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Novel Antipsychotics Specificity Profile: a clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone

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Abstract

Second generation antipsychotics (SGAs) are effective options in the treatment of schizophrenia and mood disorders, each with characteristic efficacy and safety features. In order to optimize the balance between efficacy and side effects, it is of upmost importance to match compound specificity against patient clinical profile. As the number of SGAs increased, this review can assist physicians in the prescription of three novel SGAs already on the market, namely lurasidone, brexpiprazole, cariprazine, and lumateperone, which is in the approval phase for schizophrenia treatment at the FDA.

Besides schizophrenia, EMA and/or FDA approved lurasidone for bipolar depression, brexpiprazole as augmentation in major depressive disorder and cariprazine for the acute treatment of manic or mixed episodes associated with bipolar I disorder. These new antipsychotics were developed with the aim of improving efficacy on negative and depressive symptoms and reducing metabolic and cardiovascular side effects compared to prior SGAs, while keeping the risk of extrapyramidal symptoms low. They succeeded quite well in containing these side effects, despite weight gain during acute treatment remains a possible concern for brexpiprazole, while cariprazine and lurasidone show higher risk of akathisia compared to placebo and other SGAs such as olanzapine. The available studies support the expected benefits on negative symptoms, cognitive dysfunction and depressive symptoms, while the overall effect on acute psychotic symptoms may be similar to other SGAs such as quetiapine, aripiprazole and ziprasidone.

The discussed new antipsychotics represent useful therapeutic options but their efficacy and side effect profiles should be considered to personalize prescription.

Keywords: Antipsychotics; Brexpiprazole; Cariprazine; Lumateperone; Lurasidone; Personalized Medicine

1. Introduction

Second-generation antipsychotics (SGAs) have become the mainstream pharmacological treatment for schizophrenia and they are often used as primary therapy or augmentation in affective disorders as well (Taylor et al., 2018). SGAs are not a homogeneous pharmaceutical class: each has indeed characteristic side effect profiles and specific efficacy domains. Therefore, when prescribing SGAs, best clinical practice requires to match compound specificity against the features of different subsets of patients, i.e. disease characteristics and vulnerability to side effects (Lally and MacCabe, 2015; Leucht et al., 2009). As new oral SGAs have become available over the past decade, a clinically oriented appreciation of the profile of such agents is called for and can assist clinicians in prescription. Various agents differ in terms of dosing frequency, need for titration to a therapeutic dose, drug-drug interactions, domains of efficacy, commonly encountered adverse effects, domains of efficacy and last but not least market price. Recognizing specific pros and cons is therefore of upmost importance. The aim of this review is to outline pharmacological properties, efficacy, safety and tolerability of new antipsychotics as well as to suggest their specific place in psychiatric pharmacotherapy, in the framework of precision medicine. Only adverse effects with incidence ≥ 5% having at least twice the rate of placebo are outlined in the present paper, since their broad relevance in clinical practice. The antipsychotics of interest are those approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) since 2010, i.e. lurasidone, brexpiprazole and cariprazine. Lumateperone, a drug with novel mechanism of action, will be also discussed since its Phase III clinical development has been completed and the FDA accepted a New Drug Application for lumateperone for the treatment of schizophrenia (Intra-Cellular Therapies, 2018).

2. Lurasidone

Lurasidone is approved for the acute and maintenance treatment of schizophrenia (FDA, 2010; EMA, 2014) and bipolar I depression in monotherapy or in combination with lithium or valproate (FDA, 2013) (Table 1). Distinctive of lurasidone (Table 2) is a potent antagonism at the serotonin 5-HT7 receptor, which, coupled with 5-HT1A partial agonism, could potentially be associated with improved cognition and antidepressant effects (Ishibashi et al., 2010). Of notice, lurasidone antidepressant effects in preclinical behavioral animal models were absent in 5-HT7 knockout mice; such effects therefore appear to be mediated by these receptors (Cates et al., 2013). Lurasidone shows high affinity for the 5-HT2A and dopamine D2 receptors - the latter is associated with extrapyramidal symptoms (EPS) - and low affinity for the M1, H1, 5-HT2C and alpha1 receptors, suggesting a low liability to cause peripheral and central anticholinergic side effects, somnolence, weight gain and hypotension.

Dosing instructions recommend to take lurasidone once daily in the evening, to reduce the incidence of EPS and sedation. Furthermore, a meal with the caloric value of at least 350 kcal, regardless of the fat content, should accompany lurasidone administration, considering that it optimizes lurasidone exposure acting on

relevant pharmacokinetic parameters (two- to three-fold compared to fasting conditions)[FC1] (Preskorn et al., 2013).

