Brexpiprazole is a new atypical antipsychotic for schizophrenia management and as adjunct in major depressive disorder (MDD). We searched randomized controlled trials (RCT) to review brexpiprazole efficacy and tolerability in acute management of schizophrenia and MDD using PubMed, EUDRACT, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials. A meta-analysis was conducted using the identified 14 RCT to assess its efficacy using positive and negative symptom scale (PANSS), clinical global impressions – severity of illness (CGI-S), personal and social performance scale (PSP), Montgomery–Åsberg depression rating scale (MADRS), Sheehan disability scale (SDS) and Hamilton depression rating scale (HDRS17). The mean difference comparing brexpiprazole and placebo were PANSS −4.48, CGI-S −0.23 and PSP 3.24 favoring brexpiprazole. Compared to aripiprazole and quetiapine, brexpiprazole showed similar efficacy. In MDD, brexpiprazole showed efficacy compared to placebo demonstrated by MADRS −1.25, SDS −0.37 and HDRS17 −1.28. Brexpiprazole was associated with side effects including akathisia risk ratio (RR) = 1.72; weight increase RR = 2.74 and somnolence RR = 1.87. Compared to 4 mg, brexpiprazole 2 mg was associated with less risk of akathisia and somnolence. Brexpiprazole demonstrated significant improvements in schizophrenia and MDD and is well-tolerated; however, associated with akathisia and somnolence. These findings will guide psychiatrists and pharmacists in their clinical role for supporting psychiatric patients care. Int Clin Psychopharmacol 35: 119–128 Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

International Clinical Psychopharmacology 2020, 35:119–128

Keywords: brexpiprazole, schizophrenia, major depressive disorder, psychotic disorders, akathisia

Introduction
Schizophrenia is a chronic psychiatric disorder, where patient’s perception and behavior are significantly altered; with diagnosis confirmed by a clinical psychiatrist after full psychiatric assessment (Reyad and Mishriky, 2019). In England, psychotic disorders annual incidence is 32 cases per 100 000 people, 15 of them schizophrenic (Kirkbride et al., 2012). The etiology of schizophrenia is not fully understood with genetic and environmental factors involved (Andreasen, 1999) with 80% of patients have a relapse within 5 years of recovery (Robinson et al., 1999).

There are two main groups of antipsychotics, typical (first generation) and atypical (second generation). First generation antipsychotics are dopamine (D2) receptors antagonists and could block histamine, muscarinic and alpha-1 receptors (Ayano, 2016). Second generation antipsychotics (SGA) are serotonin-dopamine antagonists (Abi-Dargham and Laruelle, 2005). 5HT-2A antagonism can increase dopaminergic neurotransmission in the nigrostriatal pathway, which reduces the risk of extrapyramidal symptoms such as akathisia and tardive dyskinesia (Correll et al., 2004). SGA are associated with side effects such as weight gain, hyperprolactinemia and glucose intolerance (Sapra et al., 2016; Ndukwe and Nishtala, 2017).

Brexpiprazole (Rxulti, Rexulti) is a new atypical antipsychotic drug approved in 2015 by the FDA for the treatment of schizophrenia and as adjunct in major depressive disorder (MDD) (Corponi et al., 2019). Brexpiprazole is a partial agonist of dopamine D2 and D3 and serotonin 5HT1A receptors similar to cariprazine, and an antagonist of 5HT2A, 5HT2B, 5HT7 and adrenergic receptors (Ward and Citrome, 2019). It possesses a high affinity for D2, 5HT1A, 5HT2A, α1B and α2C receptors, and moderate affinity for histamine H1 receptors with very low affinity for muscarinic M1 receptors (Ki > 1000 nM) (Maeda et al., 2014; Ward and Citrome, 2019). Brexpiprazole in rats led to low risk of D2 receptor sensitization while inhibiting the rebound phenomena related to D2 and 5-HT2A receptors (Amada et al., 2019). Compared to aripiprazole, brexpiprazole has lower D2 intrinsic activity, although has a more potent serotonergic 5-HT2A antagonism (Fornaro et al., 2019). Brexpiprazole also induced neurite outgrowth through 5-HT1A and 5-HT2A receptors and subsequent Ca2+ signaling (Ishima et al., 2015).
Brexpiprazole completely inhibited 5-HT neurons firing via 5-HT1A autoreceptors agonism and was more potent than aripiprazole (Oosterhof et al., 2014). The high affinity for 5HT1A and 5HT2A receptors paired with partial D2-agonist activity leads to a favorable side effects profile (Frampton, 2019). Brexpiprazole also inhibited rhAChE activity by >20% in a concentration-dependent manner with effects more potent than other antipsychotics (Obara et al., 2019). Brexpiprazole with fluoxetine produced a rapid antidepressant effect in inflammation model of depression with improved alterations in BDNF-TrkB signaling and dendritic spine density in the prefrontal cortex (Ma et al., 2017).

