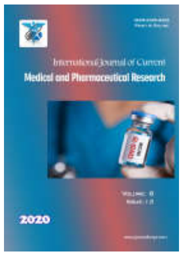
INTERNATIONAL JOURNAL OF CURRENT MEDICAL AND PHARMACEUTICAL RESEARCH
ISSN: 2395-6429, Impact Factor: 4.656
Available Online at www.journalcmpr.com
Volume 6; Issue 12(A); December 2020; Page No.5466-5471
DOI: http://dx.doi.org/10.24327/23956429.ijcmpr202012942



Research Article

BREXPIPRAZOLE IN THE ACUTE MANAGEMENT OF SCHIZOPHRENIA

Aisha Begum[1]., Raafat Mishriky[2] and Ayman Antoun Reyad*[3]

[1]School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, WV1 1LY, UK
[2]Consultant Old Age Psychiatry, Birmingham and Solihull Mental Health NHS Foundation Trust, Birmingham, B37 7JB, UK
[3]Pharmacology, School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, WV1 1LY, UK

ARTICLE INFO

Article History:
Received 13th September, 2020
Received in revised form 11th October, 2020
Accepted 8th November, 2020
Published online 28th December, 2020

Key words:
Brexpiprazole, Schizophrenia, Psychiatric Disorders, Antipsychotics

ABSTRACT

Brexpiprazole is a new atypical antipsychotic used for the management of psychiatric conditions including schizophrenia and is associated with fewer extrapyramidal side effects compared to traditional antipsychotics due to its additional serotonergic effect, which may improve cognitive symptoms associated with social function decline in schizophrenia. We searched for randomized controlled-trials (RCT) to review the efficacy and tolerability of brexpiprazole in acute management of schizophrenia using different resources including PubMed, Google Scholar, ClinicalTrials.gov and Cochrane Central Register of Controlled-Trials. Data were extracted for adverse effects, positive and negative syndrome scale (PANSS), Personal and Social Performance scale (PSP), PANSS Excited Component (PEC) and Response Rate >30%. 5 RCT were identified and showed that brexpiprazole was favorable compared to placebo in improving PANSS with a mean difference (MD) -5.40 [confidence interval (CI) -6.98, -3.82] and PSP 3.2 [CI 2.09, 4.32] (P<0.00001). Improvement in PANSS positive, PANSS negative subscales and response rate were significant (P<0.00001). Brexpiprazole led to reduced treatment discontinuation due to adverse effects (risk ratio (RR) 0.58), however an increased risk of akathisia was observed (RR= 1.31) especially at higher doses but did not reach statistical significance. In summary, brexpiprazole improved significantly the symptoms of schizophrenia and is well-tolerated, while long-term research is still required to establish its role, particularly in patients with co-morbidities. These findings will guide clinical teams in supporting patients suffering from schizophrenia.

INTRODUCTION

Schizophrenia is a chronic psychiatric disorder that affects 21 million people worldwide, making one of the leading causes of disability (Cooper *et al*., 2020), where patients' perception and behaviors are significantly altered with diagnosis confirmed after full psychiatric assessment (Antoun Reyad and Mishriky, 2019), In England, the annual incidence of psychotic disorders is 32 cases per 100,000 people, 15 of them schizophrenia (Kirkbride *et al*., 2012). Schizophrenia can be idiopathic or secondary due to another medical condition or misuse of recreational substances (Taj *et al*., 2008). The aetiology of schizophrenia is not fully understood with genetic and environmental factors involved (Andreasen, 1999) while 81.9% of patients suffer a relapse within 5 years of recovery (Robinson *et al*., 1999). Its pathophysiology involves central dopamine pathways such as the mesolimbic pathway (responsible for emotions, motivation and reward) (McCutcheon *et al*., 2019). A variety of antipsychotics are available with choice based on cost, side effect profile and patient parameters (Tavcar *et al*., 2000).

Efficacy of antipsychotic treatment is often measured by psychiatric scales such as the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression (CGI) and Brief Psychiatric Rating Scale (BPRS). The BPRS is an 18-item scoring checklist that evaluate clinical changes and takes into account clinical observation as well as the patients' perception, while CGI is based on clinicians' observations with symptoms rated on a scale of 1 to 7 (1= healthy, 7= severely ill). PANSS 30 items coverspositive, negative and general psychopathology symptoms similarly rated on a scale of 1-7 (Mortimer, 2007).