2.1 Schizophrenia

Five trials demonstrated lurasidone efficacy in acute schizophrenia (Loebel et al., 2013a; Meltzer et al., 2011; Nakamura et al., 2009; Nasrallah et al., 2013; Ogasa et al., 2013). No titration is needed to reach the minimum effective dose (40 mg/day). However, a dose-dependent efficacy gradient across the approved dose range (US: 40-160 mg/day; the equivalent in the EU: 37-148 mg/day) seemingly exists: pooling data from short-term studies, the number needed to treat (NNT) of lurasidone (versus placebo) (Table 3) for a ≥ 30% reduction in the positive and negative syndrome scale (PANSS) (Kay et al., 1987) total score was 4 (95% CI 3-5) at 160 mg/day as opposed to 6 (95% CI 5-10) at 40 mg/day (Citrome, 2012). In case of early non-response (< 20% PANSS total score improvement at week 2), dose escalation to 160 mg/day is a safe and efficacious strategy (Loebel et al., 2016). Dose increases are recommended with increments of 40 mg at approximately weekly intervals. A pooled analysis of short-term trials showed that lurasidone significantly improved each of the five PANSS factor scores in a dose-dependent fashion, albeit not completely linear (Loebel et al., 2015). However, in comparison to other SGAs, the scale of lurasidone overall impact appears modest: in a meta-analysis of 15 SGAs (Leucht et al., 2013), it ranked in the bottom half for PANSS total improvement in acute schizophrenia. Lurasidone was suggested to have higher effect size on symptom improvement when positive symptoms are prominent compared to cases without prominent positive symptoms (Potkin et al., 2016). A recent meta-analysis comparing lurasidone and brexpiprazole found that the two had similar efficacy (Ng-Mak et al., 2018). Lurasidone tackled severe cases of agitation (NNT of 8 (95% CI 5-17) for a ≥ 40% reduction in the PANSS-excited component (PANSS-EC)), while improvement was not significantly greater than placebo in patients with lower levels of agitation at baseline. The magnitude of improvement in agitation increased at higher doses of lurasidone, in the range of 120-180 mg/day (Cohen's d of 0.43 vs. 0.19 for 40-80 mg/day lurasidone) (Allen et al., 2017). Lastly, depressive symptoms of schizophrenia are another domain which lurasidone specifically addresses (NNTs ranged from 11 to 14 for response and remission according to the Montgomery–Åsberg Depression Rating Scale (MADRS)) (Nasrallah et al., 2015).

Five studies (Citrome et al., 2012; Citrome et al., 2014b; Loebel et al., 2013b; Stahl et al., 2013; Tandon et al., 2016) demonstrated that lurasidone is effective as prophylactic treatment in schizophrenia, reducing the risk of relapse by 33.7% compared to placebo in a 28-week period. In 6-12 month studies it was showed that lurasidone had similar efficacy in preventing recurrence compared to quetiapine XR but it may provide higher benefits in terms of symptom reduction, remission and risk of hospitalization or emergency service utilization (Loebel et al., 2013b). Moreover, lurasidone improved cognition more than quetiapine XR across all the examined cognitive domains (speed of processing, visual learning, working memory, reasoning/problem solving and social cognition) (Harvey et al., 2015). This favorable action on cognition was also observed in

comparison to ziprasidone in the non-acute phase of schizophrenia or schizoaffective disorder (particularly when considering processing speed) (Potkin et al., 2011).

Lurasidone was well tolerated and a similar side effects profile was recorded over both short and longer term. In 6-weeks trials, commonly encountered adverse events from lurasidone were somnolence, akathisia, nausea, parkinsonism and insomnia (Sanford, 2013). However, number needed to harm (NNH) values (Table 3) were generally in the double digits, reflecting an overall tolerable profile: the 5 most consistently encountered adverse events attributable to lurasidone were akathisia, nausea, sedation, somnolence and parkinsonism with NNH vs. placebo for lurasidone 40–120 mg/d ranging from 6 (akathisia with 120 mg/d) to 30 (parkinsonism with 80 mg/d) (Citrome, 2012). Akathisia and EPS appear to be dose-related within the dose range of 20–120 mg/day. Lurasidone was associated with a low risk of hyperprolactinaemia, QTc interval prolongation, weight gain and metabolic disturbances. Compared to olanzapine and quetiapine (Loebel et al., 2013a; Nasrallah et al., 2013), lurasidone was associated with significantly less weight gain but higher rates of akathisia, anxiety and EPS. For these side effects, lurasidone was similar to ziprasidone (Potkin et al., 2011), a metabolically friendly antipsychotic, but somnolence rates were lower with the former. Lurasidone was associated with lower weight gain and metabolic disturbances than brexpiprazole (Ng-Mak et al., 2018).

2.2 Bipolar depression

Two studies proved lurasidone efficacious in the acute treatment of depressive episodes in bipolar disorder as both monotherapy (Cohen's d value 0.51) (Loebel et al., 2014a) and adjunctive therapy to lithium or valproate (Cohen's d value 0.31) (Loebel et al., 2014b). All the considered subgroups, including patients with subsyndromal hypomania at baseline, benefitted. Another 6-week adjunctive study with lithium or valproate failed to demonstrate better improvement vs. the control group at the primary 6 week endpoint; superiority over placebo was only confined to weeks 2-5 (Suppes et al., 2016a). However, consistently with the other two trials, significant improvements on measures of anxiety and health-related quality of life were maintained throughout. Unmeasured differences between the patient populations and/or study design differences might have contributed to the discrepant findings of this study.

In a 6-months follow-up open-label study (Ketter et al., 2016), patients treated with lurasidone showed sustained improvement in depressive symptoms as well as in other secondary efficacy measures (Clinical Global Impression-Bipolar Severity of depression scale (CGI-BP-S) (Spearing et al., 1997)(Spearing et al., 1997), Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959), Sheehan Disability Scale (SDS) (Sheehan et al., 1996), and Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form (Q-LES-Q-SF) (Endicott et al., 1993)). Over 7 months, lurasidone in combination with lithium or valproate reduced the risk of recurrence of any mood episode but only in patients who were in a depressive phase at baseline (when lurasidone was initiated) (Calabrese et al., 2017).

