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BREXPIPRAZOLE AUGMENTATION IN TREATMENT RESISTANT OCD: SAFETY AND EFFICACY IN AN ITALIAN SAMPLE

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SUMMARY

Obsessive-compulsive disorder (OCD) is a common and debilitating psychiatric disorder with an approximate incidence of 2.5% in the general population. Serotonin reuptake inhibitors (SRIs) are considered the first line of pharmacological treatment but up to 50% of patients fail to achieve clinical remission or response. Atypical antipsychotics are one of the most common augmentation strategies in OCD treatment resistant patients. Brexpiprazole, a novel atypical antipsychotic with dopamine partial agonism action, has never been studied in addition to SRIs treatment in OCD resistant patients. This study retrospectively investigated the safety and efficacy of a 12 week brexpiprazole augmentation trial in 34 OCD resistant patients. SRI treatment resistance was defined as failing to improve the YBOCS total score by more than 25% from the beginning of the SRI trial. Brexpiprazole augmentation response was defined as at least a 25% improvement in the YBOCS total score. At the end of the study, 17 patients (50.0%) met the response criteria of ≥25% improvement in YBOCS total score vs. baseline. No safety issues were raised throughout the observation period. A total of 19 patients (55.9%) reported adverse experiences, generally mild and not requiring medical intervention. This is the first study to examine the safety and efficacy of brexpiprazole augmentation in resistant OCD patients. Our findings show that brexpiprazole may be a promising and well-tolerated augmentation strategy for SRI-resistant OCD patients. However, further research in larger populations is needed to confirm these results and investigate the long-term safety and tolerability of brexpiprazole in OCD patients.

Key words: *brexpiprazole – augmentation - treatment-resistant OCD – safety – SRIs*

Abbreviations: *OCD – Obsessive Compulsive Disorder; APA – American Psychiatric Association; SRIs – Serotonin Reuptake Inhibitors; EMA – European Medicine Agency; FDA – Food and Drug Administration; DSM 5 TR - Diagnostic and Statistical Manual of Mental Disorders 5th Edition Text Revised; YBOCS – Yale-Brown Obsessive-Compulsive Scale; d-TMS - deep Transcranial Magnetic Stimulation; CBT - Cognitive-Behavioral Therapy*

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a seriously debilitating psychiatric disorder characterized by the presence of obsessions and compulsions (American Psychiatric Association 2014). Similarly distributed across genders and with an approximate incidence of 2.5% in the general population, OCD is considered by the World Health Organization as the fourth most common psychiatric disease and among the top 20 causes of disability across the 15-44 years old population (Murray et al. 1996, Angst et al. 2004, Kessler et al. 2005). Obsessions are typically described as intrusive, recurrent, undesired and persistent thoughts, images or urges causing intense disconfort or anxiety. Compulsions, on the other side, are defined as repetitive behaviors or mental acts that people are driven to perform, to reduce obsessions induced distress or prevent a dreadful event (American Psychiatric Association 2014). Consensus guidelines and scientific literature generally recommend SRIs as the first-line pharmacological treatment for OCD. However, despite a brilliant safety profile and demonstrated effectiveness, a consistent rate of patients do not achieve meaningful improvements. It may be approximately estimated that up to 50% of patients do not reach response/remission after an adequate medication treatment trial (Pallanti & Quercioli 2006), although the exact proportion of patients who may be considered treatment resistant or intolerant is yet to define. Research in the last two decades has focused on SRIs augmentation strategies to address OCD treatment resistance unmet needs.