There are two main groups of antipsychotics, typical (first generation antipsychotics (FGA)) and atypical (second generation). FGA are dopamine (D2) receptors antagonists and could also block histamine, muscarinic and alpha-1 receptors (Ayano, 2016). Second generation antipsychotics (SGA) are

Corresponding author:* **Ayman Antoun Reyad
School of Pharmacy, Faculty of Science and Engineering, University of Wolverhampton, Wolverhampton, WV1 1LY, UK

serotonin-dopamine antagonists (Abi-Dargham and Laruelle, 2005). This 5HT-2A antagonism can increase dopaminergic neurotransmission in the nigrostriatal pathway, which reduces the risk of extrapyramidal symptoms associated with antipsychotic use such as akathisia and tardive dyskinesia (Correll *et al*., 2004) however, SGA are associated with weight gain, hyperprolactinemia and glucose intolerance (Ndukwe and Nishtala, 2017; Sapra *et al*., 2016)

Brexpiprazole (Rxulti®, Rexulti®) is a new 2^{nd} generation antipsychotic drug for the treatment of schizophrenia and as an adjunct in major depressive disorder (Corponi *et al*., 2019). It is a serotonin-dopamine activity modulator and acts as a partial agonist of dopamine D2, D3 and 5HT1A receptors, similar to cariprazine, and as an antagonist of 5HT2A, 5HT2B, 5HT7 and adrenergic receptors (Ward and Citrome, 2019) As a partial D2 agonist, it is effective in balancing dopamine levels in the mesolimbic pathway where hyperactivation leads to positive symptoms and the mesocortical pathway where hypoactivation leads to negative symptoms (Lieberman, 2004). Brexpiprazole also induces neurite outgrowth (Ishima *et al*., 2015) and compared to aripiprazole, brexpiprazole has lower D2 intrinsic activity with a more potent 5-HT2A antagonism (Fornaro *et al*., 2019). Brexpiprazole is primarily metabolized by CYP3A4 and CYP2D6 (Chen *et al*., 2019) with atarget dose of 2-4 mg/day in schizophrenia with dose adjustments considered in hepatic or renal dysfunction (Parikh *et al*., 2017)

Due to its promising mechanism of action, this systematic review/meta-analysis was conducted to investigate the efficacy and tolerability of brexpiprazole (2-5mg) compared to placebo in adult patients (≥ 18 years) suffering from schizophrenia using published randomized controlled-trials (RCT).

METHODS

Search strategy

The study population included adult patients (18 – 65 years old) taking part in RCT's assigned to either brexpiprazole 2-5 mg/day, or placebo for the management of acute schizophrenia. A literature search was performed using the search terms brexpiprazole (OPC-34712), acute schizophrenia and placebo in online databases including PubMed, Google Scholar, Cochrane Library and Clinicaltrials.gov. Titles were screened for relevance, narrowed down using filters for 'clinical trials' and duplicates were removed. The following exclusion criteria were applied: studies not in English, conducted on children, reviews, incomplete/unpublished data, chronic schizophrenia, other psychiatric conditions, brexpiprazole doses outside (2-5mg) range. Published phase II and III RCTs that investigate the tolerability or efficacy of brexpiprazole were included (Table 1). All RCT's were doubled blinded to reduce the risk of bias.

Outcome measures

Data was extracted for primary efficacy outcomes including Positive and Negative Syndrome Scales (PANSS), PANSS Negative and Positive scores, Clinical Global Impressions-Severity of Illness Score (CGI-S), Personal and Social Performance Scale (PSP) and PANSS Excited Component (PEC) (Depp *et al*., 2010; Mortimer, 2007) with mean changes from baseline recorded. PSP takes into account social activities, personal relationships, self-care and disturbing behaviours (Juckel, 2014). The Response Rate >30% was also determined, while safety outcomes included adverse effects and discontinuation due to adverse effects.

Statistical Methods

Efficacy and safety outcomes data were added to Review Manager (RevMan) (The Cochrane Collaboration, 2014a) version 5.3 along with the Cochrane Collaboration tool for assessing the risk of bias and to provide statistical values such as Chi^2, I^2, Z-values, P-values, risk ratios (RR) and confidence intervals (CI) (Charrois, 2015). Risk of bias was conducted to detect selection bias based on randomisation and allocation concealment, performance, detection, attrition and reporting bias (The Cochrane Collaboration, 2014b). Heterogeneity was demonstrated using I^2(Higgins *et al*., 2019), >50% suggests heterogeneity and<25% mild heterogeneity (Turlik, 2010), p-value <0.05 is significant (Ghasemi and Zahediasl, 2012). Risk Ratios were used to assess the level of risk associated with an intervention (Andrade, 2015).