As with schizophrenia, lurasidone, both monotherapy and adjunctive therapy, may exhibit a linear dose-response pattern, with greater efficacy in the 80–120 mg/d dosing range (recommended dose range 20-120

mg/day), based on a population dose-response analysis (Chapel et al., 2016). This holds true for both monotherapy and adjunctive therapy. In comparison with other treatment options for bipolar depression, a meta-analysis demonstrated that lurasidone monotherapy is similar in terms of likelihood to response to the combination olanzapine and fluoxetine, superior to quetiapine, lithium or lamotrigine (Taylor et al., 2014). Another study (Citrome et al., 2014a) comparing NNT, NNH and likelihood of being helped or harmed (LHH) for clinical response and remission concluded that lurasidone yielded benefits similar to the predecessors quetiapine and olanzapine-fluoxetine combination.
The overall pattern of safety and tolerability for lurasidone in bipolar depression is consistent with that found in patients with schizophrenia.

2.3 Major Depressive Disorder with Mixed Features

The mixed-features variant is a severe form of depression characterized by the presence of at least three manic/hypomanic symptoms. This specifier was incorporated in the Diagnostic Statistical Manual of Mental Disorders 5th edition (American Psychiatric Association, 2013) . It represents an intermediate phenotype between major depressive disorder (MDD) and bipolar depression for which standard antidepressants may be ineffective or even associated with complications including suicidal ideation and behavior, manic switch, agitation and impulsivity (Francesca et al., 2014; Pacchiarotti et al., 2013; Sani et al., 2014; Smith et al., 2009). Very few treatments have been tested in this condition (Verdolini et al., 2018). Lurasidone (20-60 mg/day) was proved efficacious and safe to treat this condition even if only one trial is available and for this reason it was not included among the approved indications as of today (Suppes et al., 2016b). It significantly improved both depressive and manic symptoms, indicating efficacy across the range of core mood symptoms associated with this disorder (NNT for response and remission 3 and 4, respectively). Anxiety symptoms and patient-reported functional impairment significantly improved as well. These clinical effects are probably due to lurasidone high affinity for 5-HT2A, 5-HT7 and D2 receptors at the low dosages utilized. Low dosages, moreover, may have contributed to good tolerability: nausea and somnolence were the two most frequently reported adverse events (NNH of 8 for both). Post-hoc analyses showed that lurasidone is significantly useful in subgroups with mild and moderate-to-severe anxiety (Tsai et al., 2017), subjects with irritability (Swann et al., 2017) and post-menopausal women (Sramek et al., 2017).

3. Brexpiprazole

Brexpiprazole is approved for the acute and maintenance treatment of schizophrenia (FDA, 2015; EMA, 2018) and adjunctive treatment of MDD (FDA, 2015) (Table 1). It acts as a partial agonist at 5-HT1A and D2 receptors at similar potencies and as an antagonist at 5-HT2A and adrenergic alpha1B/2C receptors (Table 2). Brexpiprazole has less intrinsic agonist activity at D2 receptor than aripiprazole (Maeda et al., 2014b), the first

D2 receptor partial agonist available on the market, suggesting a relatively lower tendency to cause D2 partial agonist-mediated side effects, e.g. akathisia, insomnia, restlessness and nausea (Fleischhacker, 2005).
Dose titration is recommended, starting from 1 mg/day. The typical titration schedule for schizophrenia is 2 mg/day on Day 5 to Day 7, up to 4mg/day on Day 8; in MDD dosage increases are recommended at weekly intervals and the usually recommended target dose is 2 mg/day.

3.1 Schizophrenia

Brexpiprazole is efficacious in acute schizophrenia as showed by two studies (Correll et al., 2015; Kane et al., 2015a) (Table 4). However, lower doses of brexpiprazole (2 mg) performed inconsistently between the two trials; therefore, the higher end of the recommended dosage range (4 mg) may be necessary. Furthermore, higher brexpiprazole dosage was associated with a significant improvement in PANSS-EC score and PANSS scores for the negative, disorganized though and uncontrolled hostility/excitement factors.
Maintenance treatment with brexpiprazole was associated with a significantly longer time to exacerbation than placebo in a 52-week maintenance study (Fleischhacker et al., 2017). In the same study, brexpiprazole yielded significant benefit on measures of psychosocial, occupational and cognitive functioning (particularly attention/vigilance and visual learning). Consistently, brexpiprazole was associated with significant improvements in animal models of cognitive impairment associated with schizophrenia (Maeda et al., 2014a; Yoshimi et al., 2014; Yoshimi et al., 2015), aripiprazole, contrariwise, was not (Maeda et al., 2014a). This might hint at a specific advantage of brexpiprazole over aripiprazole in cognitive impairment (Citrome, 2014). No cognitive outcome was recorded in short-term trials and no head-to-head comparison with aripiprazole has been undertaken though.
Brexpiprazole showed a good safety and tolerability profile. The only common adverse event was weight gain. A mean gain of ~1 kg greater than placebo was observed in short term studies. The mean change in body weight decreased for both brexpiprazole and placebo in the long-term. Akathisia was not significantly associated with brexpiprazole relatively to placebo and showed a dose-dependent pattern, occurring more frequently at higher doses. Most cases were mild or moderate in severity and did not result in treatment discontinuation. Other adverse effects such as headache, insomnia, sedation, agitation, diarrhea, nausea and dyspepsia were also all comparable to placebo. Effects on glucose and lipids were generally small. Minimal effects on prolactin were observed and no clinically relevant effects on the QTc interval were evident.