To date, the addition of atypical antipsychotics to SRI treatments is considered one of the most promising augmentation strategies (Koran & Saxena 2000, Maina et al. 2000, Van Roessel et al. 2023) although numerous off-label pharmacological treatments have been investigated (Van der Eynde et al. 2022, Gautam 2023). The neurobiological underpinnings of atypical antipsychotics use in resistant OCD lay in the cortico-striatal OCD

working model. According to this model, there may be an imbalance between the direct and indirect pathways, with subsequent hyperactivations of the circuitry contributing to OCD characteristics, such as repetitive thoughts and behavior (Denys et al. 2004). Accordingly, a malfunction in the physiological mechanisms of amygdala inhibition in OCD patients may be related to intrusive thoughts and chronic anxiety. The dysfunctional top-down inhibition of the amygdala itself may be affected by modifications to the mesolimbic dopaminergic system; in fact, increased dopamine inhibits the prefrontal cortex's ability to suppress anxiety-related amygdala activation (Denys et al. 2004). Thus, atypical antipsychotic add-on to SRI treatment may be a viable alternative in treating resistant OCD, given the hypothesis of dopaminergic hyperactivation in the patophysiology of the disorder.

The efficacy of several atypical antipsychotics has been demonstrated in patients with treatment-resistant OCD. Risperidone was reported to be the most effective treatment in several meta-analyses (Dold et al. 2013, Zhou et al. 2019); aripiprazole also appeared to be effective (Pessina et al. 2009, Muscatello et al. 2011); additionally quetiapine and olanzapine have been considered, however their results were inconsistent and a number of meta-analyses have failed to demonstrate their advantage over placebo (Bloch et al. 2006, Dold et al. 2013, 2015, Komossa et al. 2016); in a randomized, placebo-controlled trial conducted on treatment-resistant OCD patients, paliperidone significantly reduced Y-BOCS from baseline to post-treatment, but the difference between groups did not reach significance (Storch et al. 2013). An updated recent network meta-analysis comparing different augmentation strategies for treatment resistant OCD found that, among newer antipsychotics, both aripiprazole and risperidone were effective in significantly lowering Y-BOCS scores (Suhas et al. 2023). More recently, cariprazine has also been reported as a potential safe and effective augmentation strategy for resistance management in OCD (Martiadis et al. 2024).

Brexpiprazole is a novel atypical antipsychotic, recently approved by the European Medicines Agency (EMA) for the treatment of schizophrenia in adults and by the Food and Drug Administration (FDA) for the treatment of schizophrenia in adults and pediatric patients aged 13 years and older, as adjunctive therapy in treatment resistant major depressive disorder and for the treatment of agitation associated with Alzheimer's dementia (Siwek et al. 2023). Brexpiprazole's chemical structure resembles aripiprazole but is significantly different in its pharmacodynamic properties. In particular, brexpiprazole behaves as both a dopamine and serotonin partial agonist at D2 and 5HT1a receptors as well as a serotonin antagonist at 5HT2a receptors (Aftab & Gao 2017, Kikuchi et al. 2021). While partial agonism at D2 receptors represents the basis for its antipsychotic effect, its action on 5HT1a receptors may translate into pro-cognitive and mood-enhancing features, as well as sedative and anxiolytic effects. Moreover it exerts partial agonism on D3 dopamine receptors which might result in therapeutic effects on negative symptoms as well as on cognition and depressive symptoms (Stahl 2016). The drug also antagonizes 5HT2a, 5HT2c, 5HT7, α1, and H1 receptors. It has been suggested that the antagonism of 5HT7 might boost pro-cognitive and antidepressant effect, especially in combination with the 5HT1a partial agonism, and it might also have a positive impact on the negative schizophrenia symptoms (Siwek et al. 2023). Although low, the 5HT2c antagonism might additionally contribute to the antidepressant action (Siwek et al. 2023). Given its pharmacodynamic properties, and in particular its impact on the serotonergic system, it is possible to argue that brexpiprazole could exert a therapeutic effect when used as an augmentation strategy in treatment-resistant OCD. To date, no study has investigated this possibility. This study retrospectively investigated the safety and efficacy of brexpiprazole augmentation in OCD patients who did not respond to SRI treatment.