The inverse variance method was used to calculate the mean differences (MD) for continuous outcomes (PANSS, PANSS Negative and Positive scores, PANSS excited Component score, PSP) and Mantel-Haenszel method to calculate the RR for dichotomous outcomes (response rate, risk of discontinuation due to adverse effects and common side effects) (Egger *et al*., 2001).

RESULTS

Search Results and Included Studies

Following the database search (PubMed, Google Scholar, ClinicalTrials.gov and Cochrane Central Register of Controlled), trials were assessed and the process, with reasons for exclusion highlighted in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart (Figure 1). 5 relevant RCTs met the inclusion criteria (Table 1) (Correll *et al*., 2015; Ishigooka *et al*., 2018; Kane *et al*., 2015; Lundbeck, 2017; Otsuka Pharmaceutical Development & Commercialization., 2015). All studies used were RCTs comparing brexpiprazole (dose ranged from 2-5mg/day) and placebo in adults with acute Schizophrenia.

Risks of performance and detection bias were low due to all trials being randomised, double-blind and placebo controlled (Figure 2). Results were collected without investigators being aware of the intervention used and the outcome data were objective. The risks of selection and attrition bias were unclear due to lack of description of the methods used for allocation and concealment.

Efficacy of Brexpiprazole compared to Placebo in the management of Schizophrenia

5 RCTs for brexpiprazole role in schizophrenia management were included, where brexpiprazole was compared with placebo with a total of 1272 patients treated with brexpiprazole compared to 723 patients who received placebo. All the trials assessed PANSS, PANSS positive, PANSS negative (Figure 3).

Although individual results varied, most outcomes showed homogeneity. The mean change from baseline in PANSS total score MD = -5.4 with 95% CI [-6.98, -3.82] showed brexpiprazole was favorable compared to placebo ($p<0.00001$) with low heterogeneity between studies ($I^2 = 0\%$) (Figure 3). Similarly, PANSS positive MD was significantly greater for brexpiprazole -1.22 [CI -1.74, -0.70] ($p<0.00001$) with mild heterogeneity ($I^2$33%). PANSS negative subscale and PANSS Excited Component scores also showed brexpiprazole superiority in the management of schizophrenia MD -1.25 (P <0.00001) and -0.92 (P <0.0001) respectively (Figure 3).These results were further confirmed by changes in PSP scores with an improvement 3.2, CI [2.09, 4.32] and response rate >30% showed that brexpiprazole had a statistically significant higher response rate with moderate heterogeneity (Figure 3).

Tolerability and Safety of Brexpiprazole compared to Placebo in the management of Schizophrenia

The overall RR for trial discontinuation due to adverse effects was higher in the placebo group showing brexpiprazole to be more favourable (RR= 0.58, p<0.0001) (Figure 4) with some variation among the studies. Brexpiprazole was associated with a higher risk of akathisia (RR=1.31) (P = 0.1); I^2 = 45% - moderate heterogeneity and higher doses showed further increase in akathisia incidence. Brexpiprazole was also associated with nausea and a slight increase in cholesterol but did not reach statistical significance (Figure 4).

DISCUSSION

Brexpiprazole is a new antipsychotic drug that has been licensed for treatment of schizophrenia by the FDA but is still waiting to be licensed in the UK. It is structurally similar to aripiprazole which is currently used for schizophrenia and management of manic episodes (Consilient Health Ltd, 2019). Brexpiprazole is thought to have less activity at D_2 receptors and stronger activity at $5HT_{2a}$ receptors compared to aripiprazole, which could improve the adverse effect profile and schizophrenia negative symptoms (Das *et al*., 2016).