3.2 Major Depressive Disorder

Two studies (Thase et al., 2015a; Thase et al., 2015b) established brexpiprazole efficacy as adjunctive therapy to antidepressant treatment in MDD patients who failed at least one previous adequate antidepressant trial, with a pooled NNT of 12 (95% CI 8-26) (Citrome, 2015b) (Table 4). Brexpiprazole may be particularly useful in patients requiring a sedative pharmacological profile, such as patients with irritability (Fava et al., 2017)

and anxious distress (Hobart et al., 2018). Lastly, adjunctive brexpiprazole improved physiologic measures of sleep and daytime alertness in patients with inadequate response to antidepressant treatment and sleep disturbances (Krystal et al., 2016).

The overall safety and tolerability profile for adjunctive brexpiprazole was mainly consistent with what described in patients with schizophrenia. Akathisia was more frequently reported in MDD trials compared to schizophrenia trials and, alongside weight gain, was recorded as common adverse reaction.

4. Cariprazine

Cariprazine is approved for the acute and maintenance treatment of schizophrenia (FDA, 2015; EMA, 2017) and for the acute treatment of manic or mixed episodes associated with bipolar I disorder (FDA, 2015) (Table 1). It is a dopamine D3-preferring D3/D2 receptor partial agonist. Its receptor biding profile (Table 2) is similar to aripiprazole, except for D3 tenfold greater affinity than that for D2, so high that extremely small doses are sufficient to get maximal D3 occupancy (Kiss et al., 2010). D3 receptor blockade could have pro-cognitive and antidepressant effects as well as potential effects on negative symptoms of schizophrenia (Gross et al., 2013). This property is unique of cariprazine since D3 receptor occupancy is low or negligible with other SGAs, as reported by positron emission tomography studies (Girgis et al., 2015; Graff-Guerrero et al., 2009; Mizrahi et al., 2011).

Cariprazine metabolites, desmethyl-cariprazine and didesmethyl-cariprazine, have pharmacological properties similar to the parental drug but didesmethyl-cariprazine half-life is considerably longer (1-3 weeks vs. 2–4 days, approximately). Systemic exposure to didesmethyl-cariprazine is thus several times higher than that for cariprazine. Further characterization of didesmethyl-cariprazine is important as its long terminal half-life may allow the development of a once-weekly oral formulation, which could improve medication adherence. Due to its long-life metabolite, a missed dose of cariprazine may be associated, theoretically, with lower risk from sub-optimal receptor binding as compared to a drug with a shorter half-life. On the flip-side, the longer half-life may also imply a prolonged duration of hypothetical adverse events, beyond discontinuation of treatment (Citrome, 2013).

4.1 Schizophrenia

Four trials established cariprazine efficacy in acute schizophrenia (Durgam et al., 2015a; Durgam et al., 2016b; Durgam et al., 2014; Kane et al., 2015b) (Table 5). Cariprazine primary asset is its action on negative symptoms. After a post hoc analysis suggested this therapeutic effect (Debelle et al., 2015), a double blind, randomized, risperidone-controlled 6 months study was designed to specifically assess cariprazine effect on negative symptoms. This study supported the efficacy of cariprazine as compared risperidone in the treatment of predominant negative symptoms of schizophrenia (Nemeth et al., 2017). The separation between the two drugs emerged only after 14 weeks, which is significantly later than in studies in patients with acute, positive

symptoms, implying a potentially different mechanism of action. Improvement in PANSS total and positive subscale scores was similar between cariprazine and risperidone. Furthermore, the superiority of cariprazine over placebo and aripiprazole in improving PANSS-factor score for negative symptoms (PANSS-FSNS) emerged in post-hoc analyses of data pooled from two randomized, double-blind, placebo- and active-controlled studies in patients with acute schizophrenia with moderate/severe negative symptoms and no predominance of positive symptoms. The benefit of cariprazine on negative symptoms was at least partially independent from improvements in positive symptoms and EPS (Earley et al., 2018b). A meta-analysis confirmed this specific domain of efficacy (Corponi et al., 2017) and it also suggested that young patients with a relatively short history of disease may benefit the most from cariprazine. However, this meta-analysis included short-term studies which are more likely to capture secondary negative symptoms, i.e. a consequence of positive symptoms, depression or antipsychotics side effects. Hostility is another symptom domain targeted by cariprazine, as found by post-hoc analyses of the three positive trials (Citrome et al., 2016). Notably, this effect was partially independent from PANSS positive symptom items and independent from sedation. On the flipside, the impact on acute positive symptoms appears modest in comparison to other SGAs such as risperidone and olanzapine (Corponi et al., 2017).

Cariprazine is also a viable option for long-term treatment as showed by a 26- to 72-week study investigating time to first relapse in schizophrenia (Durgam et al., 2016a). Furthermore, a 6-months, risperidone-controlled study ascertained that cariprazine was significantly more efficacious than risperidone in improving PANSS-FSNS over 26 weeks in patients with predominantly negative symptoms (Nemeth et al., 2017).

Overall, cariprazine was safe and well tolerated. In a pooled post-hoc analysis (Earley et al., 2017), common adverse events with cariprazine were EPS and akathisia. A dose-response relationship was observed for akathisia and overall EPS. Small increases in mean body weight (~1 to 2 kg) versus placebo were observed. On the plus side, cariprazine does not elicit changes in metabolic parameters or prolactine levels and it does not prolong the QTc interval. Another noteworthy safety consideration is the low tendency to produce sedation and somnolence. Tolerability data over longer periods of time were similar to those observed in the 6-week trials (Durgam et al., 2015a; Durgam et al., 2016a; Durgam et al., 2016b; Durgam et al., 2014; Kane et al., 2015b; Nemeth et al., 2017).