Brexpiprazole is primarily metabolized by CYP3A4 and CYP2D6 with inactive major metabolite, while mutations around CYP3A4 active site might lead to enzymatic activity loss (Chen et al., 2019). No information is available on the use of brexpiprazole during breastfeeding (Brexpiprazole, 2006). Brexpiprazole C_{max} and AUC showed accumulation of 2.5- to 5.5-fold on day 14, compared to day 1 with median t_{max} 4–5 hours and mean elimination half-life 52–92 hours (Ishigooka et al., 2018a). Brexpiprazole target dose is 2–4 mg/d in schizophrenia and 2 mg in depression with dose adjustments considered in hepatic or renal dysfunction (Parikh et al., 2017).

In this systematic review/meta-analysis, we investigate the efficacy, tolerability and safety of Brexpiprazole in adult patients (≥18 years) suffering from different psychiatric conditions using published randomized controlled trials (RCT). This meta-analysis update our knowledge on the role of brexpiprazole in managing schizophrenia and depressive symptoms while discussing recent progress in establishing its possible role in managing personality disorders, post-traumatic stress disorder (PTSD) and aggression in Alzheimer disease (AD).

Methods
Study population and search strategy
The study population includes adult patients (18–65 years old) taking part in phase II/III RCT’s assigned to either brexpiprazole 1–4 mg/d, or placebo or active control SGA (quetiapine, aripiprazole) for the management of schizophrenia and MDD. A literature search was performed using the search terms ‘brexpiprazole’ to search PubMed, EUDRACT, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials. No restrictions on study size, year of study or duration were set. Titles were screened for relevance and duplicates were removed. Abstracts were then screened before the remaining relevant full texts were screened to see if they met the inclusion criteria (Fig. 1).

Inclusion and exclusion criteria
Published phase II and III RCT that investigate the tolerability, safety or efficacy of brexpiprazole in patients suffering from schizophrenia and MDD were included (Table 1). All RCTs were doubled blinded to reduce the risk of bias.

Outcome measures
The primary efficacy outcomes of brexpiprazole in schizophrenia were positive and negative syndrome scale (PANSS), PANSS negative and positive scores, PANSS excited component score, clinical global impressions – severity of illness score (CGI-S), clinical global impressions-improvement (CGI-I), personal and social performance scale (PSP) and response rate with mean changes from baseline recorded. Brexpiprazole treatment
groups (1–4 mg/d) were compared with placebo or active control, while brexpiprazole doses outside this range were excluded.

The primary efficacy outcomes of brexpiprazole in MDD were Montgomery–Åsberg depression rating scale (MADRS), Sheehan disability scale (SDS), CGI-S, CGI-I, Hamilton depression rating scale (HDRS17), MADRS response, MADRS remission, CGI-I response, response rate with mean changes from baseline recorded. Brexpiprazole treatment groups (1–4 mg/d) were compared with placebo or active control, while brexpiprazole doses outside this range were excluded. The primary tolerability and safety outcomes for brexpiprazole were discontinuation due to adverse effects and adverse events.

**Statistical methods**

Review Manager 5.3 (RevMan) along with the Cochrane Collaboration tool for assessing the risk of bias (Higgins et al., 2011; The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) were used to assess the levels of selection, performance, detection, attrition and reporting bias in each of the RCTs. ‘Characteristics of study’ tables were completed in RevMan for each of the individual studies and a summary table was created (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Funnels plots for each of the outcomes were also created (Guyatt et al., 2011a; Guyatt et al., 2011b; Sterne et al., 2011).

