Efficacy and Safety of Brexpiprazole in Acute Management of Psychiatric Disorders: A Meta-Analysis of Randomized Controlled Trials

Ayman Antoun[1], Eriny Girgis[2] and Raafat Mishriky[3]

[1] Senior Lecturer of Pharmacology, School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wulfruna Street, Wolverhampton, WV1 1LY, UK

[2] Dental officer, Community Dental Service, City of Coventry Health Centre, Coventry and Warwickshire Partnership NHS trust, CV1 4FS

[3] Consultant Old Age Psychiatry, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, B37 7JB, UK

*Corresponding Author: a.antounreyad@wlv.ac.uk

Running Head: Brexpiprazole in Psychiatric Disorders

Word Count: 3315

Number of Figures: 4

Number of tables: 4

Abstract

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 syndrome 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 (MD) 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 RR=1.72; weight increase RR=2.74 and somnolence RR=1.87. Compared to 4mg, brexpiprazole 2mg 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.

Keywords: Brexpiprazole, Schizophrenia, Major Depressive Disorder, Psychiatric 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 & Mishriky, 2019). In England, psychotic disorders annual incidence is 32 cases per 100,000 people, 15 of them schizophrenia (Kirkbride et al., 2012). The aetiology 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 (FGA's) 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 & 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, Leucht, & Kane, 2004). Second generation antipsychotics are associated with side effects such as weight gain, hyperprolactinemia and glucose intolerance (Ndukwe & Nishtala, 2017; Sapra et al., 2016).

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 (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 & 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 & 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 Ca^{2+} signaling (Ishima et al., 2015). Brexpiprazole completely inhibited 5-HT neurons firing via 5-HT1A autoreceptors agonism and was more potent than aripiprazole (Oosterhof, El Mansari, & Blier, 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., 2018). Brexpiprazole target dose is 2-4 mg/day in schizophrenia and 2 mg in depression with dose adjustments considered in hepatic or renal dysfunction (Parikh, Robinson, & Clayton, 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/day, or placebo or active control second generation antipsychotic (quetiapine, aripiprazole) for the management of schizophrenia and major depressive disorder. 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 (Figure 1).

Inclusion and Exclusion Criteria

Published phase II and III randomized controlled trials that investigate the tolerability, safety or efficacy of brexpiprazole in patients suffering from schizophrenia and major depressive disorder (MDD) were included (Table 1). All RCT's 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 (1-4mg/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 (1-4mg/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 RCT's. '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, G. et al., 2011; Guyatt, G. H. et al., 2011; Sterne et al., 2011).

The inverse variance method with random effects model was used to calculate the mean differences 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, Smith, & Altman, 2001). RevMan was used for all statistical analysis, 95% confidence intervals were used for all outcomes and p-value <0.05 was regarded as statistically significant (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Search Results and Included Studies

Figure 1 shows the selection process of RCT's 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) (Citrome et al., 2016; Correll et al., 2015; Hobart, Skuban, Zhang, Augustine et al., 2018; Hobart, Skuban, Zhang, Josiassen et al., 2018; Ishigooka, Iwashita, & Tadori, 2018; Kane et al., 2015; NCT00797966, 2016; NCT00905307, 2015; NCT01052077, 2015; NCT01810380, 2017; NCT01838681, 2017; NCT02194933, 2018; Thase, Youakim, Skuban, Hobart, Augustine et al., 2015; Thase, Youakim, Skuban, Hobart, Zhang et al., 2015) (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 4mg/day. 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

7 RCTs for brexpiprazole role in schizophrenia management were included in this meta-analysis, 5 RCTs, where brexpiprazole was compared with placebo (including two trials (NCT00905307, 2015; NCT01810380, 2017) also containing active control) with a total of 1618 patients treated with brexpiprazole compared to 742 patients who received placebo and 3 RCTs, where brexpiprazole was compared with active control (Citrome et al., 2016; NCT00905307, 2015; 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 (Figure 2).