4.2 Manic or mixed episodes

Three trials demonstrated cariprazine efficacy in adult patients with acute manic or mixed episodes associated with bipolar I disorder, with significantly higher response and remission rates compared to placebo [FC-f2](Calabrese et al., 2015; Durgam et al., 2015b; Sachs et al., 2015). Importantly, improvement in manic symptoms was not associated with worsening depressive symptom or emerging depressive episodes (Earley et al., 2018a). In post hoc analyses (Vieta et al., 2015), statistically significant differences in favor of cariprazine over placebo were observed on every item of the Young Mania Rating Scale (YMRS) (Young et al., 1978), effect sizes being quite robust (Cohen's d range, 0.31-0.55). The impact was strongest on the

irritability item, which is an important aspect since many patients with acute mania have irritability as a predominant presenting feature (American Psychiatric Association, 2013). The safety profile in acute manic or mixed episodes matches the findings reported by studies in patients with schizophrenia. No new safety or tolerability concern emerged in a 16-week open-label study (Ketter et al., 2018).

5. Lumateperone

Lumateperone is a first-in-class drug providing selective and simultaneous modulation of serotonin, dopamine and glutamate. It is in the approval phase for schizophrenia and in phase III clinical development for the treatment of bipolar depression and agitation associated with dementia, including Alzheimer's disease. Lumateperone is a high-affinity 5-HT2A receptor antagonist, having 60-fold higher affinity for these receptors compared to D2 receptors. As the dose is increased, it acts at D2 receptors as a presynaptic partial agonist and post-synaptic antagonist with functional mesolimbic and mesocortical selectivity. In addition, lumateperone acts as inhibitor at serotonin transporter and increases phosphorylation of glutamatergic N-methyl-D-aspartate (NMDA) GluN2B receptors in a mesolimbic-specific manner (Snyder et al., 2015). These unique pharmacological features predict enhancement of sleep and reduction of agitation and aggression at lower doses, antipsychotic and antidepressant efficacy at higher doses. Three clinical trials evaluated lumateperone in acute schizophrenia (ClinicalTrials.gov identifiers: NCT01499563, NCT02282761 and NCT02469155). NCT02469155 reported negative results and an unusually high placebo response was observed in this study (-15.1 points change from baseline on PANSS total score in contrast to -7.4 points in NCT01499563 and -10.3 points in NCT02282761). In the other two studies (NCT01499563 and NCT02282761) lumateperone 60 mg/day demonstrated statistically significant superiority over placebo, while lumateperone 120 mg/day did not (NCT02282761), supposedly due to the higher frequency of somnolence/sedation. In preplanned and post-hoc subgroup analyses lumateperone 60 mg was associated with significant improvement across a broad range of symptoms including general psychopathology, depressive symptoms and measures of social function. Moreover, cognition enhancement may be anticipated since lumateperone increases glutamatergic transmission, but this was still not evaluated in patients with schizophrenia. Thus, based on the pharmacodynamic profile of this drug and preliminary clinical data, depressive and negative symptoms as well as cognition may be the specific domains of lumateperone action. Specifically designed trials are needed to test this hypothesis.

Lumateperone showed good tolerability with a safety profile similar to placebo for motor disturbances, prolactin changes, weight gain, cardiovascular and metabolic side effects. Sedation/somnolence was a common adverse event. Data on longer-term safety and tolerability are not available.

Trials evaluating lumateperone in bipolar depression are currently in the recruitment phase.

5. Discussion

SGAs represent valid alternatives to first generation antipsychotics with similar efficacy but different side effect profiles and different action on specific symptom domains. The first developed SGAs were characterized by reduced risk of extrapyramidal side effects, reduced sedation, and less prolactin dysfunction (Solmi et al., 2017). However, the challenge was to address other relevant adverse effects, i.e. weight gain and metabolic syndrome, and to improve negative symptoms and cognitive deficits (Pompili et al., 2017). The novel SGAs discussed in this review were developed to address these unmet needs. Appreciating their efficacy/safety features is of great importance in the clinical practice in order to identify the specific subsets of patients that may benefit the most from these medications. The present paper mainly drew from indirect comparisons as well as pre-clinical data to outline the overall place in psychiatric pharmacotherapy for each of the novel SGAs. Appropriately designed head-to-head clinical trials will be necessary to fully appreciate and accurately establish the extent to which such agents are endowed with specific domains of efficacy and drawbacks as compared to other therapeutic options.

Lurasidone was among the 15 antipsychotics for acute schizophrenia evaluated in the most comprehensive meta-analysis to date (Leucht et al., 2013). It had the lowest risk for ECG abnormalities and was one of only three agents (along with haloperidol and ziprasidone) with placebo-like effects on weight. While PANSS total improvement may not be outstanding in comparison to other SGAs, potential for prominent positive symptoms (Potkin et al., 2016), cognitive enhancement (Potkin et al., 2011) and depressive symptoms improvement (Nasrallah et al., 2015) make lurasidone appropriate for patients where such aspects are of clinical relevance. As suggested by NNH, the tolerability profile is good, with somnolence, akathisia, nausea, parkinsonism and insomnia (Sanford, 2013) being the most frequent adverse events. The starting dose falls at the bottom of the recommended therapeutic range, titration might nonetheless be needed since a dose-dependent efficacy gradient was observed (Kay et al., 1987; Loebel et al., 2016). However, dose increases are associated with higher risk of akathisia and EPS. Lurasidone is also in the pharmacologic armamentarium for mood disorders: monotherapy or combination therapy with lithium or valproate is recommended as a first-line treatment for acute bipolar depression, according to the most recently updated guidelines, issued by the Canadian Network for Mood and Anxiety Disorders (Yatham et al., 2018). Prior to lurasidone, the FDA-approved arsenal for bipolar depression was limited to quetiapine and olanzapine-fluoxetine combination, while at present only quetiapine is EMA-licensed for this condition. Albeit widely used in the clinical practice (Baldessarini et al., 2007), not only do antidepressants show flimsy evidence of efficacy in bipolar depression but they may also be detrimental in terms of switch to mania/hypomania, rapid cycling, suicidal behavior (Pacchiarotti et al., 2013). Antidepressants shortcomings in bipolar depression likely reflect physiopathological underpinnings different from the ones of unipolar depression. Of interest, lurasidone is a good fit for one current theory which postulates that, unlike unipolar depression, norepinephrine reuptake and 5-HT1A agonism are heavily implicated as core deficits in bipolar depression (Fountoulakis et al., 2015). Lastly, preliminary evidence provided by one trial demonstrated that lurasidone is efficacious and safe in MDD with mixed features (Suppes et al., 2016b).