The inverse variance method with random effects model was used to calculate the mean differences (MD) for continuous outcomes (PANSS, PANSS Negative and Positive scores, PANSS excited component score, CGI-S, CGI-I, PSP, MADRS, SDS, HDRS17). The Mantel–Haenszel method with random effects model was used to calculate the risk ratio for all dichotomous outcomes (MADRS response, MADRS remission, CGI-I response, response rate, risk of discontinuation due to adverse effects and common side effects) (Egger et al., 2001). RevMan was used for all statistical analysis, 95% confidence intervals (CIs) were used for all outcomes and P-value <0.05 was regarded as statistically significant (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

### Table 1 Randomized controlled trials included in the meta-analysis (all are double blinded randomized controlled-trials)

| Study | Other ID | Design | Indication | Duration (weeks) | Dose range (mg/d) | Population |
|-------|----------|--------|------------|-----------------|-------------------|------------|
| Correll et al. (2015) | NCT01396421, 2011-002538-38 | Placebo control | Schizophrenia | 6 | Placebo | 184 |
| | | | | | Brex 2 mg/d | 182 |
| | | | | | Brex 4 mg/d | 180 |
| Ishigooka et al. (2018) | NCT01451164 | Placebo control | Schizophrenia | 6 | Placebo | 116 |
| | | | | | Brex 1 mg/d | 115 |
| | | | | | Brex 2 mg/d | 114 |
| | | | | | Brex 4 mg/d | 113 |
| | | | | | Brex 8 mg/d | 184 |
| Kane et al. (2015) | NCT01393613 | Placebo control | Schizophrenia | 6 | Placebo | 184 |
| | | | | | Brex 1 mg/d | 120 |
| | | | | | Brex 2 mg/d | 186 |
| | | | | | Brex 4 mg/d | 184 |
| NCT00905307 | Placebo | Schizophrenia | 6 | Placebo | 93 |
| | | | | | Brex 1 mg/d | 88 |
| | | | | | Brex 2.5 mg/d | 90 |
| | | | | | Brex 5 mg/d | 92 |
| NCT01810380 | Placebo Quetiapine controlled | Schizophrenia | 6 | Placebo | 163 |
| | | | | | Brex 2.4 mg/d | 151 |
| Citrome et al. (2016) | NCT02054702 | Aripiprazole controlled | Schizophrenia | 6 | Brex | 64 |
| | | | | | Arip | 33 |
| NCT02194933 | Double blinded | Schizophrenia | 6 | Brex 2 mg/d | 19 |
| | | | | | Brex 4 mg/d | 19 |
| NCT02196506, 2014-000062-22 | Placebo control | Adjunct in MDD | 6 | Placebo | 200 |
| | | | | | Brex 2 mg/d | 191 |
| Hobart et al. (2018) | NCT01727726, 2012-003948-67 | Placebo Quetiapine controlled | Adjunct in MDD | 6 | Placebo | 206 |
| | | | | | Brex 2–3 mg/d | 197 |
| | | | | | Que 150–300 mg/d | 100 |
| | | | | | Placebo | 178 |
| Thase et al. (2015) | NCT01360645 | Placebo control | Adjunct in MDD | 6 | Placebo | 175 |
| | | | | | Brex 2 mg/d | 175 |
| | | | | | Placebo | 203 |
| Thase et al. (2015b) | NCT01360632, 21011-001349-33 | Placebo control | Adjunct in MDD | 6 | Placebo | 203 |
| | | | | | Brex 1 mg/d | 211 |
| | | | | | Brex 3 mg/d | 213 |
| NCT01838681 | 2012-001380-76 | Placebo control | Adjunct in MDD | 6 | Placebo | 442 |
| | | | | | Brex 1–3 mg/d | 444 |
| NCT00797966 | Placebo control | Adjunct in MDD | 6 | Placebo | 126 |
| | | | | | Brex 1.5 mg/d | 121 |
| | | | | | Placebo | 187 |
| NCT01052077 | Placebo control | Adjunct in MDD | 6 | Placebo | 185 |

