Emerging Trends in Drugs, Addictions, and Health 2 (2022) 100031

Contents lists available at ScienceDirect

Emerging Trends in Drugs, Addictions, and Health

journal homepage: www.elsevier.com/locate/etdah

# Brexpiprazole as a new approach of treatment in somatization disorder

Stefania Chiappini[a,b,*], Alessio Mosca[a], Giovanni Martinotti[a,b], Francesco Di Carlo[a], Andrea Miuli[a], Luigi Dattoli[c], Mauro Pettorruso[a], Massimo Di Giannantonio[a]

[a] Department of Neurosciences, Imaging and Clinical Sciences, Università degli Studi G. D'Annunzio, Chieti-Pescara, Italy
[b] Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, School of Life and Medical Sciences, University of Hertfordshire, Hertfordshire, Northern Ireland AL10 9AB, United Kingdom
[c] Villa Maria Pia, Via del Forte Trionfale 36, Roma 00135, Italy

ARTICLE INFO

Handling Editor: Ornella Corazza.

*Keywords:*
Brexpiprazole
Somatic symptom disorder
Third-generation antipsychotic drug

ABSTRACT

Introduction: Somatic symptom disorder (SSD) is a mental disorder that involves one or more physical symptoms (e.g. palpitations, dizziness, diarrhoea, limb weakness, pain, and pseudo neurological symptoms) accompanied by one or more thoughts, feelings, and/or behaviours related to the somatic symptom(s) resulting in significant distress and/or dysfunction lasting for more than 6 months. At now the SSD can be refractory to psychiatric intervention including antidepressants, antiepileptics, and antipsychotics as well as the effectiveness of many of these treatments is limited. The objective of this study was to report the effectiveness of a third-generation antipsychotic drug brexpiprazole for treatment of a case of SSD together with the serotonin selective reuptake inhibitor (SSRI) fluvoxamine. Methods: A single case study of a 59-year-old female with SSD was here performed. Findings: After 4 weeks of treatment brexpiprazole, together with lamotrigine and fluvoxamine, was here effective in decreasing both depressive and anxiety symptoms, normalising previous unusual thought contents and of related behaviours. The patient reported an overall good response and started to function again in important domains of life. No adverse events occurred. Conclusion: To our knowledge, this is the first case showing Brexpiprazole effective for the treatment of a case of SSD as add-on to other drugs.

## 1. Introduction

### 1.1. Somatization disorder – an overview

Disorders related to somatization have had a troubled history and have undergone multiple classifications and definitions from ancient to modern times. Starting from the Briquet Syndrome, coined by Pierre Briquet who provided the basis for the Somatization Disorder (SD) (Briquet, 1859; Mai and Merskey, 1981; Mai and Merskey, 1980), different nosographic entities have succeeded or split into different disorders, and today the overlap between somatization disorders, meant as chronic conditions consisting of multiple medically unexplained bodily complaints, and the concepts of hysteria, hypochondria, anxiety and conversion disorder is still debated (Maggio et al., 2020).

Nowadays, according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Somatic symptom disorder (SSD) is a mental disorder that involves one or more physical symptoms accompanied by one or more thoughts, feelings, and/or behaviours related to the somatic symptom(s) resulting in significant distress and/or dysfunction. These two main criteria are associated with a chronicity criterion, referred to symptoms lasting for more than 6 months (American Psychiatric Association, 2013). Patients may suffer from bodily complaints, such as pain or fatigue, and from perceived disturbances of the cardiovascular, gastrointestinal, or other organ functions, including palpitations, dizziness, diarrhoea, limb weakness, etc. Those bodily complaints are usually associated with psychological and behavioural aspects like high health anxiety and checking behaviours (Henningsen, 2018). The spectrum of severity is wide, from mild symptoms with little functional impairment to severely disabling condition, associated with impaired physical and mental quality of life, with the possibility to develop comorbidities like depressive and anxiety disorders (Rosic et al., 2016).