This systematic review investigated the safety and efficacy of brexpiprazole for the management of schizophrenia compared to placebo using the available clinical trials. Our results showed that brexpiprazole improved psychiatric scales used for measuring symptom severity in patients with psychosis such as PANSS total and its subscales (MD for PANSS (-5.4), PANSS positive subscale (-1.22)) (Figure 3). An improvement in PANSS, PSP and CGI was also demonstrated (Antoun Reyad *et al*., 2020) and (Kishi *et al*., 2018) who showed brexpiprazole superiority over placebo, however, the (Otsuka Pharmaceutical Development & Commercialization., 2015) trial found no significant improvement in PANSS scores; this could be due to a lack of assay sensitivity in this particular trial as the active comparator also showed no improvement in PANSS (Kishi *et al*., 2018).

As far as we are aware, these results update and are consistent with previous meta-analysis that showed brexpiprazole efficacy such as (Citrome, 2015) and (Antoun Reyad *et al*., 2020; Kishi *et al*., 2018).Our results confirm its superiority in management of schizophrenia over placebo (Figure 3) and are in agreement with a meta-analysis (Kishi *et al*., 2018), however this meta-analysis did not include some of the recent trials included in our meta-analysis. Brexpiprazole is considered to have a favorable side effect profile, mainly due to its high affinity for 5HT1A and 5HT2A receptors with partial D2-agonist activity (Frampton, 2019). In terms of safety, brexpiprazole was associated with increased risk of headache (p= 0.74), nausea (p= 0.06), anxiety (p= 0.66), insomnia (p= 0.31) and akathisia (p=0.1) (Figure 4) but did not reach statistical significance. A trend in changes in cholesterol levels were detected but these results were not statistically significant (p=0.11); more studies would be required to clarify the effect of brexpiprazole on cholesterol level as only two trials contained data regarding this side effect. Higher doses of brexpiprazole had similar efficacy and were observed to have increased incidences of akathisia, in particular Otsuka 5mg (RR=3.58) and Correll 4mg (RR=3.32) consistent with findings by (Antoun Reyad *et al*., 2020) and (Kishi *et al*., 2018). This meta-analysis focused on patients suffering from acute schizophrenia whereas (Antoun Reyad *et al*., 2020) looked at acute psychiatric disorders and included trials in patients with major depressive disorder and trials comparing brexpiprazole with active comparators (quetiapine and aripiprazole). There are some limitations such as the lack of an active comparator in 3 trials, if included, this could determine the safety and efficacy of brexpiprazole compared to the currently available antipsychotics and establish its cost-effectiveness. Adults with insufficient outcomes on aripiprazole or bupropion may benefit from switching to brexpiprazole (Aladeen *et al*., 2018). In elderly patients, adjunctive brexpiprazole was generally well tolerated with improvements in depressive symptoms and social functioning (Lepola *et al*., 2018). Currently, brexpiprazole is under investigation for management of other psychiatric conditions such as bipolar disorders, borderline personality, agitation in AD and Post Traumatic Stress Disorder (PTSD).

This review shows that brexpiprazole is well tolerated and significantly improves schizophrenia; however, the results need to be interpreted with caution as the treatment length was short, with several doses of brexpiprazole used with different efficacy and side effect profiles. Therefore, further research using different doses over longer periods is recommended for a more comprehensive understanding of the safety and efficacy of brexpiprazolein the management of chronic schizophrenia, especially for patients who have inadequately controlled schizophrenia/ require titration to higher doses. There is also the implication of co-morbidities and polypharmacy that was not taken into consideration for the purpose of these short-term trials.