The mean change from baseline in PANSS total score was significantly greater for brexpiprazole compared to placebo, with a mean difference (MD) of -4.48 [95% Confidence Interval (CI) -6.29, -3.47] favouring brexpiprazole treatment ($p<0.00001$)

(Figure 2A). The forest plot shows the mean differences for all the studies individually favor brexpiprazole, with low heterogeneity between the studies (x^2=10.5, I^2=0%). Similarly, PANSS positive score MD was significantly greater for brexpiprazole -0.99 [95% CI -1.45, -0.52] favoring brexpiprazole treatment (p<0.00001) (Figure 2B) with moderate heterogeneity (x^2=20.3, I^2=46%), while PANSS negative score, MD -1.16 [95% CI -1.51, -0.80] favoring brexpiprazole (p<0.00001) (Figure 2C).

CGI-S mean change from baseline was also significantly greater for brexpiprazole MD -0.23 [95% CI -0.31, -0.15], p<0.00001, which was clinically and statistically significant (Figure 2D) with very low heterogeneity between the studies (I^2=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 (Figure 2E), showing positive effect MD 3.24 [95% CI 2.22, 4.25], with very low heterogeneity (I^2=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 (Figure 2F, Table 2).

Brexpiprazole 2mg and 4 mg doses were compared in four RCT (Correll et al., 2015; Ishigooka et al., 2018; Kane et al., 2015; 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

7 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 (Figure 3, 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, -0.76] favouring brexpiprazole ($p<0.00001$) (Figure 3A). All the studies individually favour brexpiprazole, with low heterogeneity between the studies ($X^2=4.82$, $I^2=0\%$).

SDS mean change was significantly greater for brexpiprazole compared to placebo, with MD -0.37 [95% CI -0.52, -0.21] ($p<0.00001$) (Figure 3B). Similar positive outcomes for brexpiprazole are highlighted as changes in CGI-S score (MD -0.19[-0.27, -0.11]) (Figure 4C), HDRS17 (MD -1.28[-1.79, -0.76]) (figure 4D), CGI score (MD -0.21 [-0.30, -0.12]), MADRS response (MD 1.36 [1.20, 1.55]) , CGI-I response (MD 1.29 [1.18, 1.41]) and MADRS remission (MD 1.36 [1.16, 1.61]) (Table 2).

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 to 1.10], $p=0.30$ (Figure 4A). There is variation among the studies with some favoring brexpiprazole, while others favoring placebo; with a moderate to high heterogeneity ($I^2 = 53\%$). Brexpiprazole was associated with some side effects including akathisia RR=1.72 [1.38 to 2.14], $p<0.00001$; weight increase RR=2.74

[2.16 to 3.48], p<0.00001 and somnolence RR=1.87 [1.30 to 2.71], p=0.0008 (Figure 4, Table 3).

Brexpiprazole in patients suffering from MDD was also associated with restlessness RR=4.11 [2.19 to 7.71], p<0.00001, increased appetite RR=3.88 [1.47 to 10.3], p=0.006 and in patients suffering from schizophrenia, brexpiprazole was associated with nausea RR=2.58 [1.34 to 5.00], p=0.005.

Compared to brexpiprazole 4 mg, brexpiprazole lower dose (2mg) 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 MDD

3 trials were identified comparing brexpiprazole with active control (aripiprazole and quetiapine) in schizophrenia management and only one trial comparing brexpiprazole with active control (quetiapine) in MDD. 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 to 2.42], p=0.19 (Table 3) and reduced risk of dry mouth RR=0.27 [0.12 to 0.61], p=0.002.

Brexpiprazole compared with quetiapine was associated with less risk of somnolence RR=0.25 [0.15 to 0.43], p<0.00001, dry mouth RR=0.16 [0.05 to 0.48], p=0.001 and weight increase RR=0.59 [0.32 to 1.08], p=0.09 and higher risk of Akathisia RR=1.73 [0.79 to 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, post-traumatic stress disorder, personality disorders and agitation in AD patients.