The aetiology of SSD is unclear although some risk factors have been identified, including sexual abuse, chaotic lifestyle, and history of alcohol and substance abuse (Kurlansik and Maffei, 2016). From a phenomenological point of view SSD is characterized by an acute aware-

* Corresponding author.
*E-mail addresses:* stefaniachiappini9@gmail.com (S. Chiappini), andreamiuli@live.it (A. Miuli), digiannantonio@unich.it (M. Di Giannantonio).

https://doi.org/10.1016/j.etdah.2022.100031
Received 13 October 2021; Received in revised form 19 January 2022; Accepted 19 January 2022
Available online 21 January 2022

ness of various bodily sensations, which are interpreted as indicative of a physical illness (D'Souza and Hooten, 2021). Furthermore, severe somatization has been associated with a morbid personality, in particular the avoidant, the paranoid and the obsessive-compulsive (Rost et al., 1992). Its prevalence is estimated to be 5% to 7% of the general population, with higher female representation (Kurlansik and Maffei, 2016). However, data vary considerably in dependence on the underlying study population and the diagnostic criteria applied in the single studies (Piontek et al., 2018).

### 1.2. Management of SD

As for the treatment, while cognitive behaviour therapy (CBT) and mindfulness-based therapy have given good results (Tyrer et al., 2014; Kroenke, 2007; Williams and Kuyken, 2012; O'Malley et al., 1999), somatization disorders can be refractory to psychiatric intervention including antidepressants, antiepileptics, and antipsychotics (O'Malley et al., 1999; Kleinstäuber et al., 2014) and the effectiveness of many of these treatments has limited support (Kurlansik and Maffei, 2016). For this reason, patients are subjected to long treatments with multiple drugs and little benefit, resulting in frustration for both patient and physician (Henningsen, 2018; Rice et al., 2016). Given the remarkable comorbidity of somatization disorders with anxiety and depressive disorders (de Waal et al., 2004), selective serotonin reuptake inhibitors (SSRI) treatment proved effective in some cases (Noyes et al., 1998; Muller et al., 2008); furthermore, very good results were shown by augmentation with atypical antipsychotics such as paliperidone (Huang et al., 2012) and aripiprazole (Nagoshi et al., 2014) especially in resistant cases. Recently, a growing use of antipsychotic drugs as add-on treatments in sever mood or anxiety disorder has been recorded; in fact, data from the United Kingdom (UK) General Practice Research Database (GPRD) during years 1991–2000 in the general population, reported that less than 10% of first-time users were treated for schizophrenia or other psychotic disorders, whereas frequent indications for use of antipsychotic drugs were anxiety states, depression, and panic disorders, which combined accounted for over 50% of prescriptions (Kaye et al., 2003). Similarly, in a Danish population-based study identifying all users of antipsychotics in Denmark during years 1997–2018, users without diagnoses relevant to antipsychotic treatment including depression-spectrum, anxiety, and personality disorders, etc. comprised of the largest group (37%), followed by schizophrenia and bipolar-spectrum disorders (34%). Quetiapine was most commonly used, both overall (51%) and amongst users without diagnoses relevant to antipsychotic treatment (58%) (Højlund et al., 2021). Similarly, a Chinese study investigating the off-label use of antipsychotic medications in psychiatric inpatients, excluding patients with schizophrenia spectrum disorder or bipolar disorder, found antipsychotics were used in a wide spectrum of psychiatric disorders, with the rate being the highest amongst patients with dissociative (conversion) disorders, and other mental disorders, including somatoform disorders, major depression disorder, anxiety disorder, and insomnia; and the top three most commonly used antipsychotics being olanzapine (29.1%), quetiapine (20.3%) and risperidone (6.8%) (Wang et al., 2021).

### 1.3. Brexpiprazole as a new therapeutic opportunity available

Similarly to Aripiprazole and Cariprazine, Brexpiprazole is a third-generation antipsychotic drug, with dopamine D2 and serotonin 5-HT1A partial agonism (Solmi et al., 2017; Stahl, 2016; Orsolini et al., 2016), antagonist activity at serotonergic 5-HT2A receptors, with similar high affinities at all of these receptors (Ki: 0.1 nM to 0.5 nM) and antagonist activity at noradrenergic $\alpha$1B/2C [29]. Brexpiprazole (RXULTI®) is approved by the European Medicines Agency (EMA) for the treatment of schizophrenia in adult patients with a maximum recommended daily dose of 4 mg (EMA, 2021). Moreover, it has been shown to be an effective and safe drug for the treatment of major depressive disorder (MDD) as an augmentation therapy of SSRI antidepressants (Thase et al., 2015a, 2015b; Hobart et al., 2018; Cha et al., 2019), and in the 2015 received approval by the Food and Drug Administration (FDA) as an adjunctive agent in the treatment of MDD (Stahl, 2016; FDA, 2021). Brexpiprazole has also shown to be effective for the treatment of obsessive compulsive disorder (OCD) in augmentation with antidepressants (Dold et al., 2015), as well as for the treatment of anxious distress (Cha et al., 2019; Thase et al., 2019; Beyer and Weisler, 2016).