Brexpiprazole and cariprazine, along with aripiprazole, belong to the D2 receptor partial agonists. These agents allow to obtain clinical efficacy while minimizing dopamine-related adverse events, through the maintenance of a partial activation threshold that mimics the natural tonic dopamine signal in the brain (Lieberman, 2004). Although all three agents are dosed once daily, only for aripiprazole the recommended starting dose is the same as the recommended maintenance dose in both schizophrenia and mania. For cariprazine, dose titration may not be needed in schizophrenia, while titration is needed when treating mania. Regarding brexpiprazole, titration is recommended for both schizophrenia and MDD. Availability as injectable formulation and as generic product currently are strong points in favor of aripiprazole. While accurately designed head-to-head trials are needed to conclusively establish efficacy/safety differences, some indications can be given. All three agents are safe and tolerable: all the NNH values for weight gain, somnolence and akathisia were >10, with the exception of mood disorders, where in general, akathisia was more frequently observed. Despite dopamine partial agonists share similar adverse events, the propensity for these varies: for the indication of schizophrenia, the rank order for propensity for weight gain appears to be brexpiprazole > aripiprazole > cariprazine, for somnolence aripiprazole > brexpiprazole > cariprazine, and for akathisia cariprazine > aripiprazole > brexpiprazole (Citrome, 2015a). In terms of efficacy on specific symptom domains, brexpiprazole may target cognitive impairment in schizophrenia more favorably than aripiprazole, as suggested by animal models (Maeda et al., 2014a; Yoshimi et al., 2014; Yoshimi et al., 2015), but clinical trials using cognition as primary outcome are necessary to support that claim (Miskowiak et al., 2017). A meta-analysis (Romeo et al., 2018) reported that brexpiprazole has comparable efficacy to aripiprazole as augmentation in MDD, but a more anxiolytic and sedative profile (Fava et al., 2017; Hobart et al., 2018; Krystal et al., 2016). Cariprazine most important area of action in schizophrenia is negative symptomatology: a medium term trial specifically designed to assess primary negative symptoms (Nemeth et al., 2017) demonstrated superiority over risperidone (Nemeth et al., 2017). This feature differentiates cariprazine from aripiprazole, which did not demonstrate efficacy against negative symptoms (Earley et al., 2018b). This suggests that cariprazine unique D3-greater-than-D2 affinity underlies its impact on negative symptoms, while a profile unbalanced towards D2 antagonism primarily benefits schizophrenia positive symptoms (Gross et al., 2013). In a meta-analysis (Romeo et al., 2018) cariprazine had similar effect size to high-dose aripiprazole in treating mania and may specifically address irritability.

Lumateperone is a first-in-class drug that selectively and simultaneously modulates serotonin, dopamine and glutamate. In December 2018 a New Drug Application for the treatment of schizophrenia was accepted by the FDA. Preliminary data suggest that depressive and negative symptoms improvement as well as cognition enhancement may be the hallmark of lumateperone action. Most commonly encountered adverse event was sedation/somnolence, while liability to EPS, prolactin changes, weight gain, cardiovascular and metabolic abnormalities was similar to placebo. The preliminary results with lumateperone lend support to 5-HT2A antagonism, lumateperone's most prominent feature, as addressing positive, negative and affective symptoms of schizophrenia (Davis and Correll, 2016; Eggers, 2013).

In conclusion, there is no one-fits-all antipsychotic. Specific strengths and weaknesses distinguish each compound. Thus, in order to capitalize on the various agents optimizing the trade-off between efficacy and side effects burden, clinicians should be familiar with the specificity profile of novel antipsychotics and prescribe them accordingly to each patient's clinical profile. The new antipsychotics discussed in this review have overall a good tolerability in terms of cardiometabolic side effects and risk of hyperprolactinaemia, while akathisia risk remains still significant with lurasidone and cariprazine and sedation/somnolence with lumateperone. The main domains of improved efficacy of lurasidone compared to other SGAs in schizophrenia treatment are represented by depressive symptoms (Nasrallah et al., 2015) and cognitive dysfunction (Potkin et al., 2011), whereas cariprazine specific advantage, over aripiprazole as well (Earley et al., 2018b), is against negative symptoms (Nemeth et al., 2017). On the other hand, lurasidone (Leucht et al., 2013) and cariprazine (Corponi et al., 2017) may be less effective on overall psychotic symptomatology in acute schizophrenia compared to other SGAs, such as risperidone and olanzapine. Animal models hint that brexpiprazole may address cognitive impairment in schizophrenia to a greater extent than aripiprazole (Maeda et al., 2014a; Yoshimi et al., 2014; Yoshimi et al., 2015). Finally, it useful to mention that personalized antipsychotic prescription would benefit from the use of a different nomenclature based on pharmacological domains and modes of action and not on drug main indication. This was recently provided by the Neuroscience-based Nomenclature (NbN) which helps in moving forward compared to the Anatomical-Therapeutic-Chemical (ATC) classification and the arbitrary first vs. second generation antipsychotic distinction. Implementing the NbN would provide clinicians immediate information that can guide treatment choice based on the symptoms domains targeted by specific pharmacological domains and modes of action (Zohar et al., 2015).