SUBJECTS AND METHODS

Clinical records of inpatients and outpatients diagnosed with Obsessive-Compulsive Disorder according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition Text Revised (DSM-5 TR) criteria, treated in the Departments of Mental Health of ASL Cuneo 2 (Cuneo, Italy), ASL Napoli 1 Centro (Naples, Italy), ASL Biella (Biella, Italy) from January 2022 and December 2023 were analyzed. Patients had to have a Yale-Brown Obsessive-Compulsive Scale (YBOCS) (Goodman et al. 1989) total score ≥16 and not respond to at least one adequate SRI trial (citalopram, clomipramine escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline). Treatment resistance was defined as failing to improve the YBOCS total score by more than 25% from the beginning of the SRI trial. Trials were considered adequate if they lasted at least 12 weeks and used an appropriate dose of SRIs according to America Psychiatric Association guidelines (APA 2007). To be included in the analyses patients must have undergone a twelve-week brexpiprazole augmentation trial. Brexpiprazole's starting dose was 1 mg/day for all patients. Dosage changes were established according to clinical judgment (no specific guidelines were followed) while the SRI dose remained unchanged during add-on. A written informed consent was previously obtained from all participants authorizing potential use of their anonymously collected data for teaching or research purposes. Written consent was also obtained for off-label treatment. Data on socio-demographics, clinical features,

Table 1. Socio-demographic and clinical characteristics of the sample

Parameters	N=34
Age, years (mean ± SD)	22.4 ± 10.7
Sex, n (%)	
Male	16 (47.1)
Female	18 (52.9.)
Marital status, n (%)	
Single	16 (47.1)
Married	17 (50.0)
Divorced	1 (2.9)
Educational level, years (mean ± SD)	12.2 ± 3.2
Working for pay, n (%)	
Yes	15 (44.1)
No	19 (55.9)
Age at onset, years (mean ± SD)	18.7 ± 4.1
Psychiatirc comorbidities, n (%)	
Yes	25 (73.5)
No	9 (26.5)
Type of psychiatric comorbities, n (%)	
Major Depression	13 (38.2)
Bipolar Disorder[1]	2 (5.8)
Substance Use Disorder[2]	4 (11.7)
Panic Disorder	1 (2.9)
Generalized Anxiety Disorder	1 (2.9)
ADHD	2 (5.8)
Kleptomania	1 (2.9)
Trichotillomania	1 (2.9)
Antidepressant, n (%)	
Clomipramine	11 (32.4)
Escitalopram	7 (20.6)
Fluoxetine	7 (20.6)
Fluvoxamine	4 (11.8)
Sertraline	5 (14.7)

[1]Bipolar Disorder Type II; [2]alcohol use disorder (n=2) and benzodiazepine use disorder (n=2);
ADHD: Attention deficit hyperactivity disorder

safety and tolerability issues was collected from medical records for each participant. Patients underwent control visits according to common clinical practice. All psychiatric diagnoses and clinical evaluations were made by experienced psychiatrists in OCD treatment. Medical records have been analyzed at the start of brexpiprazole treatment and every 4 weeks, for a total duration of 12 weeks. Treatment response was measured by the change in the YBOCS total score from baseline to the final 12 weeks. A responder was defined as a patient who experienced at least a 25% improvement in the YBOCS total score during the study. Accordingly, the percentage of brexpiprazole augmentation responders was calculated. The UKU Side Effect Rating Scale (Lingjaerde et al. 1987) was used at each visit to record all adverse experiences volunteered by patients or observed by investigators. Paired t-tests were used to evaluate YBOCS differences between baseline and the 12-week timepoint. The differences in participants' scores over time were also evaluated with repeated measures ANOVA. Statistical analysis was carried out using SPSS® software version 19. Significance was set at $p<0.05$.