*Aim of the study*: Currently, there are not published studies in the literature that have evaluated the role of Brexpiprazole in the treatment of SSD. After reviewing theoretical and experimental backgrounds available, here we report a successful case where brexpiprazole have been effective in the treatment of the SSD used in augmentation to an SSRI antidepressant.

## 2. Case description

### 2.1. Initial assessment

Our patient is a 59-year-old female who presented to our centre with a psychiatric personal history of psychosis and current severe depressive symptoms, hyperarousal, anxiety, insomnia, comorbid obsessive-compulsive symptoms with polarization on gastrointestinal disorders, such as constipation, indigestion, abdominal bloating, and digestive difficulties, including circular thoughts related to a so-considered abnormal morphology of bowels, and long-lasting (2–3 h/day) rituals including use of laxatives, specific foods and beverages and cigarettes. Also, before the admission, she had been doing for months several specialistic visits and unnecessary diagnostic exams. She was at her second psychiatric admission; the first one was in 2003, determined by a similar symptomatology, and was followed by a three-week compulsory hospitalisation in a public hospital in Rome, from where she was discharged with a diagnosis of Brief Psychotic Episode and a pharmacological treatment composed by fluvoxamine 50 mg/day, quetiapine 100 mg/day, lorazepam 5 mg/day. During the following years, she continued pharmacological treatments monitored by the public psychiatric service and started a cognitive behavioural therapy. However, in the past three years, several events, such as her mother's sudden death, health problems (multiple tooth extraction), job loss, and personal/familiar difficulties related with the CoViD-19 disease, triggered again symptoms, which had occurred before. Subsequent treatment strategies, such as extensive pharmacotherapy (antidepressants agents, e.g. paroxetine, mirtazapine; second-generation antipsychotic medications, e.g. quetiapine, olanzapine) had not significantly improved her situation for over three years, leading to despair, pervasive anxiety, subtotal insomnia, reduced appetite, and weight, increase in negativism and anankastic behaviours, social withdrawal, reduction in personal functioning. Before admission to our centre she accessed the public Emergency Department several times for panic attacks. When arrived, collecting personal information from her was very difficult, because her thoughts were polarised on the somatic disease and was not possible to understand her emotional experience; thus, in the first phase her husband and her psychiatrist were the major source of information regarding her. She appeared asthenic, careless, agitated, and worried. Initial psychodiagnostic evaluation included: Montgomery-Asberg Depression Rating Scale (MADRS) scored 45/50; Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scored 30/40, with current somatic obsessions focused on constipation and compulsions related to the alvus control through rituals including laxatives and specific foods (e.g. kiwifruit) and beverages (e.g. coffee), no insight and high global severity (scored 5/5); Hamilton Anxiety Scale (HAM-A) scored 44/56; Toronto Alexithymia Scale (TAS-20) scored 64/100 which is indicative of alexithymia; Positive and Negative Syndrome Scale (PANSS) scored 126/210 with highest scores on tension, anxiety, somatic worries, unusual thoughts, rigid and stereotyped ideation, and active/passive social withdrawal; Self-report Symptom Inventory (SCL-90) resulted in highest scores in the following items: Somatization (1.16), Obsession-

Compulsion (2.7), Depression (2.7), Anxiety (3.1), Sleep Disturbances (3.3).

### 2.2. Treatment

Because of the severe clinical conditions, haloperidol 3 mg/day, promazine 50 mg/day, and delorazepam 3.5 mg/day were initiated, together with fluvoxamine and lamotrigine at low doses in order to avoid induction side effects. After five days, fluvoxamine has been increased to 50 mg/day and brexpiprazole started at 1 mg/day, then titrated to 3 mg/day during 7 days. Lamotrigine was titrated up to 200 mg/day during 15 days. In the meanwhile, haloperidol and delorazepam, firstly used to manage acute symptoms, have been gradually reduced and then interrupted in 10 days. Promazine, used only for the sleeping problems, was then substituted by trazodone 75 mg. Vital signs were stable. No adverse events occurred.