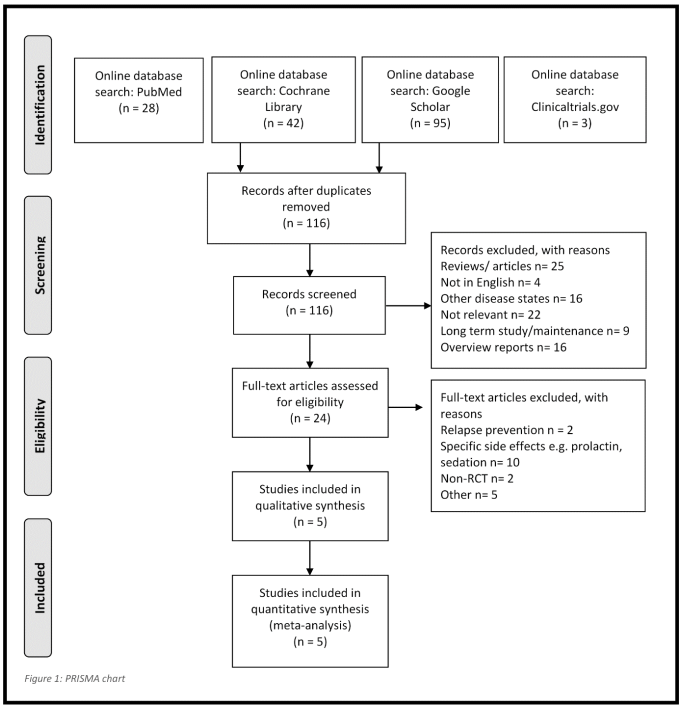


Figure 1 Flowchart summarizing the studies selection process

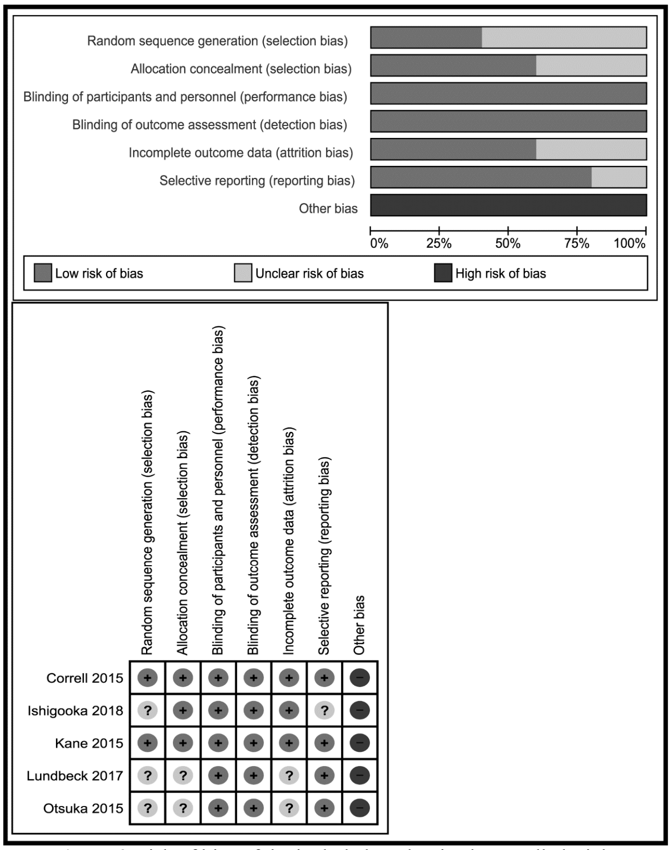


Figure 2 Risk of bias of the included randomized controlled trials

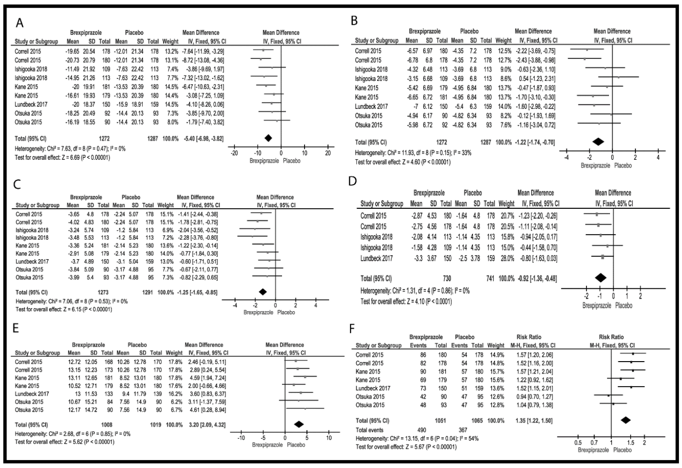


Figure 3 Efficacy of Brexpiprazole compared with placebo in the management of schizophrenia determined by the changes from baseline for (A) Positive and Negative Syndrome Scale (PANSS) total score; (B) PANSS positive; (C) PANSS negative; (D) PANSS excited component score; (E) Personal and Social Performance (PSP) compared with placebo and (F) Response rate >30%