RESULTS

34 patients fulfilled the entry criteria and were eligible for the study. Table 1 shows the socio-demographic and clinical characteristics of the 34 patients included and available data for all patients in the 12 week flexible dose augmentation period. 27 patients (79.4%) took the minimum dose (1 mg/day) of brexpiprazole; 6 patients (17.6%) used 2 mg/day and 1 (2.9%) took 3 mg/day. Patients showed a significant improvement over the 12-week study period: the total YBOCS score decreased from 27.4 (±DS 2.4) to 20.8 (±DS 3.2) (paired test: $t=9.973$, $df=33$, $p<0.001$) (Figure 1). When examining the YBOCS obsession and compulsion subscores we also found a significant improvement at week 12 compared to baseline. Table 2 shows YBOCS scores (total and subscale)

Table 2. Efficacy results for patients with obsessive-compulsive disorder who received brexpiprazole as add-on therapy. Score (SD)

	Baseline (T0)	4 weeks (T1)	8 weeks (T2)	12 weeks (T3)	Statistics
YBOCS total	27.4 (2.4)	24.3 (2.3)	22.4 (2.5)	20.8 (3.2)	T0 vs T1 t=8.483 p<0.001 T1 vs T2: t=6.843 p<0.001 T2 vs T3: t=5.469 p<0.001 ANOVA: F=32.406 p<0.001
YBOCS *Obsession*	13.9 (1.6)	12.3 (1.4)	11.4 (1.3)	10.6 (1.7)	T0 vs T1 t=5.939 p<0.001 T1 vs T2: t=6.197 p<0.001 T2 vs T3: t=4.451 p<0.001 ANOVA: F=21.178 p<0.001
YBOCS *Compulsion*	13.4 (1.5)	12.0 (1.3)	11.1 (1.4)	10.3 (1.8)	T0 vs T1 t=7.455 p<0.001 T1 vs T2: t=5.759 p<0.001 T2 vs T3: t=4.958 p<0.001 ANOVA: F=25.973 p<0.001

YBOCS: Yale-brown Obsessive-Compulsive Scale

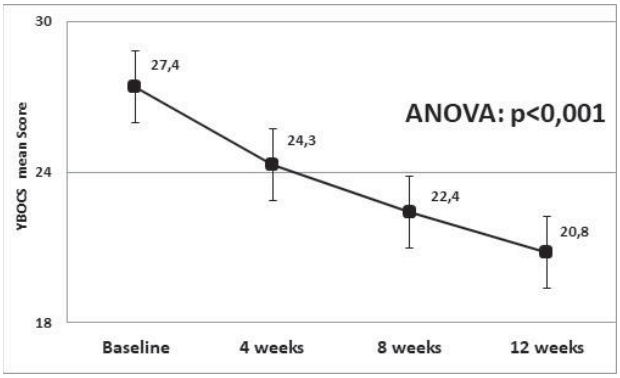

Figure 1. Mean reduction of Yale-Brown Obsessive-Compulsive Scale (YBOCS) scores during the observation period

during the 12-week period. At the end of the study, 17 patients (50.0%) met response criteria of ≥25% improvement in YBOCS total score vs. baseline. No safety issues related to the brexpiprazole add-on were raised throughout the observation period. A total of 19 patients (55.9%) reported adverse experiences. All side effects reported were mild and did not require any specific medical intervention. The most common adverse event was sleepiness, experienced by 9 patients (26.5%). Table 3 summarizes all adverse events observed in the sample.

Table 3. Adverse events reported in patients with obsessive-compulsive disorder who received brexpiprazole as add-on therapy

Adverse events	n (%)
Sleepiness/Sedation	9 (26.5)
Tension/Inner unrest	4 (11.8)
Tremor	4 (11.8)
Nausea/vomiting	1 (2.9)