### 2.3. Outcome and follow-up

Evaluation after 4 weeks revealed a decrease in both depressive and anxiety symptoms, a normalisation of the previous unusual thought contents, which were now criticised, and of related behaviours. The patient reported an overall good response and started to function again in important domains of life. Before discharge from the clinical centre, a psychodiagnostic evaluation has been performed, being all scales showing a reduction in scores: MADRS from 45/50 to 5/50; Y-BOCS from 30/40 to 0/40, with current excellent insight and no level of severity scored 0/5; HAM-A from 44/56 to 2/56; TAS-20 64/100 to 46/100 which is not anymore indicative of alexithymia; PANSS from 126/210 to 30/210; SCL-90 resulted in an evident reduction of the scores previously recorded, such as Somatization (from 1.16 to 0.16), Obsession-Compulsion (from 2.7 to 0.1), Depression (from 2.7 to 0.15), Anxiety (from 3.1 to 0), and Sleep Disturbances (from 3.3 to 0.6). She was discharged with a diagnosis of Somatic Symptom Disorder and currently continues brexpiprazole treatment, and has been in remission for 2 months now. We systematically monitor symptoms and possible adverse effects.

## 3. Discussion

To our knowledge, this is the first report to show the efficacy of brexpiprazole in improving depressive and anxiety symptoms in patients with an SSD. In this case, brexpiprazole has been used as an augmentation therapy considered the limited efficacy of SSRIs in the induction phase on pervasive anxiety and depressive symptoms, and in order to avoid eventual side effects related to higher dosages of fluvoxamine. Atypical antipsychotics, specifically aripiprazole, olanzapine, and quetiapine, may be able to improve symptoms in patients with an inadequate response to common antidepressants such as SSRIs (Mulder et al., 2018). However, they might be associated with side effects related to specific pharmacologic profiles and interactions, including symptoms of akathisia, weight gain, and sedation/somnolence, making them unsuitable for some patients and reducing the compliance to treatments (Mulder et al., 2018; Thase, 2016).

Specifically, in respect to factors and neurobiological mechanisms explaining the effectiveness of brexpiprazole, it was possibly related to its pharmacological profile, showing affinity for multiple receptors, including the 5-HT2A, 5-HT2B, 5-HT7, noradrenaline, histamine H1, and muscarinic M1 receptors (Solmi et al., 2017; Stahl, 2016; Orsolini et al., 2016). Moreover, it has shown to have a good tolerability profile; in fact, no adverse effects have been recorded. On this regard, compared to aripiprazole, brexpiprazole has lower intrinsic activity at the D2 receptor, but exhibits a more potent 5-HT2A antagonism, which is why it appears to be less likely to induce extrapyramidal symptoms (EPS) (Stahl, 2016). Pharmacodynamic drug-drug interactions between brexpiprazole and fluvoxamine may have been successfully used here. In fact, fluvoxamine is a potent SSRI with a very high affinity for the serotonin transporter and a negligible affinity for all other receptors and transporters, with the exception of the opioid receptor $\sigma 1$, on which it acts as a potent agonist, this contributing to its antidepressant and anxiolytic properties. It has been approved as treatment of OCD, social anxiety disorder, depression, panic disorder, generalized anxiety disorder (GAD), and posttraumatic stress disorder (PTSD) with dosages ranging from 50 mg/day up to 300 mg/day[40]. Furthermore, considering the involvement of serotonin in mediating certain aspects of dopamine-related actions, such as locomotion, reward, and threat avoidance, and the beneficial effects of the treatments proposed here, a serotonergic dysfunction might be considered, as might be in a number of psychopathological disorders affecting emotions, memory, sleep, etc. such as depression, anxiety disorders, eating disorders, impulse control disorders, etc., all conditions where drugs with main activities on 5-HT, such as SSRIs, are reasonably effective therapeutic agents (Marazziti, 2017; Lin et al., 2014). Finally, lamotrigine, a glutamate, voltage-gated sodium channel blocker (Glu-CB) used as anticonvulsant and mood stabilizer, has been added. Apart for seizures, it is commonly prescribed for maintenance treatment of bipolar I disorder, and neuropathic pain/chronic pain, and as adjunctive treatment for psychosis, schizophrenia and major depressive disorder (StahlStephen GM, 2021). The three drugs did not show pharmacokinetic interactions that might have been associated with side effects. Despite the therapeutic indications recorded (EMA, 2021), the use of brexpiprazole was effective in this context. This use is called as off-label and refers to the use of mediation for a diagnosis, age group, or biological condition (such as pregnancy) that is not an officially approved use of that medication. Even though inappropriate, unjustified, or reflexive off-label prescribing may determine unnecessary risks for side effects, or not be efficacious, and may have medico-legal consequences (Wang et al., 2021), as in the presented case, in most settings it is common and legal, and may be reasonable and necessary when e.g. current treatments options have failed, and might give prescribers an opportunity to provide their patients the latest possible treatment options. For example, although there have been no randomized, controlled trials, aripiprazole, which is quite similar as pharmacological profile to brexpiprazole, has been found to be effective in treating anxiety disorders in two open-label trials (Pae et al., 2008; Katzman, 2011). Many factors contribute to off-label use of medication in psychiatry, including an incomplete biological understanding of the pathophysiology of mental illnesses and the evidence that current pharmacologic treatments generally act on a broad range of receptor systems in the brain (Carton et al., 2015). In this means a personalized medicine approach is desirable. Moreover, at now there are a limited number of medications available for a relatively large number of mental disorders, and there is often a slow, expensive process for approval for a new indication which may disincentivize pharmaceutical companies. Then, possibly brexpiprazole might be approved in the future for several other indications than the current ones.

