer-term studies are limited in number. Based on short-term studies, all three newer antipsychotics appear to be promising, specifically due to fewer metabolic side effects and possible efficacy on negative symptoms in schizophrenia (Table 1). Further research focusing on comparative effectiveness will aid in identifying whether brexpiprazole, cariprazine, and lumateperone are truly better than their precursors. Future studies should compare the safety and efficacy of these newer antipsychotics with older antipsychotic medications to provide patterns or predictors with respect to efficacy in particular patient groups.

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