Ari, Aripiprazole; Brex, Brexpiprazole; MDD, major depressive disorder; Que, Quetiapine.
Results

Search results and included studies

Figure 1 shows the selection process of RCTs included. PubMed, EUDRACT, ClinicalTrials.gov and Cochrane Central Register of Controlled Trials were searched for ‘brexpiprazole’ giving 399 records in total. After removing duplicates and screening titles and abstracts, 19 studies were included in full text screening; while 14 RCTs met the inclusion criteria (seven for schizophrenia acute management and seven as adjunct in the management of MDD) (Correll et al., 2015; Kane et al., 2015; NCT01052077, 2015; NCT010505307, 2015; NCT01838681, 2017; NCT02194933, 2018; Hobart et al., 2018a; Hobart et al., 2018b; Ishigooka et al., 2018b) (Table 1).

Table 1 shows the characteristics of the included RCTs; all of them were double blinded. Treatment duration was 6 weeks in schizophrenia management and MDD and brexpiprazole dose ranged from 1 to 4 mg/d. Studies were undertaken in regions including USA, Russia, Ukraine and India with similar prevalence and incidence rates to the UK (Steel et al., 2014).

For the risk of bias, the sequence generation, allocation concealment and blinding were mostly with ‘unclear’ risk due to insufficient information. The patients in all the studies were randomly assigned and there was certain level of blinding for both participants and personnel. The domains relating to the completeness of data and reporting of outcomes were ‘low’ risk of bias (data not shown).

Efficacy of brexpiprazole in the management of schizophrenia

Seven RCTs for brexpiprazole role in schizophrenia management were included in this meta-analysis, five RCTs, where brexpiprazole was compared with placebo [including two trials (NCT0905307, 2015; NCT01810380, 2017) also containing active control] with a total of 1618 patients treated with brexpiprazole compared to 742 patients who received placebo and three RCTs, where brexpiprazole was compared with active control (NCT0905307, 2015; Citrome et al., 2016; NCT01810380, 2017) with a total of 486 patients treated with brexpiprazole compared to 236 patients who received active control. All the trials included in brexpiprazole role in schizophrenia management assessed PANSS, PANSS positive, PANSS negative, CGI-I, CGI-S, response rate, while Four RCTs assessed PSP (Fig. 2).

The mean change from baseline in PANSS total score was significantly greater for brexpiprazole compared to placebo, with a MD of −4.48 (95% CI −6.29 to −3.47) favoring brexpiprazole treatment (P < 0.00001) (Fig. 2a). The forest plot shows the MD for all the studies individually favor brexpiprazole, with low heterogeneity between the studies (x² = 10.5, I² = 0%). Similarly, PANSS positive score MD was significantly greater for brexpiprazole −0.99 (95% CI −1.45 to −0.52) favoring brexpiprazole treatment (P < 0.00001) (Fig. 2b) with moderate heterogeneity (x² = 20.3, I² = 46%), while PANSS negative score, MD −1.16 (95% CI −1.51 to −0.80) favoring brexpiprazole (P < 0.00001) (Fig. 2c).

CGI-S mean change from baseline was also significantly greater for brexpiprazole MD −0.23 (95% CI −0.31 to −0.15), P < 0.00001, which was clinically and statistically significant (Fig. 2d) with very low heterogeneity between the studies (I² = 0%). PANSS excited component, CGI-I and response rate also supported brexpiprazole efficacy in management of schizophrenia compared to placebo (Table 2).

Four RCTs measured the effect of brexpiprazole on PSP scale (Fig. 2e), showing positive effect MD 3.24 (95% CI 2.22–4.25), with very low heterogeneity (I² = 0%).

When compared to active control (aripiprazole and quetiapine), brexpiprazole showed similar efficacy to these two SGA as highlighted by the changes in PANSS, PANSS positive, PANSS negative, CGI-I, CGI-S, PSP scales and response rate (Fig. 2f and Table 2).

Brexpiprazole 2 and 4 mg doses were compared in four RCT (Correll et al., 2015; Kane et al., 2015; Ishigooka et al., 2018a; NCT02194933, 2018), where both brexpiprazole doses showed similar efficacy in schizophrenia management (Table 4).