A latter point which might not be underestimated is that there are high heterogeneity and substantial differences in data regarding prevalence of SSD in primary care patients, e.g. detection rates vary according to the use of diagnostic criteria, such as the International Classification of Diseases (ICD) or the DSM. As low detection of SSD in primary care means a low management of them, SSD poses a highly relevant public health problem, and this is particularly alarming as the primary care practice serves as the patient's first point of entry into the health care system and access to mental health services (Piontek et al., 2018). In this means, a specific training and reliable diagnostic tools improving the early detection of SSD are needed.

## 4. Conclusion

These data indicate that adjunctive brexpiprazole 3 mg/day could be a safe and efficacious treatment option in reducing both depressive and

anxiety symptoms in patients with clinically relevant symptomatology who have not responded to an SSRI therapy.

## Funding

None.

## Patient consent for publication

Data in the manuscript were collected and reported with patient's informed consent.

## Declaration of Competing Interest

GM: has been a consultant and/or a speaker and/or has received research grants from Angelini, Doc Generici, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, Recordati.

SC, AM, AMi, FDC, LD, MP: nothing to be declared. MDG: has been a consultant and/or a speaker and/or has received research grants from Angelini, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Servier, Recordati.

## CRediT authorship contribution statement

**Stefania Chiappini:** Conceptualization, Writing – original draft. **Alessio Mosca:** Conceptualization, Writing – original draft. **Giovanni Martinotti:** Conceptualization, Writing – review & editing. **Francesco Di Carlo:** Writing – review & editing. **Andrea Miuli:** Writing – original draft. **Luigi Dattoli:** Writing – review & editing. **Mauro Pettorruso:** Writing – review & editing. **Massimo Di Giannantonio:** Writing – review & editing.

## Acknowledgments

None.

## References

Briquet P.*Traite´ Clinique et Therapeutique de l'hyste´rie*. (J.B. Bailliere et fils, ed.). Paris; 1859.

Mai, F.M., Merskey, H., 1981. Briquet's concept of hysteria: an historical perspective. Can. J. Psychiatry 26 (1), 57–63. doi:10.1177/070674378102600112.

Mai, F.M., Merskey, H., 1980. Briquet's Treatise on hysteria. A synopsis and commentary. Arch. Gen. Psychiatry 37 (12), 1401–1405. doi:10.1001/archpsyc.1980.01780250087010.

Maggio, J., Alluri, P.R., Paredes-Echeverri, S., et al., 2020. Briquet syndrome revisited: implications for functional neurological disorder. Brain Commun. 2 (2), fcaa156. doi:10.1093/braincomms/fcaa156.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed.,. 2013.

Henningsen, P., 2018. Management of somatic symptom disorder. Dialogues Clin. Neurosci. 20 (1), 23–31. doi:10.31887/DCNS.2018.20.1/phenningsen.