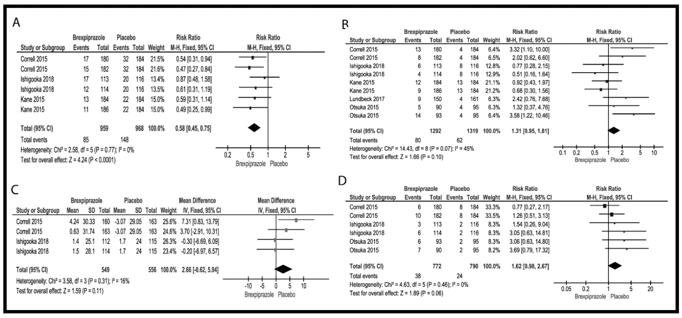


Figure 4 Tolerability and Safety of Brexpiprazole compared to Placebo (A) Discontinuation from Trials due to Adverse Events; (B) Side Effect-Akathisia; (C) Side Effect-Cholesterol; (D) Side Effect-Nausea

Table 1 Randomized controlled study included in the meta-analysis

Title	Doses	Outcome Measures
Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: a 6 week, randomised, double-blind, placebo-controlled study (Ishigooka, 2018)	2mg 4mg	PANSS, CGI-S, CGI-I, PANSS positive and negative subscale, PSP, Response rate, PANSS Excited Component Score, PANSS Marder Factor and Safety Profile
A multicentre, randomised, double-blind, controlled phase 3 trial of fixed dose brexpiprazole for the treatment of adults with acute schizophrenia (Kane *et al.* , 2015)	2mg 4mg	PANSS, CGI-S, CGI-I, PANSS positive and negative subscale, PSP, Response rate, PANSS Excited Component Score, Discontinuation due to lack of efficacy, PANSS Marder Factor and Safety Profile
Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia: a 6 week randomised, double-blind, placebo- controlled trial (Correll *et al*., 2015)	2mg 4mg	PANSS, CGI-S, CGI-I, PANSS positive and negative subscale, PSP, Response rate, PANSS Excited Component Score, Discontinuation due to lack of efficacy, PANSS Marder Factor and Safety Profile
Multicentre, randomized, double-blind, placebo-controlled study to assess tolerability, safety, and efficacy of OPC-34712 (0.25 to 6.0 mg) for treatment of adults hospitalized with an acute relapse of schizophrenia. Aripiprazole (10 to 20 mg) included as a positive control to confirm the assay sensitivity of the study (Otsuka, 2015).	2.5mg 5mg	PANSS, CGI-S, CGI-I, PANSS positive and negative subscale, PSP, Response rate, PANSS Excited Component Score, Discontinuation due to lack of efficacy, PANSS Marder Factor and Safety Profile
Interventional, randomised, double-blind, parallel-group, placebo-controlled, active-reference, flexible-dose study of brexpiprazole in patients with acute schizophrenia. NCT01810380 (Lundbeck, 2017)	Brexpiprazole 2-4mg	PANSS, CGI-S, CGI-I, PANSS positive and negative subscale, PSP, Response rate, PANSS Excited Component Score, Discontinuation due to lack of efficacy, PANSS Marder Factor and Safety Profile

References

1. Cooper, H.; Mishriky, R.; Reyad, A. A. Efficacy and Safety of Cariprazine in Acute Management of Psychiatric Disorders: a Meta-Analysis of Randomized Controlled Trials. *Psychiatr. Danub* 2020*, 32*, 36-45.
2. Antoun Reyad, A.; Mishriky, R. Cariprazine: pharmacology and clinical management of psychiatric disorders. *Psychiatric Annals* 2019*, 49*, 129-134.
3. Kirkbride, J. B.; Errazuriz, A.; Croudace, T. J.; Morgan, C.; Jackson, D.; Boydell, J.; Murray, R. M.; Jones, P. B. Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. *PLoS One* 2012*, 7*, e31660.
4. Taj, M.; Tirupati, S.; Thara, R. *Specific Mental Health Disorders: Psychotic Disorders;* 2008; Vol. 6, pp 187-196.
5. Andreasen, N. C. Understanding the Causes of Schizophrenia. *N. Engl. J. Med.* 1999*, 340*, 645-647.
6. Robinson, D.; Woerner, M. G.; Alvir, J. M.; Bilder, R.; Goldman, R.; Geisler, S.; Koreen, A.; Sheitman, B.; Chakos, M.; Mayerhoff, D.; Lieberman, J. A. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch. Gen. Psychiatry* 1999*, 56*, 241-247.