Efficacy of brexpiprazole as adjunct therapy in the management of major depressive disorder

Seven RCTs for brexpiprazole role in MDD were included, where brexpiprazole was compared with placebo [including one trial (Hobart et al., 2018) containing active control] with a total of 1783 patients treated with brexpiprazole compared to 1577 patients who received placebo. All the seven trials assessed MADRS, SDS, CGI-S, MADRS response, MADRS remission, while six assessed CGI-I, CGI-I response and five assessed HDRS17 (Fig. 3 and Table 2).

The mean change from baseline in MADRS score was significantly greater for brexpiprazole compared to placebo, MD −1.25 (95% CI −1.74 to −0.76) favoring brexpiprazole (P < 0.00001) (Fig. 3a). All the studies individually favor brexpiprazole, with low heterogeneity between the studies (x² = 4.82, I² = 0%).

SDS mean change was significantly greater for brexpiprazole compared to placebo, with MD −0.37 (95% CI −0.52 to −0.21) (P < 0.00001) (Fig. 3b). Similar positive outcomes for brexpiprazole are highlighted as changes in CGI-I score [MD −0.19 (−0.27 to −0.11)] (Fig. 4c), HDRS17 [MD −1.28 (−1.79 to −0.76)] (Fig. 4d), CGI score [MD −0.21 (−0.30 to −0.12)], MADRS response...
Brexpiprazole in psychiatric disorders  Antoun et al. 123

Tolerability and safety of brexpiprazole compared to placebo in the management of schizophrenia and major depressive disorder

In a total of 3401 patients treated with brexpiprazole compared to 3514 patients who received placebo, the overall risk ratio for trial discontinuation due to adverse effects is 0.90 (0.74–1.10), P = 0.30 (Fig. 4a). There is variation among the studies with some favoring brexpiprazole, while others favoring placebo; with a moderate to high heterogeneity (I² = 53%). Brexpiprazole was associated with some side effects including akathisia risk ratio (RR) = 1.72 (1.38–2.14), P < 0.00001; weight increase RR = 2.74 (2.16–3.48), P < 0.00001 and somnolence RR = 1.87 (1.30–2.71), P = 0.0008 (Fig. 4 and Table 3).

Brexpiprazole in patients suffering from MDD was also associated with restlessness RR = 2.74 (2.16–3.48), P < 0.00001, increased appetite RR = 3.88 (1.47–10.3), P = 0.006 and in patients suffering from schizophrenia, brexpiprazole was associated with nausea RR = 2.58 (1.34–5.00), P = 0.005.

Funnel plots for Efficacy of Brexpiprazole in the management of Schizophrenia determined by the changes from baseline for (a) positive and negative syndrome scale (PANSS) total score compared with placebo; (b) PANSS positive compared with placebo; (c) PANSS negative compared with placebo; (d) clinical global impressions – severity of illness (CGI-S) compared with placebo; (e) personal and social performance (PSP) compared with placebo and (f) PANSS total score compared with active controls.
Compared to brexpiprazole 4 mg, brexpiprazole lower dose (2 mg) was associated with less risk of akathisia (22/501 compared to 32/496 (RR = 0.68); somnolence (7/387 vs. 13/383 (RR = 0.53) and trial withdrawal due to adverse events 38/482 vs. 48/477 (RR = 0.78) (Table 4).

**Tolerability and safety of brexpiprazole compared to active control in the management of schizophrenia and major depressive disorder**

Three trials were identified comparing brexpiprazole with active control (aripiprazole and quetiapine) in schizophrenia management and only one trial comparing
Brexpiprazole in psychiatric disorders
Antoun et al. 125

In a total of 683 patients treated with brexpiprazole compared to 336 patients who received active control, the overall risk ratio for trial discontinuation due to adverse effects is 1.43 (0.84–2.42), \( P = 0.19 \) (Table 3) and reduced risk of dry mouth RR = 0.27 (0.12–0.61), \( P = 0.002 \).