Brexpiprazole (3mg/day) 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, H E et al., 2017). Open-label results 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, Zhang, Weiss et al., 2019) 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, Figure 5). Brexpiprazole compared with quetiapine was associated with less risk of somnolence, dry mouth and weight increase (Table 3, Figure 4) as brexpiprazole has moderate affinity for histamine H1 receptors with very low affinity for muscarinic M1 receptors. Brexpiprazole 2mg lower dose had similar efficacy to the higher 4mg 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 QT interval (Aronow & Shamliyan, 2018). Brexpiprazole is 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, Zhang, Skuban et al., 2019). 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. *European Psychiatry : The Journal of the Association of European Psychiatrists, 20*(1), 15-27. doi:S0924-9338(04)00267-6 [pii]

Aladeen, T., Westphal, E., Lee, Y., Rong, C., Rainka, M., Capote, H., & McIntyre, R. S. (2018). The use of brexpiprazole amongst individuals with insufficient outcomes with aripiprazole or bupropion: A case series. *Perspectives in Psychiatric Care, 54*(4), 507-513. doi:10.1111/ppc.12258 [doi]

Amada, N., Akazawa, H., Ohgi, Y., Maeda, K., Sugino, H., Kurahashi, N., . . . Futamura, T. (2019). Brexpiprazole has a low risk of dopamine D2 receptor sensitization and inhibits rebound phenomena related to D2 and serotonin 5-HT2A receptors in rats. *Neuropsychopharmacology Reports,* doi:10.1002/npr2.12076 [doi]

Andreasen, N. C. (1999). Understanding the causes of schizophrenia. *The New England Journal of Medicine, 340*(8), 645-647. doi:10.1056/NEJM199902253400811 [doi]

Aronow, W. S., & Shamliyan, T. A. (2018). Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. *Annals of Translational Medicine, 6*(8), 147. doi:10.21037/atm.2018.03.17 [doi]

Ayano, G. (2016). First Generation Antipsychotics: Pharmacokinetics, Pharmacodynamics, Therapeutic Effects and Side Effects: A Review. *Research & Reviews: Journal of Chemistry, 5*(3), 53-63.

Brexpiprazole. (2006). *Drugs and Lactation Database (LactMed)* (). Bethesda (MD): doi:NBK500749 [bookaccession]

Broder, M. S., Greene, M., Yan, T., Chang, E., Hartry, A., & Yermilov, I. (2019). Medication Adherence, Health Care Utilization, and Costs in Patients With Major Depressive Disorder Initiating Adjunctive Atypical Antipsychotic Treatment. *Clinical Therapeutics, 41*(2), 221-232. doi:S0149-2918(18)30604-0 [pii]

Brown, E. S., Khaleghi, N., Van Enkevort, E., Ivleva, E., Nakamura, A., Holmes, T., . . . Escalante, C. (2019). A pilot study of brexpiprazole for bipolar depression. *Journal of Affective Disorders, 249*, 315-318. doi:S0165-0327(18)32885-4 [pii]

Chen, B., Zhang, X. D., Wen, J., Zhang, B., Chen, D., Wang, S., . . . Hu, G. X. (2019). Effects of 26 Recombinant CYP3A4 Variants on Brexpiprazole Metabolism. *Chemical Research in Toxicology,* doi:10.1021/acs.chemrestox.9b00186 [doi]

Citrome, 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? *International Journal of Clinical Practice, 69*(9), 978-997. doi:10.1111/ijcp.12714 [doi]

Citrome, L., Ota, A., Nagamizu, K., Perry, P., Weiller, E., & Baker, R. A. (2016). The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute

schizophrenia: results from a randomized, exploratory study. *International Clinical Psychopharmacology, 31*(4), 192-201. doi:10.1097/YIC.0000000000000123 [doi]

Cohen, H., Zohar, J., Kaplan, Z., & Arnt, 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. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 28*(1), 63-74. doi:S0924-977X(17)32022-9 [pii]

Corponi, F., Fabbri, C., Bitter, I., Montgomery, S., Vieta, E., Kasper, S., . . . Serretti, A. (2019). Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 29*(9), 971-985. doi:S0924-977X(19)30266-4 [pii]