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Table 1. Lurasidone, brexpiprazole and cariprazine clinic profile. EMA: European Medicines Agency; FDA: Food and Drug Administration; * incidence ≥ 5% and at least twice the rate of placebo.

	Approved indications	Starting dose	Recommended dose	Specific efficacy domains	Common side effects*
Lurasidone	Acute and maintenance treatment of schizophrenia (FDA, EMA)	40 mg/day (FDA) 37 mg/day (EMA)	40-160 mg/day (FDA) 37-148 mg/day (EMA)	• Cognition (speed of processing, visual learning, working memory, reasoning/problem solving and social cognition) • Depressive symptoms	• Somnolence • Akathisia • Nausea • Parkinsonism • Insomnia
	Depressive Episodes associated with Bipolar I Disorder (Bipolar Depression), as monotherapy and as adjunctive therapy with lithium or valproate (FDA)	20 mg/day (FDA)	20-120 mg/day (FDA)	• Efficacious also if sub-syndromal hypomania at baseline	
Brex pipr	Acute and maintenance treatment of	1 mg/day (FDA, EMA)	2-4 mg/day (FDA, EMA)	• Cognition (attention/vigilance, visual learning)	• Weight gain

	schizophrenia (FDA, EMA)				
	Adjunctive therapy to antidepressant for the treatment of Major Depressive Disorder (FDA)	0.5 mg/day or 1 mg/day (FDA)	2 mg/day (FDA)	• Anxiety • Irritability	
Cariprazine	Acute and maintenance treatment of schizophrenia (FDA, EMA)	1.5 mg/day (FDA, EMA)	1.5-6 mg/day (FDA, EMA)	• Negative symptoms • Hostility	• Extrapyramidal symptoms • Akathisia
	Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults (FDA)	1.5 mg/day (FDA)	3-6 mg/day (FDA)	• Irritability	

Table 2. Lurasidone (a), brexpiprazole (b), cariprazine (c) pharmacokinetic and pharmacodynamic profile. AUC: area under the curve; C_{max}: maximum concentration; CYP, cytochrome P450; K_i: inhibitor constant; T_{max}: time to C_{max}

(a)

Pharmacokinetic Profile		**Pharmacodynamic Profile**		
Bioavailability	9-19%	Receptors	K_i (nM)	Functional activities
T_{max}	1-3 Hours	5-HT_{1A}	6.4	Partial agonism
Food	Administration with food increases the AUC and the C_{max} approximately 2- and 3-times approximately. At least 350 kcal of food, regardless of the fat content, is recommended.	5-HT_{2A}	0.5	Antagonism
Volume of distribution	6173 L	5-HT_7	0.495	Antagonism
Protein binding	>99%	D_2	1	Antagonism
Breast milk concentrations	Present in milk rat; it is not known whether this drug is excreted in human milk	α_{2A}	40.7	Antagonism
Metabolism	Hepatic by CYP3A4	α_{2C}	10.8	Antagonism
Elimination	Primarily by hepatic metabolism	H_1	>1000	Antagonism
Half-life	18 Hours	M_1	>1000	Antagonism
Time to steady-state concentration	7 Days			
Special populations	A dose adjustment is recommended for patients with moderate to severe hepatic/renal impairment			

(b)

Pharmacokinetic Profile		Pharmacodynamic Profile		
Bioavailability	95%	Receptors	K_i (nM)	Functional activities
T_{max}	4 Hours	5-HT_{1A}	0.12	Partial agonism
Food	No effect on C_{max} or AUC	5-HT_{2A}	0.47	Antagonism
Volume of distribution	1.56 ± 0.42 L/kg following intravenous administartion	5-HT_{2B}	1.9	Antagonism
Protein binding	>99%	5-HT_7	3.7	Antagonism
Breast milk concentrations	Present in milk rat; it is not known whether this drug is excreted in human milk	D_{2L}	0.3	Partial agonism
Metabolism	Hepatic by CYP3A4 and CYP2D6	D_3	1.1	Partial agonism
Elimination	Primarily by hepatic metabolism	α_{1B}	0.17	Antagonism
Half-life	91 Hours	α_{2C}	0.59	Antagonism
Time to steady-state concentration	10-12 Days	H_1	19	Antagonism
Special populations	A dose adjustment is recommended for patients with moderate to severe hepatic/renal impairment			

(c)

Pharmacokinetic Profile		Pharmacodynamic Profile		
Bioavailability	95%	Receptors	K_i (nM)	Functional activities
T_{max}	3-6 Hours	5-HT_{1A}	2.6	Partial agonism
Food	No effect on C_{max} or AUC	5-HT_{2A}	18.8	Antagonism
Volume of distribution	916 L	5-HT_{2B}	0.58	Antagonism
Protein binding	97%	5-HT_7	3.7	Antagonism
Breast milk concentrations	Present in milk rat; it is not known whether this drug is excreted in human milk	D_2	0.49	Partial agonism
Metabolism	Hepatic by CYP3A4 and CYP2D6	D_3	0.085	Partial agonism
Elimination	Primarily by hepatic metabolism	α_{1A}	155	Antagonism
Half-life	2-4 Days	H_1	23.2	Antagonism
Time to steady-state concentration	10-20 Days			
Special populations	No dose adjustment is recommended for patients with mild to moderate hepatic/renal impairment; cariprazine is not recommended in patients with severe hepatic/renal impairment			

Table 3. Lurasidone number needed to treat and number needed to harm for common adverse events vs placebo. MADRS: Montgomery Asberg Depression Rating Scale; NNH: number needed to harm; NNT: number needed to treat; ns=not significant (the 95% CI contains "infinity"); PANSS: Positive and Negative Syndrome Scale; *a negative NNH denotes an advantage for study medication regarding the potential harm.