Table 3  Safety and tolerability of brexpiprazole

| Compared to | Outcome | RR (CI) | \( P \) value |
|-------------|---------|---------|--------------|
| Placebo     | Trial withdrawal due to adverse events | 0.90 (0.74–1.10) | 0.30 |
|             | Weight increase | 2.74 (2.16–3.48) | <0.00001* |
|             | Akathisia | 1.72 (1.38–2.14) | <0.00001* |
|             | Headache | 0.89 (0.76–1.05) | 0.18 |
|             | Somnolence | 1.87 (1.30–2.71) | 0.0008* |
|             | Insomnia | 0.86 (0.60–1.26) | 0.7 |
| Quetiapine  | Trial withdrawal due to adverse events | 1.67 (0.77–3.63) | 0.19 |
|             | Weight increase | 0.59 (0.32–1.08) | 0.09 |
|             | Akathisia | 1.73 (0.79–3.79) | 0.17 |
|             | Headache | 1.64 (0.61–4.36) | 0.32 |
|             | Somnolence | 0.25 (0.15–0.43) | <0.00001* |
|             | Dry mouth | 0.16 (0.05–0.48) | 0.001* |
| Aripiprazole| Trial withdrawal due to adverse events | 1.25 (0.61–2.58) | 0.54 |
|             | Weight increase | 1.22 (0.64–2.35) | 0.55 |
|             | Akathisia | 1.28 (0.69–2.38) | 0.43 |
|             | Headache | 1.38 (0.75–2.56) | 0.2 |
|             | Somnolence | 4.63 (0.86–24.9) | 0.07 |
|             | Dry mouth | 0.86 (0.22–3.38) | 0.83 |

*statistically significant.

CI, confidence interval; RR, risk ratio.
Brexpiprazole compared with quetiapine was associated with less risk of somnolence RR = 0.25 (0.15–0.43), P < 0.00001, dry mouth RR = 0.16 (0.05–0.48), P = 0.001 and weight increase RR = 0.59 (0.32–1.08), P = 0.09 and higher risk of Akathisia RR = 1.73 (0.79–3.79), P = 0.17 (Table 3).

Efficacy of brexpiprazole in management of other psychiatric disorders

Currently, there are several RCT trials studying the role of brexpiprazole in the management of bipolar disorders, PTSD, personality disorders and agitation in AD patients.

Brexpiprazole (3 mg/d) was effective in the management of irritability co-morbidity with MDD as shown in changes of Sheehan irritability scale total and item 1 (irritable mood) scores (NCT01942785) (Fava et al., 2016). A modest reduction in impulsivity was observed with brexpiprazole, but not aripiprazole (Citrome et al., 2016). Brexpiprazole has shown promising preliminary results in managing agitation in dementia (Garay et al., 2016), while improving cognitive dysfunction in animal models through 5-HT1A receptor-mediated increase in neuron activity (van den Munkhof et al., 2017). Open-label studies support the anxiolytic effects of adjunctive brexpiprazole as determined by changes in HAM-A scale (Davis et al., 2016).

Results from one RCT (NCT03257865) published recently regarding brexpiprazole efficacy in bipolar disorders [change from baseline in Young mania rating scale (YMRS) score at week 3 was −12.3 (162 patients) compared with −10.7 for placebo (168 patients) with increased risk of akathisia and insomnia for brexpiprazole] (NCT03257865, 2020); the clinical field is still awaiting another two trials (NCT03287869 and NCT03259555) results to be released to establish brexpiprazole role in bipolar disorders management.

In a pilot study, brexpiprazole was effective in bipolar depression with decrease in MADRS score and improvement of quality of life; however YMRS and cognitive scores did not change significantly (Brown et al., 2019).

In a rat model of PTSD, brexpiprazole with escitalopram exhibited a lower anxiety index and reduced startle amplitude (Cohen et al., 2018).