7. McCutcheon, R. A.; Abi-Dargham, A.; Howes, O. D. Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. *Trends in Neurosciences* 2019*, 42*, 205-220.
8. Tavcar, R.; Dernovsek, M. Z.; Zvan, V. Choosing Antipsychotic Maintenance Therapy - A Naturalistic Study. *Pharmacopsychiatry* 2000*, 33*, 66-71.
9. Mortimer, A. M. Symptom rating scales and outcome in schizophrenia. *British Journal of Psychiatry* 2007*, 191*, s7-s14.
10. Ayano, G. First generation antipsychotics: pharmacokinetics, pharmacodynamics, therapeutic effects and side effects: a review. *RRJChem* 2016*, 5*, 53-63.
11. Abi-Dargham, A.; Laruelle, M. Mechanisms of action of second generation antipsychotic drugs in schizophrenia: insights from brain imaging studies. *European Psychiatry* 2005*, 20*, 15-27.
12. Correll, C. U.; Leucht, S.; Kane, J. M. Lower Risk for Tardive Dyskinesia Associated With Second-Generation Antipsychotics: A Systematic Review of 1-Year Studies. *Am. J. Psychiatry* 2004*, 161*, 414-425.
13. Ndukwe, H. C.; Nishtala, P. S. Glucose monitoring in new users of second-generation antipsychotics in older people. *Arch. Gerontol. Geriatr.* 2017*, 70*, 136-140.
14. Sapra, M.; Lawson, D.; Iranmanesh, A.; Varma, A. Adiposity-independent hypoadiponectinemia as a potential marker of insulin resistance and inflammation in schizophrenia patients treated with second generation antipsychotics. *Schizophr. Res.* 2016*, 174*, 132-136.
15. Corponi, F.; Fabbri, C.; Bitter, I.; Montgomery, S.; Vieta, E.; Kasper, S.; Pallanti, S.; Serretti, A. Novel antipsychotics specificity profile: A clinically oriented review of lurasidone, brexpiprazole, cariprazine and lumateperone. *European Neuropsychopharmacology* 2019*, 29*, 971-985.
16. Ward, K.; Citrome, L. Brexpiprazole for the maintenance treatment of adults with schizophrenia: An evidence-based review and place in therapy. *Neuropsychiatric Disease and Treatment* 2019*, olume 15*, 247-257.
17. Lieberman, J. A. Dopamine partial agonists: a new class of antipsychotic. *CNS Drugs* 2004*, 18*, 251-267.
18. Ishima, T.; Futamura, T.; Ohgi, Y.; Yoshimi, N.; Kikuchi, T.; Hashimoto, K. Potentiation of neurite outgrowth by brexpiprazole, a novel serotonin-dopamine activity modulator: a role for serotonin 5-HT1A and 5-HT2A receptors. *Eur. Neuropsychopharmacol.* 2015*, 25*, 505-511.
19. Fornaro, M.; Fusco, A.; Anastasia, A.; Cattaneo, C. I.; De Berardis, D. Brexpiprazole for treatment-resistant major depressive disorder. *Expert Opin. Pharmacother.* 2019*, 20*, 1925-1933.
20. Chen, B.; Zhang, X.; Wen, J.; Zhang, B.; Chen, D.; Wang, S.; Cai, J.; Hu, G. Effects of 26 Recombinant CYP3A4 Variants on Brexpiprazole Metabolism. *Chem. Res. Toxicol.* 2019*, 33*, 172-180.
21. Parikh, N. B.; Robinson, D. M.; Clayton, A. H. Clinical role of brexpiprazole in depression and schizophrenia. *Therapeutics and clinical risk management* 2017*, 13*, 299-306.
22. Depp, C. A.; Loughran, C.; Vahia, I.; Molinari, V. Chapter 5 - Assessing Psychosis in Acute and Chronic Mentally Ill Older Adults. *Handbook of Assessment in Clinical Gerontology (Second Edition)* 2010, 123-154.
23. Juckel, G. In *Personal and Social Performance Scale;* Michalos, A. C., Ed.; Encyclopedia of Quality of Life and Well-Being Research; Springer Netherlands: Dordrecht, 2014; pp 4719-4724.
24. The Cochrane Collaboration Review Manager (RevMan). 2014a*, Version 5.3*.
25. Charrois, T. L. Systematic reviews: what do you need to know to get started? *Can. J. Hosp. Pharm.* 2015*, 68*, 144-148.
26. The Cochrane Collaboration RevMan 5 User Guide. 2014b.
27. Higgins, J.; Thomas, J.; Chandler, J., et al. Chapter 10: Analysing data and undertaking meta-analyses . https://training.cochrane.org/handbook/current/chapter-10 (accessed March 15th, 2020).
28. Turlik, M. Evaluating the results of a systematic review/meta-analysis...evidence-based medicine requires statistical analysis of data. *PODIATRY MANAGE* 2010*, 29*, 193-198.
29. Ghasemi, A.; Zahediasl, S. Normality tests for statistical analysis: a guide for non-statisticians. *International journal of endocrinology and metabolism* 2012*, 10*, 486-489.
30. Andrade, C. Understanding Relative Risk, Odds Ratio, and Related Terms. *Journal of Clinical Psychiatry* 2015*, 76*, 857-861.
31. Egger, M.; Smith, G.; Altman, D. Systematic Reviews in Health Care: Meta-Analysis in Context. *BMJ* 2001*, 323*.
32. Lundbeck, H. Brexpiprazole in Patients With Acute Schizophrenia (Clinicaltrials.gov identifier: NCT01810380). https://clinicaltrials.gov/ct2/show/NCT01810380?term=nct01810380&draw=2&rank=1 (accessed March 2nd, 2020).
33. Otsuka Pharmaceutical Development & Commercialization. Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 and Aripiprazole for Treatment of Acute Schizophrenia (STEP 203) (Clinicaltrials.gov identifier: NCT00905307). https://clinicaltrials.gov/ct2/show/NCT00905307 (accessed March 2nd, 2020).
34. Ishigooka, J.; Iwashita, S.; Tadori, Y. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. *Psychiatry Clin. Neurosci.* 2018*, 72*, 692-700.
35. Correll, C. U.; Skuban, A.; Ouyang, J.; Hobart, M.; Pfister, S.; McQuade, R. D.; Nyilas, M.; Carson, W. H.; Sanchez, R.; Eriksson, H. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. *Am. J. Psychiatry* 2015*, 172*, 870-880.
36. Kane, J. M.; Skuban, A.; Ouyang, J.; Hobart, M.; Pfister, S.; McQuade, R. D.; Nyilas, M.; Carson, W. H.; Sanchez, R.; Eriksson, H. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. *Schizophr. Res.* 2015*, 164*, 127-135.