Correll, C. U., Skuban, A., Ouyang, J., Hobart, M., Pfister, S., McQuade, R. D., . . . Eriksson, H. (2015). Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. *The American Journal of Psychiatry, 172*(9), 870-880. doi:10.1176/appi.ajp.2015.14101275 [doi]

Correll, C. U., Leucht, S., & Kane, J. M. (2004). Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *The American Journal of Psychiatry, 161*(3), 414-425. doi:10.1176/appi.ajp.161.3.414 [doi]

Davis, L. L., Ota, A., Perry, P., Tsuneyoshi, K., Weiller, E., & Baker, R. A. (2016). Adjunctive brexpiprazole in patients with major depressive disorder and anxiety

symptoms: an exploratory study. *Brain and Behavior*, *6*(10), e00520. doi:10.1002/brb3.520 [doi]

Egger, M., Smith, G. D., & Altman, D. G. (2001). In Egger M., Smith G. D. and Altman D. G. (Eds.), *Systematic reviews in health care : meta-analysis in context* (2nd ed.). London: BMJ Books.

Fava, M., Menard, F., Davidsen, C. K., & Baker, R. A. (2016). Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study. *The Journal of Clinical Psychiatry*, *77*(12), 1695-1701. doi:10.4088/JCP.15m10470 [doi]

Fornaro, M., Fusco, A., Anastasia, A., Cattaneo, C. I., & De Berardis, D. (2019). Brexpiprazole for treatment-resistant major depressive disorder. *Expert Opinion on Pharmacotherapy, 20*(16), 1925-1933. doi:10.1080/14656566.2019.1654457 [doi]

Frampton, J. E. (2019). Brexpiprazole: A Review in Schizophrenia. *Drugs*, *79*(2), 189-200. doi:10.1007/s40265-019-1052-5 [doi]

Garay, R. P., Citrome, L., Grossberg, G. T., Cavero, I., & Llorca, P. M. (2016). Investigational drugs for treating agitation in persons with dementia. *Expert Opinion on Investigational Drugs, 25*(8), 973-983. doi:10.1080/13543784.2016.1193155 [doi]

Guyatt, G. H., Oxman, A. D., Montori, V., Vist, G., Kunz, R., Brozek, J., . . . Schunemann, H. J. (2011). GRADE guidelines: 5. Rating the quality of evidence--publication bias. *Journal of Clinical Epidemiology, 64*(12), 1277-1282. doi:10.1016/j.jclinepi.2011.01.011 [doi]

Guyatt, G., Oxman, A. D., Akl, E. A., Kunz, R., Vist, G., Brozek, J., . . . Schunemann, H. J. (2011). GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of

findings tables. *Journal of Clinical Epidemiology, 64*(4), 383-394. doi:10.1016/j.jclinepi.2010.04.026 [doi]

Higgins, J. P., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., . . . Cochrane Statistical Methods Group. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research Ed.), 343*, d5928. doi:10.1136/bmj.d5928 [doi]

Hobart, M., Skuban, A., Zhang, P., Augustine, C., Brewer, C., Hefting, N., . . . McQuade, R. D. (2018). A Randomized, Placebo-Controlled Study of the Efficacy and Safety of Fixed-Dose Brexpiprazole 2 mg/d as Adjunctive Treatment of Adults With Major Depressive Disorder. *The Journal of Clinical Psychiatry, 79*(4), 10.4088/JCP.17m12058. doi:10.4088/JCP.17m12058 [doi]

Hobart, M., Skuban, A., Zhang, P., Josiassen, M. K., Hefting, N., Augustine, C., . . . McQuade, R. D. (2018). Efficacy and safety of flexibly dosed brexpiprazole for the adjunctive treatment of major depressive disorder: a randomized, active-referenced, placebo-controlled study. *Current Medical Research and Opinion, 34*(4), 633-642. doi:10.1080/03007995.2018.1430220 [doi]