Discussion

This systematic review/meta-analysis investigated the efficacy and safety of brexpiprazole for the management of psychiatric conditions including schizophrenia and MDD using the available clinical trials. Brexpiprazole improved PANSS total and subscales – psychiatric scales used for measuring symptom severity in patients with psychosis. Brexpiprazole also showed significant improvements in CGI-S, MADRS and HDRS17. As far as our awareness, this meta-analysis covered the role of brexpiprazole in different psychiatric conditions and our results update and are in consistency with previous meta-analysis that showed brexpiprazole significant efficacy (Citrome, 2015). Our results confirm brexpiprazole superiority in management of schizophrenia over placebo (Table 2) with similar efficacy to SGA such as quetiapine and aripiprazole (Table 2). Our data also confirm brexpiprazole role as adjunct to antidepressant in improving functioning in patients with MDD (Hobart et al., 2019b) and are in agreement with another meta-analysis (Kishi et al., 2019), however, this meta-analysis did not include some of the recent trials included in our meta-analysis especially in the management of MDD. Brexpiprazole was well-tolerated and associated with moderate side effects such as increased risk of akathisia and somnolence, weight increase, dry mouth and nausea (Table 3 and Fig. 4). Brexpiprazole compared with quetiapine was associated with less risk of somnolence, dry mouth and weight increase (Table 3 and Fig. 4) as brexpiprazole has moderate affinity for histamine H1 receptors with very low affinity for muscarinic M1 receptors. Brexpiprazole 2 mg lower dose had similar efficacy to the higher 4 mg dose, but with less risk of akathisia and somnolence, in agreement with finding of a previous meta-analysis (Kishi et al., 2019). In clinical practice, brexpiprazole was associated with lower risks of discontinuation, hospital care and all-cause medical costs compared with quetiapine (Broder et al., 2019) and did not increase time from the start of the Q wave to the end of the T wave interval (Aronow and Shamliyan, 2018). Brexpiprazole is
Brexpiprazole in psychiatric disorders Antoun et al. 127

considered to have a favorable side effects profile mainly due to its high affinity for 5HT1A and 5HT2A receptors with partial D2-agonist activity (Frampton, 2019).

Adults with insufficient outcomes on aripiprazole or bupropion benefit from switching to brexpiprazole (Aladeen et al., 2018) and in patients with inadequate response to antidepressant and sleep disturbances, adjunctive brexpiprazole improved physiologic measures of sleep and daytime alertness (Krystal et al., 2016).

Currently, brexpiprazole is under investigation for management of other psychiatric conditions such as bipolar disorders, borderline personality, agitation in AD and PTSD and in combination with osimertinib was shown as a potential therapy for brain tumors with poor prognosis.

This systematic review/meta-analysis shows that brexpiprazole is well tolerated and significantly improves schizophrenia and MDD; however, the results need to be interpreted with caution as the treatment length was short (6 weeks), with several doses of brexpiprazole used with different efficacy and side effects profile. The scant evidence regarding long-term usage of brexpiprazole highlighted its association with mild or moderate in severity side effects such as weight increase (17.7%) – mean increase in body weight was 2.7 kg, somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%) and anxiety (5.2%) (Hobart et al., 2019a).

In elderly, adjunctive brexpiprazole was generally well-tolerated with improvements in depressive symptoms and social functioning (Lepola et al., 2018). Therefore, it is recommended that further research using different doses with long-treatment is conducted for a more comprehensive understanding of brexpiprazole role in the management of psychiatric conditions.

References

Abi-Dargham A, Laruelle M (2005). Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. Eur Psychiatry 20:15–27.

Aladeen T, Westphal E, Lee Y, Rong C, Rainka M, Capote H, McIntyre RS (2018). The use of brexpiprazole amongst individuals with insufficient outcomes with aripiprazole or bupropion: a case series. Perspect Psychiatr Care 54:507–513.

Amada N, Akazawa H, Ohgy Y, Maeda K, Sugino H, Kurahashi, N, et al. (2019). Brexpiprazole has a low risk of dopamine D2 receptor sensitization and inhibits its rebound phenomena related to D2 and serotonin 5-HT2A receptors in rats. Neuropsychopharmacol Rep 39:279–298.

Andreasen NC (1998). Understanding the causes of schizophrenia. The New England Journal of Medicine 340:845–847.

Anowon WS, Shamliyan TA (2018). Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. Annals of Translational Medicine 6:147.

Ayano G (2016). First generation antipsychotics: pharmacokinetics, pharmacodynamics, therapeutic effects and side effects: a review. Research & Reviews: Journal of Pharmacy 3:53–63.

Brexpiprazole. (2006). Drugs and Lactation Database (LactMed) (I. Bethesda (MD).