37. Consilient Health Ltd Aripiprazole 5mg tablets. https://www.medicines.org.uk/emc/product/3543/smpc (accessed March 17th, 2020).
38. Das, S.; Barnwal, P.; Blessed, W. A.; Mondal, S.; Saha, I. Brexpiprazole: so far so good. *Therapeutic advances in psychopharmacology* 2016*, 6*, 39-54.
39. Antoun Reyad, A.; Girgis, E.; Mishriky, R. Efficacy and safety of brexpiprazole in acute management of psychiatric disorders: a meta-analysis of randomized controlled trials. *Int. Clin. Psychopharmacol.* 2020.
40. Kishi, T.; Oya, K.; Matsui, Y.; Nomura, I.; Sakuma, K.; Okuya, M.; Matsuda, Y.; Fujita, K.; Funahashi, T.; Yoshimura, R.; Iwata, N. Comparison of the efficacy and safety of 4 and 2 mg/day brexpiprazole for acute schizophrenia: a meta-analysis of double-blind, randomized placebo-controlled trials. *Neuropsychiatric disease and treatment* 2018*, 14*, 2519-2530.
41. Citrome, L. 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.* 2015*, 69*, 978-997.
42. Frampton, J. E. Brexpiprazole: A Review in Schizophrenia. *Drugs* 2019*, 79*, 189-200.
43. Aladeen, T.; Westphal, E.; Lee, Y.; Rong, C.; Rainka, M.; Capote, H.; McIntyre, R. S. The use of brexpiprazole amongst individuals with insufficient outcomes with aripiprazole or bupropion: A case series. *Perspect. Psychiatr. Care* 2018*, 54*, 507-513.
44. Lepola, U.; Hefting, N.; Zhang, D.; Hobart, M. Adjunctive brexpiprazole for elderly patients with major depressive disorder: An open-label, long-term safety and tolerability study. *Int. J. Geriatr. Psychiatry* 2018*, 33*, 1403-1410.

How to cite this article:

Aisha Begum *et al* (2020) 'Brexpiprazole In The Acute Management of Schizophrenia', *International Journal of Current Medical and Pharmaceutical Research,* 06(12), pp 5466-5471.

****