Hobart, M., Zhang, P., Skuban, A., Brewer, C., Hefting, N., Sanchez, R., & McQuade, R. D. (2019). A Long-Term, Open-Label Study to Evaluate the Safety and Tolerability of Brexpiprazole as Adjunctive Therapy in Adults With Major Depressive Disorder. *Journal of Clinical Psychopharmacology, 39*(3), 203-209. doi:10.1097/JCP.0000000000001034 [doi]

Hobart, M., Zhang, P., Weiss, C., Meehan, S. R., & Eriksson, H. (2019). Adjunctive Brexpiprazole and Functioning in Major Depressive Disorder: A Pooled Analysis of Six

Randomized Studies Using the Sheehan Disability Scale. *The International Journal of Neuropsychopharmacology, 22*(3), 173-179. doi:10.1093/ijnp/pyy095 [doi]

Ishigooka, J., Iwashita, S., Higashi, K., Liew, E. L., & Tadori, Y. (2018). Pharmacokinetics and Safety of Brexpiprazole Following Multiple-Dose Administration to Japanese Patients With Schizophrenia. *Journal of Clinical Pharmacology, 58*(1), 74-80. doi:10.1002/jcph.979 [doi]

Ishigooka, J., Iwashita, S., & Tadori, Y. (2018). Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. *Psychiatry and Clinical Neurosciences, 72*(9), 692-700. doi:10.1111/pcn.12682 [doi]

Ishima, T., Futamura, T., Ohgi, Y., Yoshimi, N., Kikuchi, T., & Hashimoto, K. (2015). Potentiation of neurite outgrowth by brexpiprazole, a novel serotonin-dopamine activity modulator: a role for serotonin 5-HT1A and 5-HT2A receptors. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 25*(4), 505-511. doi:10.1016/j.euroneuro.2015.01.014 [doi]

Kane, J. M., Skuban, A., Ouyang, J., Hobart, M., Pfister, S., McQuade, R. D., . . . Eriksson, H. (2015). A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophrenia Research, 164*(1-3), 127-135. doi:10.1016/j.schres.2015.01.038 [doi]

Kirkbride, J. B., Errazuriz, A., Croudace, T. J., Morgan, C., Jackson, D., Boydell, J., . . . Jones, P. B. (2012). Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. *PloS One, 7*(3), e31660. doi:10.1371/journal.pone.0031660 [doi]

Kishi, T., Sakuma, K., Nomura, I., Matsuda, Y., Mishima, K., & Iwata, N. (2019). Brexpiprazole as Adjunctive Treatment for Major Depressive Disorder Following Treatment Failure With at Least One Antidepressant in the Current Episode: a Systematic Review and Meta-Analysis. *The International Journal of Neuropsychopharmacology, 22*(11), 698-709. doi:10.1093/ijnp/pyz040 [doi]

Krystal, A. D., Mittoux, A., Meisels, P., & Baker, R. A. (2016). Effects of Adjunctive Brexpiprazole on Sleep Disturbances in Patients With Major Depressive Disorder: An Open-Label, Flexible-Dose, Exploratory Study. *The Primary Care Companion for CNS Disorders, 18*(5), 10.4088/PCC.15m01914. doi:10.4088/PCC.15m01914 [doi]

Lepola, U., Hefting, N., Zhang, D., & Hobart, M. (2018). Adjunctive brexpiprazole for elderly patients with major depressive disorder: An open-label, long-term safety and tolerability study. *International Journal of Geriatric Psychiatry, 33*(10), 1403-1410. doi:10.1002/gps.4952 [doi]

Ma, M., Ren, Q., Yang, C., Zhang, J. C., Yao, W., Dong, C., . . . Hashimoto, K. (2017). Antidepressant effects of combination of brexpiprazole and fluoxetine on depression-like behavior and dendritic changes in mice after inflammation. *Psychopharmacology, 234*(4), 525-533. doi:10.1007/s00213-016-4483-7 [doi]

Maeda, K., Sugino, H., Akazawa, H., Amada, N., Shimada, J., Futamura, T., . . . Kikuchi, T. (2014). Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. *The Journal of Pharmacology and Experimental Therapeutics, 350*(3), 589-604. doi:10.1124/jpet.114.213793 [doi]