DISCUSSION

To the extent of our knowledge, our study is the first to report evidence that the addition of brexpiprazole to ongoing SRI treatment can improve obsessive-compulsive symptoms in patients who did not respond to SRI monotherapy. Due to lack of data about brexpiprazole as an augmentation strategy in patients with OCD resistant to SRIs treatment, it is not possible to compare our findings with the existing literature. In our sample 50% of patients reached response (defined as more than 25% improvement in Y-BOCS baseline scores) at the 12 weeks endpoint. The response rate of brexpiprazole patients in our study was lower than that found recently by our group in a similar sample of OCD resistant patients treated with a low dose cariprazine add-on (Martiadis et al. 2024). However, the relatively small size of the two populations studied needs further larger studies to confirm this difference. Risperidone has been the most studied atypical antipsychotic for this purpose and current evidence suggests its efficacy at lower range doses (not exceeding 4 mg/day), though adverse effects such as sedation and weight gain may limit its tolerability (de Oliveira et al. 2023). Regular basis monitoring of potential adverse events is thus essential (de Oliveira et al. 2023). Aripiprazole, which is the most similar to brexpiprazole pharmacodynamic properties, is considered one of the first-line interventions in resistant OCD, together with deep Transcranial Magnetic Stimulation (d-TMS), ondansetron, and therapist administered Cognitive-Behavioral Therapy (CBT), as shown by a recent network meta-analysis of 55 RCTs examining 19 treatments or placebo involving 2011 participants (Suhas et al. 2023). Aripiprazole is generally well tolerated and associated with less adverse effects such as weight gain, sedation, or hyperprolactinemia, as well as a lower risk of akathisia compared to risperidone (Veale et al. 2014, Brakoulias & Stockings 2019). Although antipsychotic augmentation is currently considered the first-line treatment for SRI resistant patients (Fineberg et al. 2020), augmentation with those agents has been complexively found to be effective only in one third of patients (Grassi et al. 2021a,b). Our superior response rate may be the result of the small sample examined and needs to be confirmed. Considering the limited availability of long term data on the safety or efficacy of antidopaminergic medication in OCD, and given the significant long term risks of dopamine blocking medications, including cardiometabolic and tardive extrapyramidal symptoms risks, care should be taken not to prolong medication trials in the absence of clear evidence of benefit (Del Casale et al. 2019). However, from this perspective, in our study brexpiprazole showed an acceptable tolerability profile. The majority of adverse events were mild and transient, and didn't require medical interventions, without safety issues detected throughout the observation period. This reinforced treatment persistence, confirmed by the fact that no patients discontinued treatment. Moreover, when used as an SRIs augmentation strategy in resistant major depression, similarly to our study as for dosages and concomitant psychopharmacological treatments, brexpiprazole demonstrated better acceptability and tolerability compared to aripiprazole, quetiapine and olanzapine, as showed by a recent network meta-analysis on 20 studies comprising 6524 patients (Wang et al. 2023). This evidence further supports the safety and tolerability of this treatment strategy also in OCD resistant patients. There are several limitations to our study that need to be acknowledged. Caution should be exercised when interpreting the findings because of the small sample size, retrospective nature of data collection and the lack of a control group that limit results' generalizability; moreover the lack of randomization might have introduced a selection bias that could have affected the response rate.

CONCLUSIONS

This is the first study showing brexpiprazole's efficacy in reducing obsessive-compulsive symptoms in SRI resistant OCD patients over a 12-week low-dosage augmentation trial. These findings suggest that brexpiprazole may be a promising and well-tolerated augmentation strategy for SRI-resistant OCD patients. However, further research in larger populations is needed to confirm these results and investigate the long-term safety and tolerability of brexpiprazole in OCD patients. Additionally, future studies should compare the efficacy of brexpiprazole with other augmentation strategies, particularly atypical antipsychotics, to determine the most effective treatment options for resistant OCD patients.

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Contribution of individual authors:

Vassilis Martiadis: study design, data collection, interpretation of data and manuscript writing.

Enrico Pessina & Azzurra Martini: study design, data collection and literature search.

Fabiola Raffone, Filippo Besana & Miriam Olivola: literature search and manuscript review.

Carlo Ignazio Cattaneo: data collection, literature search and manuscript review.