	Lurasidone					
	Dose		40 mg/day	80 mg/day	120 mg/day	160 mg/day
Schizophrenia Citrome, 2012	NNT (95% CI)	Response (≥30% Reduction from Baseline in PANSS Total Score)	6 (5-10)	6 (5-10)	7 (5-12)	4 (3-5)
	NNH (95% CI)	Akathisia	12 (9–20)	10 (8–16)	6 (5–7)	22 (ns)
		Nausea	19 (11–58)	17 (11–43)	14 (9–33)	82 (ns)
		Sedation	17 (11–38)	20 (12–52)	13 (9–26)	-38 (ns)*
		Somnolence	19 (12–51)	23 (14–71)	10 (7–16)	36 (ns)
		Insomnia	67 (ns)	58 (ns)	68 (ns)	-198 (ns)*
		Parkinsonism	19 (13–39)	30 (18–98)	13 (9–23)	20 (11–198)
		Weight Increase ≥7% from Baseline	47 (ns)	43 (ns)	70 (ns)	150 (ns)
	Dose		Adjunctive 20-120 mg/day	Monotherapy 20-60 mg/day	Monotherapy 80-120 mg/day	
Depressive Episodes associated with Bipolar I Disorder Citrome et al., 2014a	NNT (95% CI)	Response (≥50% Reduction from Baseline in MADRS Total Score)	7 (4-24)	5 (3-8)	5 (4-11)	
		Remission (Final MADRS Total Score ≤12)	7 (4-23)	6 (4-14)	7 (4-21)	
	NNH (95% CI)	Akathisia	30 (ns)	18 (10–124)	12 (8–32)	
		Nausea	16 (ns)	39 (ns)	11 (6–39)	
		Somnolence (hypersomnia, sedation, somnolence)	19 (ns)	130 (ns)	14 (8–126)	
		Insomnia	64 (ns)	-29 (ns)*	-58 (ns)*	
		Extrapyramidal symptoms	19 (ns)	40 (ns)	16 (9-60)	
		Weight Increase ≥7% from Baseline	42 (ns)	29 (15–52318)	5550 (ns)	

Table 4. Brexpiprazole number needed to treat and number needed to harm for common adverse events vs placebo. MADRS: Montgomery Asberg Depression Rating Scale; NNH: number needed to harm; NNT: number needed to treat; ns=not significant (the 95% CI contains "infinity"); PANSS: Positive and Negative Syndrome Scale.

	Brexpiprazole		
	Dose		2-4 mg/day
Schizophrenia Citrome, 2015b	NNT (95% CI)	Response (≥30% Reduction from Baseline in PANSS Total Score)	7 (5–12)
	NNH (95% CI)	Akathisia	112 (ns)
		Sedation	78 (ns)
		Weight Increase ≥7% from Baseline	50 (26–1773)
	Dose		2-3 mg/day
Adjunctive therapy to antidepressant for the treatment of Major Depressive Disorder Citrome, 2015b	NNT (95% CI)	Response (≥50% Reduction from Baseline in MADRS Total Score)	12 (8–26)
		Remission (Final MADRS Total Score ≤12)	21 (12–138)
	NNH (95% CI)	Akathisia	15 (11–23)
		Somnolence (hypersomnia, sedation, somnolence)	24 (17–42)
		Weight Increase ≥7% from Baseline	22 (15–42)

Table 5. Cariprazine number needed to treat and number needed to harm for common adverse events vs placebo. ND, no difference or rate with medication is lower than rate with placebo; NNH: number needed to harm; NNT: number needed to treat; ns=not significant (the 95% CI contains "infinity"); PANSS: Positive and Negative Syndrome Scale; YMRS: Young Mania Rating Scale

	Cariprazine		
	Dose		1.5-6 mg/day
Schizophrenia Citrome, 2015a	NNT (95% CI)	Response (≥30% Reduction from Baseline in PANSS Total Score)	10 (7-19)

	Dose		1.5-3 mg/day	4.5-6 mg/day
	NNH (95% CI)	Akathisia	20 (13–48)	12 (9–18)
		Nausea	ND	50 (ns)
		Somnolence and sedation	ND	34 (18–610)
		Insomnia	100 (ns)	50 (ns)
		Extrapyramidal symptoms	15 (10–31)	10 (7–15)
		Weight Increase ≥7% from Baseline	50 (28–287)	100 (ns)
	Dose		3-6 mg/day	
Manic or Mixed Episodes Associated with Bipolar I Disorder Citrome, 2015a	NNT (95% CI)	Response (≥50% Reduction from Baseline in YMRS Total Score)	5 (4-8)	
	NNH (95% CI)	Akathisia	7 (5-9)	
		Nausea	24 (12-363)	
		Insomnia	ND	
		Extrapyramidal symptoms	15 (9-35)	
		Weight Increase ≥7% from Baseline	ND	