NCT00797966. (2016). Study of the Safety and Efficacy of OPC-34712 as Adjunctive Therapy in the Treatment of Patients With Major Depressive Disorder. Retrieved from https://clinicaltrials.gov/ct2/show/NCT00797966

NCT00905307. (2015). Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 and Aripiprazole for Treatment of Acute Schizophrenia (STEP 203). Retrieved from https://clinicaltrials.gov/ct2/show/NCT00905307

NCT01052077. (2015). Study of the Safety and Efficacy of OPC-34712 as Adjunctive Therapy in the Treatment of Adults With Major Depressive Disorder (STEP-D222). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01052077

NCT01810380. (2017). Brexpiprazole in Patients With Acute Schizophrenia. Retrieved from https://www.clinicaltrials.gov/ct2/show/NCT01810380

NCT01838681. (2017). Brexpiprazole as Adjunctive Treatment in Patients With Major Depressive Disorder With an Inadequate Response to Antidepressant Treatment. Retrieved from https://clinicaltrials.gov/ct2/show/NCT01838681

NCT02194933. (2018). Monotherapy Brexpiprazole (OPC-34712) Trial in the Treatment of Adults With Schizophrenia With Impulsivity. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02194933

NCT03257865. (2020). A Trial to Assess Brexpiprazole Versus Placebo for the Treatment of Acute Manic Episodes, Associated With Bipolar I Disorder. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03257865

Ndukwe, H. C., & Nishtala, P. S. (2017). Glucose monitoring in new users of second-generation antipsychotics in older people. *Archives of Gerontology and Geriatrics, 70*, 136-140. doi:S0167-4943(17)30022-5 [pii]

Obara, K., Fujii, A., Arie, C., Harada, N., Yamaki, F., Matsuo, K., . . . Tanaka, Y. (2019). Inhibition of Recombinant Human Acetylcholinesterase Activity by Antipsychotics. *Pharmacology, 104*(1-2), 43-50. doi:10.1159/000500227 [doi]

Oosterhof, C. A., El Mansari, M., & Blier, P. (2014). Acute effects of brexpiprazole on serotonin, dopamine, and norepinephrine systems: an in vivo electrophysiologic characterization. *The Journal of Pharmacology and Experimental Therapeutics, 351*(3), 585-595. doi:10.1124/jpet.114.218578 [doi]

Parikh, N. B., Robinson, D. M., & Clayton, A. H. (2017). Clinical role of brexpiprazole in depression and schizophrenia. *Therapeutics and Clinical Risk Management, 13*, 299-306. doi:10.2147/TCRM.S94060 [doi]

Reyad, A. A., & Mishriky, R. (2019). Asenapine: Pharmacological Aspects and Role in Psychiatric Disorders. *Psychiatria Danubina, 31*(2), 157-161. doi:10.24869/psyd.2019.157 [doi]

Robinson, D., Woerner, M. G., Alvir, J. M., Bilder, R., Goldman, R., Geisler, S., . . . Lieberman, J. A. (1999). Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Archives of General Psychiatry, 56*(3), 241-247.

Sapra, M., Lawson, D., Iranmanesh, A., & Varma, A. (2016). Adiposity-independent hypoadiponectinemia as a potential marker of insulin resistance and inflammation in

schizophrenia patients treated with second generation antipsychotics. *Schizophrenia Research, 174*(1-3), 132-136. doi:10.1016/j.schres.2016.04.051 [doi]

Steel, Z., Marnane, C., Iranpour, C., Chey, T., Jackson, J. W., Patel, V., & Silove, D. (2014). The global prevalence of common mental disorders: a systematic review and meta-analysis 1980-2013. *International Journal of Epidemiology, 43*(2), 476-493. doi:10.1093/ije/dyu038 [doi]

Sterne, J. A., Sutton, A. J., Ioannidis, J. P., Terrin, N., Jones, D. R., Lau, J., . . . Higgins, J. P. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ (Clinical Research Ed.), 343*, d4002. doi:10.1136/bmj.d4002 [doi]