References

1. *Aftab A & Gao K: The preclinical discovery and development of brexpiprazole for the treatment of major depressive disorder. Expert Opin. Drug Discov 2017; 12:1067–81*
2. *American Psychiatric Association. Committee on Nomenclature and Statistics; Diagnostic and Statistical Manual of Mental Disorders, 5th ed; American Psychiatric Press: Washington, DC, 2014*
3. *American Psychiatric Association. Practice Guidelines for the Treatment of Patients with Obsessive-Compulsive Disorder; American Psychiatric Association: Arlington, VA, 2007*
4. *Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D et al.: Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. Eur Arch Psychiatry Clin Neurosci 2004; 254:156-64*
5. *Bloch MH, Landeros-Weisenberger A, Kelmendi B, Coric V, Bracken MB, Leckman JF: A systematic review: Antipsychotic augmentation with treatment refractory obsessive-compulsive disorder. Mol Psychiatry 2006; 11:622–32*
6. *Brakoulias V & Stockings E: A systematic review of the use of risperidone, paliperidone and aripiprazole as augmenting agents for obsessive-compulsive disorder. Expert Opin Pharmacother 2019; 20:47-53*
7. *de Oliveira MVS, de Barros PMF, de Mathis MA, Boavista R, Chacon P, Echevarria MAN, et al.: Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders guidelines for the treatment of adult obsessive-compulsive disorder. Part I: pharmacological treatment. Braz J Psychiatry 2023; 45:146-61*
8. *Del Casale A, Sorice S, Padovano A, Simmaco M, Ferracuti S, Lamis DA, et al.: Psychopharmacological Treatment of Obsessive-Compulsive Disorder (OCD). Curr Neuropharmacol 2019; 17:710-36*
9. *Denys D, Zohar J, Westenberg HG: The role of dopamine in obsessive-compulsive disorder: preclinical and clinical evidence. J Clin Psychiatry 2004; 65(S 14):11-7*
10. *Dold M, Aigner M, Lanzenberger R, Kasper S: Anti-psychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. Int J Neuropsychopharmacol 2013; 16:557–74*
11. *Dold M, Aigner M, Lanzenberger R, Kasper S: Anti-psychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: an update meta-analysis of double-blind, randomized, placebo controlled trials. Int J Neuropsychopharmacol 2015; 18:pyv047*
12. *Fineberg NA, Hollander E, Pallanti S, Walitza S, Grünblatt E, Dell'Osso BM, et al.: Clinical advances in obsessive-compulsive disorder: a position statement by the international college of obsessive-compulsive spectrum disorders. International Clinical Psychopharmacology 2020; 35:173-93*
13. *Gautam M: Clinical recommendations for augmentation agents in obsessive-compulsive disorder partially responsive to serotonin reuptake inhibitors. J Clin Psychopharmacol 2023; 43:369-77*
14. *Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, et al.: The yale–brown obsessive compulsive scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46:1006–11*
15. *Grassi G, Cecchelli C, Mazzocato G, Vignozzi L: Early onset obsessive–compulsive disorder: the biological and clinical phenotype. CNS Spectrums 2022a; 27:421-7*
16. *Grassi G, Cecchelli C, Vignozzi L, Pacini S: Investigational and experimental drugs to treat obsessive-compulsive disorder. J Exp Pharmacol 2021b; 12:695-706*
17. *Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:593-602*
18. *Kikuchi T, Maeda K, Suzuki M, Hirose T, Futamura T, Mcquade RD: Discovery research and development history of the dopamine D2 receptor partial agonists, aripiprazole and brexpiprazole. Neuropsychopharmacol Rep 2021; 41:134–43*
19. *Komossa K, Depping AM, Meyer M, Kissling W, Leucht S. Second-generation antipsychotics for obsessive compulsive disorder. Cochrane Database Syst Rev 2010; 12:CD008141*
20. *Koran ML & Saxena S: Proceedings From the Fourth Annual IOCDC. CNS Spectr 2000; 5(S 4):24-31*
21. *Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K: The UKU side effect rating scale. A new comprehensive*

rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987; 334:1-100

22. *Maina G, Albert U, Pessina E, Salvi V: Antipsychotics in obsessive-compulsive disorder. Curr Psychiatry Rev 2005; 1:293-301*
23. *Martiadis V, Pessina E, Martini A, Raffone F, Cattaneo CI, De Berardis D, et al.: SRIs augmentation with cariprazine in patients with treatment resistant obsessive-compulsive disorder: a retrospective observational study. CNS Spectr 2024; 22:1-9*
24. *Murray CJ & Lopez AD: Evidence-based health policy lessons from the Global Burden of Disease Study. Science 1996; 274:740-43*
25. *Muscatello MRA, Bruno A, Pandolfo G, Micò U, Scimeca G, Romeo VM et al.: Effect of aripiprazole augmentation of serotonin reuptake inhibitors or clomipramine in treatment-resistant obsessive-compulsive disorder: a double-blind, placebo-controlled study. J Clin Psychopharmacol 2011; 31:174-9*
26. *Pallanti S & Quercioli L: Treatment-refractory obsessive-compulsive disorder: Methodological issues, operational definitions and therapeutic lines. Pro Neuro-Psychopharmacol Biol Psychiatry 2006; 30:400-12*
27. *Pessina E, Albert U, Bogetto F, Maina G. Aripiprazole augmentation of serotonin reuptake inhibitors in treatment resistant obsessive-compulsive disorder: a 12-week open-label preliminary study. Int Clin Psychopharmacol 2009; 24:265-9*
28. *Siwek M, Wojtasik-Bakalarz K, Krupa AJ, Chrobak AA: Brexpiprazole - Pharmacologic Properties and Use in Schizophrenia and Mood Disorders. Brain Sci 2023; 13:397*
29. *Stahl SM: Mechanism of action of cariprazine. CNS Spectrums 2016; 21:123–7*
30. *Storch EA, Goddard AW, Grant JE, De Nadai AS, Goodman WK, Mutch PJ et al.: Double-blind, placebo-controlled, pilot trial of paliperidone augmentation in serotonin reuptake inhibitor-resistant obsessive-compulsive disorder. J Clin Psychiatry 2013; 74:e527–32*
31. *Suhas S, Malo PK, Kumar V, Issac TG, Chithra NK, Bhaskarapillai B et al.: Treatment strategies for serotonin reuptake inhibitor-resistant obsessive compulsive disorder: A network meta-analysis of randomised controlled trials. World J Biol Psychiatry 2023; 24:162-77*
32. *Suhas S, PK Malo, V Kumar, TG Issac, NK Chithra, B Bhaskarapillai, et al.: Treatment strategies for serotonin reuptake inhibitor-resistant obsessive-compulsive disorder: A network meta-analysis of randomised controlled trials. World J Biol Psychiatry 2023; 24:162-77*
33. *Talaei A, Hosseini FF, Aghili Z, Akhondzadeh S, Asadpour E, Mehramiz NJ, et al.: A comparative, single-blind, randomized study on quetiapine and aripiperazole augmentation in treatment of selective serotonin reuptake inhibitor refractory obsessive-compulsive disorder. Can J Physiol Pharmacol 2020; 98:236-42*
34. *Van den Eynde V, Abdelmoemin WR, Abraham MM, Amsterdam JD, Anderson IM, Andrade C et al.: The prescriber's guide to classic MAO inhibitors (phenelzine, tranylcypromine, isocarboxazid) for treatment-resistant depression. CNS Spectr 2022; 15:1-14*
35. *van Roessel PJ, Grassi G, Aboujaoude EN, Menchón JM, Van Ameringen M, Rodríguez CI: Treatment-resistant OCD: Pharmacotherapies in adults. Compr Psychiatry 2023; 120:152352*
36. *Veale D, Miles S, Smallcombe N, Ghezai H, Goldacre B, Hodsoll J: Atypical antipsychotic augmentation in SSRI treatment refractory obsessive-compulsive disorder: a systematic review and meta-analysis. BMC Psychiatry 2014; 14:317*
37. *Wang J, Li W, Li M, Wu H, Qiu Z: Comparative efficacy and safety of 4 atypical antipsychotics augmentation treatment for major depressive disorder in adults. A systematic review and network meta-analysis. Medicine 2023; 102:38(e34670)*
38. *Zhou DD, Zhou XX, Li Y, Zhang KF, Lv Z, Chen XR et al.: Augmentation agents to serotonin reuptake inhibitors for treatment-resistant obsessive-compulsive disorder: A network meta-analysis. Pro Neuro-Psychopharmacol Biol Psychiatry 2019; 90:277–87*

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