Broder MS, Greene M, Yan T, Chang E, Harty A, Yermilov I (2019). Medication adherence, health care utilization, and costs in patients with major depressive disorder initiating adjunctive atypical antipsychotic treatment. Clin Ther 41:221–232.

Brown ES, Khaleghi N, Van Enkevort E, Ileva E, Nakamura A, Holmes T, et al. (2019). A pilot study of brexpiprazole for bipolar depression. J Affect Disord 249:149–158.

Chen B, Zhang XD, Wen J, Zhang B, Chen D, Wang S, Hu GX (2019). Effects of 26 recombinant CYP3A4 variants on brexpiprazole metabolism. Chem Res Toxicol 33:172–180.

Citrone L (2015). Brexpiprazole for schizophrenia and as adjunct for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antipsychotic - what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? Int J Clin Pract 69:978–997.

Citrone L, Ota A, Nagamizu K, Perry P, Weiller E, Baker RA (2016). The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomized, exploratory study. Int Clin Psychopharmacol 31:192–201.

Cohen H, Zohar J, Kaplan Z, Amit J (2018). Adjunctive treatment with brexpiprazole and escitalopram reduces behavioral stress responses and increase hypothalamic NPY immunoreactivity in a rat model of PTSD-like symptoms. Eur Neuropsychopharmacol 28:63–74.

Corporini P, Fabbini C, Bitter I, Montgomery S, Vieta E, Kasper S, et al. (2019). Novel antipsychotics specificity profile: a clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. Eur Neuropsychopharmacol 29:971–985.

Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McCuaide RD, et al. (2015). Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6-week randomized, double-blind, placebo-controlled trial. Am J Psychiatry 172:870–880.

Correll CU, Leucht S, Kane JM (2004). Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. Am J Psychiatry 161:414–425.

Davis LL, Ota A, Perry P, Tsuneyoshi K, Weiller E, Baker RA (2016). Adjunctive brexpiprazole in patients with major depressive disorder and anxiety symptoms: an exploratory study. Brain Behav 6:00520.

Egger M, Smith GD, Altman DG (2001). In Egger M, Smith GD, Altman DG. Systematic Reviews: Meta-Analysis in Context. 2nd ed. London: BMJ Books.

Fava M, Menard F, Davidsen CK, Baker RA (2016). Adjunctive brexpiprazole in patients with major depressive disorder and irritability: an exploratory study. J Clin Psychiatry 77:1695–1701.

Fernando M, Fusco A, Anastasia A, Cattaneo CL, De Berardis D (2019). Brexpiprazole for treatment-resistant major depressive disorder. Expert Opin Pharmacother 20:1925–1933.

Frampton JE (2019). Brexpiprazole: a review in schizophrenia. Drugs 79:189–200.

Garay RP, Citrone L, Grossberg GT, Caveri I, Llorca PM (2018). Investigational drugs for treating agitation in persons with dementia. Expert Opin Investig Drugs 25:973–983.

Guyatt GH, OXman AD, Montori V, Vist G, Kunz R, Brozek, J, et al. (2011a). GRADE guidelines: 5. Rating the quality of evidence–publication bias. J Clin Epidemiol 64:1277–1282.

Guyatt G, OXman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. (2011b). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 64:383–394.

Higgins JP, Altman DG, Gatsche PC, Juni P, Moher D, OXman AD, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. (2011). The cochrane collaboration’s tool for assessing risk of bias in randomised trials. BMJ 343:d5920.

Hobart M, Skuban A, Zhang P, Augustine C, Brewer C, Hefting N, McCuaide RD (2018a). A randomized, placebo-Controlled Study of the efficacy and safety of fixed-dose brexpiprazole 2mg/d as adjunctive treatment of adults with major depressive disorder. J Clin Psychiatry 79:112058.

Hobart M, Skuban A, Zhang P, Josiassen MK, Hefting N, Augustine C, et al. (2018b). Efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of adults with major depressive disorder. Am J Psychiatry 175:120–129.

Ishigooka J, Iwashita S, Hirashita K, Liew EL, Tadoi Y (2018a). Pharmacokinetics and safety of brexpiprazole following multiple-dose administration to Japanese patients with schizophrenia. J Clin Pharmacol 58:74–80.