Thase, M. E., Youakim, J. M., Skuban, A., Hobart, M., Augustine, C., Zhang, P., . . . Eriksson, H. (2015). Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. *The Journal of Clinical Psychiatry, 76*(9), 1224-1231. doi:10.4088/JCP.14m09688 [doi]

Thase, M. E., Youakim, J. M., Skuban, A., Hobart, M., Zhang, P., McQuade, R. D., . . . Eriksson, H. (2015). Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. *The Journal of Clinical Psychiatry, 76*(9), 1232-1240. doi:10.4088/JCP.14m09689 [doi]

The Nordic Cochrane Centre, The Cochrane Collaboration. (2014). *Review Manager (RevMan)* (Version 5.3 ed.). Copenhagen: The Nordic Cochrane Centre.

van den Munkhof, H E, Arnt, J., Celada, P., & Artigas, F. (2017). The antipsychotic drug brexpiprazole reverses phencyclidine-induced disruptions of thalamocortical networks. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology, 27*(12), 1248-1257. doi:S0924-977X(17)30968-9 [pii]

Ward, K., & Citrome, L. (2019). Brexpiprazole for the maintenance treatment of adults with schizophrenia: an evidence-based review and place in therapy. *Neuropsychiatric Disease and Treatment, 15*, 247-257. doi:10.2147/NDT.S169369 [doi]

Table 1 Randomized Controlled trials included in the meta-analysis (all are double blinded RCT): Brex: Brexpiprazole, Que: Quetiapine, Ari: Aripiprazole

Study	Other ID	Design	Indication	Duration (weeks)	Dose range (mg/d)	Population
Correll 2015	NCT01396421 2011-002538-38	Placebo control	Schizophrenia	6	Placebo Brex 2mg/day Brex 4mg/day	184 182 180
Ishigooka 2018	NCT01451164	Placebo control	Schizophrenia	6	Placebo Brex 1mg/day Brex 2mg/day Brex 4mg/day	116 115 114 113
Kane 2015	NCT01393613	Placebo control	Schizophrenia	6	Placebo Brex 1mg/day Brex 2mg/day Brex 4mg/day	184 120 186 184
NCT00905307		Placebo Ari Controlled	Schizophrenia	6	Placebo Brex 1mg/day Brex2.5mg/day Brex 5mg/day Ari	93 88 90 92 50
NCT01810380		Placebo Quetiapine controlled	Schizophrenia	6	Placebo Brex 2-4mg/day Que 400-800mg/day	163 151 154
Citrome 2016	NCT02054702	Aripiprazole controlled	Schizophrenia	6	Brex Arip	64 33
NCT02194933		Double blinded	Schizophrenia	6	Brex 2mg/day Brex 4mg/day	19 19
Hobart 2018	NCT02196506 2014-000062-22	Placebo control	Adjunct in MDD	6	Placebo Brex 2mg/day	202 191
Hobart 2018b	NCT01727726 2012-003948-67	Placebo Quetiapine controlled	Adjunct in MDD	6	Placebo Brex 2-3mg/day Que 150-300mg/day	206 197 100
Thase 2015	NCT01360645	Placebo control	Adjunct in MDD	6	Placebo Brex 2mg/day	178 175
Thase 2015b	NCT01360632 21011-001349-33	Placebo control	Adjunct in MDD	6	Placebo Brex 1mg/day Brex 3mg/day	203 211 213
NCT01838681	2012-001380-76	Placebo control	Adjunct in MDD	6	Placebo Brex 1-3mg/day	442 444
NCT00797966		Placebo control	Adjunct in MDD	6	Placebo Brex 1.5mg/day	126 121
NCT01052077		Placebo control	Adjunct in MDD	6	Placebo Brex 1-	187 185

3mg/day

Table 2: Efficacy of Brexpiprazole as measured by different psychiatric scales

Psychiatric condition	Compared to	Psychiatric Scale	MD (CI)/ RR (CI)	p-value	Comments
Schizophrenia	Placebo	PANSS total	-4.88 (-6.29, -3.47)	<0.00001*	Brexpiprazole showed significant response
		CGI-S	-0.23 (-0.31, -0.15)	<0.00001*	
		CGI score	-0.2 (-0.34, -0.06)	0.005*	
		PANSS positive	-0.99 (-1.45, -0.52)	<0.00001*	
		PANSS negative	-1.16 (-1.51, -0.8)	<0.00001*	
		PANSS excited component	-0.76 (-1.09, -0.43)	<0.00001*	
		Response rate	1.31 (1.19, 1.43)	<0.00001*	
		PSP	3.24 (2.22, 4.25)	<0.00001*	
	Active Control	PANSS total	0.98 (-1.64, 3.59)	0.46	Brexpiprazole showed similar efficacy to Active controls
		CGI-S	0.04 (-0.13, 0.21)	0.66	
		CGI score	0.13 (-0.07, 0.34)	0.2	
		PANSS negative	-0.01 (-0.79, -0.78)	0.99	
		PSP	-0.78 (-2.74,1.19)	0.44	
		PANSS positive	1.04 (0.06, 2.03)	0.04*	Significant small difference between Brexpiprazole and active control
		Response rate	0.86 (0.76, 0.98)	0.02*	
Major Depressive Disorder	Placebo	MADRS	-1.25 (-1.74, -0.76)	<0.00001*	Brexpiprazole showed significant response
		SDS	-0.37 (-0.52, -0.21)	<0.00001*	
		CGI-S	-0.19 (-0.27, -0.11)	<0.00001*	
		HDRS17	-1.28 (-1.79, -0.76)	<0.00001*	
		CGI-I score	-0.21 (-0.30, -0.12)	<0.00001*	
		MADRS response	1.36 (1.20, 1.55)	<0.00001*	
		CGI-I response	1.29 (1.18, 1.41)	<0.00001*	

		MADRS remission	1.36 (1.16, 1.61)	0.0002*	

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	0.96 (0.80, 1.16)	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)	0.3
	Somnolence	4.63 (0.86, 24.9)	0.07
	Dry mouth	0.86 (0.22, 3.38)	0.83

Table 4: Efficacy and safety of Brexpiprazole 2mg compared to Brexpiprazole 4mg in schizophrenia management

Psychiatric Scale	MD (CI)/ RR (CI)	p-value	Comments
PANSS total	0.5 (-1.87, 2.88)	0.68	Brexpiprazole 2 and 4 mg doses show similar efficacy
CGI-S	-0.03 (-0.11, 0.17)	0.67	
CGI score	-0.29 (-0.57, -0.01)	0.05	
PANSS positive	0.23 (-0.59, 1.05)	0.59	
PANSS negative	-0.18 (-0.79, 0.43)	0.56	
PSP	-0.67 (-2.38, 1.03)	0.44	
Weight increase	1.08 (0.68, 1.70)	0.75	Brexpiprazole 2mg has fewer incidences of side effects compared to higher dose (4mg), albeit not statistically significant.
Akathisia	0.68 (0.40, 1.15)	0.15	
Headache	1.05 (0.72, 1.55)	0.79	
Somnolence	0.53 (0.22, 1.32)	0.17	
Insomnia	0.95 (0.64, 1.40)	0.78	
Trial withdrawal due to adverse events	0.78 (0.52, 1.17)	0.24	

Figure Legends

Figure 1: Flowchart summarizing the studies selection process.

Figure 2: 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.

Figure 3: Funnel Plots for Efficacy of Brexpiprazole in the management of Major Depressive Disorders determined by the changes from baseline for (A) Montgomery Asberg depression rating scale (MADRS); (B) Sheehan Disability Scale (SDS) Clinical Global Impressions – Severity of Illness Score; (C) Clinical Global Impressions – Severity of Illness (CGI-S); (D) Hamilton-D rating scale for depression (HDRS17)

Figure 4: Funnel Plots for Tolerability and Safety of Brexpiprazole (A) Discontinuation from Trials due to Adverse Events; (B) Side Effect-weight Increase; (C) Side Effect-Akathisia; (D) Side Effect-Somnolence.