Kurlansik, S.L., Maffei, M.S., 2016. Somatic symptom disorder. Am. Fam. Physician 93 (1), 49–54.

D'Souza R.S., Hooten W.M. Somatic syndrome disorders. In: treasure Island (FL); 2021.

Rost, K.M., Akins, R.N., Brown, F.W., Smith, G.R., 1992. The comorbidity of DSM-III-R personality disorders in somatization disorder. Gen. Hosp. Psychiatry 14 (5), 322–326. doi:10.1016/0163-8343(92)90066-j.

Piontek, K., Shedden-Mora, M.C., Gladigau, M., Kuby, A., Löwe, B., 2018. Diagnosis of somatoform disorders in primary care: diagnostic agreement, predictors, and comaprisons with depression and anxiety. BMC Psychiatry 18 (1), 1–9. doi:10.1186/s12888-018-1940-3.

Tyrer, P., Cooper, S., Salkovskis, P., et al., 2014. Clinical and cost-effectiveness of cognitive behaviour therapy for health anxiety in medical patients: a multicentre randomised controlled trial. Lancet 383 (9913), 219–225. doi:10.1016/S0140-6736(13)61905-4.

Kroenke, K., 2007. Efficacy of treatment for somatoform disorders: a review of randomized controlled trials. Psychosom. Med. 69 (9), 881–888. doi:10.1097/PSY.0b013e31815b00c4.

Williams, J.M.G., Kuyken, W., 2012. Mindfulness-based cognitive therapy: a promising new approach to preventing depressive relapse. Br. J. Psychiatry 200 (5), 359–360. doi:10.1192/bjp.bp.111.104745.

O'Malley, P.G., Jackson, J.L., Santoro, J., Tomkins, G., Balden, E., Kroenke, K., 1999. Antidepressant therapy for unexplained symptoms and symptom syndromes. J. Fam. Pract. 48 (12), 980–990.

Kleinstäuber, M., Witthöft, M., Steffanowski, A., van Marwijk, H., Hiller, W., Lambert, M.J., 2014. Pharmacological interventions for somatoform disorders in adults. Cochrane Database Syst. Rev. (11), CD010628 doi:10.1002/14651858.CD010628.pub2.

Rosic, T., Kalra, S., Samaan, Z., 2016. Somatic symptom disorder, a new DSM-5 diagnosis of an old clinical challenge. BMJ Case Rep. 2016. doi:10.1136/bcr-2015-212553.

Rice, A.S.C., Smith, B.H., Blyth, F.M., 2016. Pain and the global burden of disease. Pain 157 (4), 791–796. doi:10.1097/j.pain.0000000000000454.

de Waal, M.W.M., Arnold, I.A., Eekhof, J.A.H., van Hemert, A.M., 2004. Somatoform disorders in general practice: prevalence, functional impairment and comorbidity with anxiety and depressive disorders. Br. J. Psychiatry 184, 470–476. doi:10.1192/bjp.184.6.470.

Noyes, R.J., Happel, R.L., Muller, B.A., et al., 1998. Fluvoxamine for somatoform disorders: an open trial. Gen. Hosp. Psychiatry 20 (6), 339–344. doi:10.1016/s0163-8343(98)00044-9.

Muller, J.E., Wentzel, I., Koen, L., Niehaus, D.J.H., Seedat, S., Stein, D.J., 2008. Escitalopram in the treatment of multisomatoform disorder: a double-blind, placebo-controlled trial. Int. Clin. Psychopharmacol. 23 (1), 43–48. doi:10.1097/YIC.0b013e32825ea301.

Huang, M., Luo, B., Hu, J., et al., 2012. Combination of citalopram plus paliperidone is better than citalopram alone in the treatment of somatoform disorder: results of a 6-week randomized study. Int. Clin. Psychopharmacol. 27 (3), 151–158. doi:10.1097/YIC.0b013e328351c7e8.

Nagoshi, Y., Tominaga, T., Fukui, K., 2014. Effect of aripiprazole augmentation for treatment-resistant somatoform disorder: a case series. J. Clin. Psychopharmacol. 34 (3), 397–398. doi:10.1097/JCP.0000000000000063.

Kaye, J.A., Bradbury, B.D., Jick, H., 2003. Changes in antipsychotic drug prescribing by general practitioners in the United Kingdom from 1991 to 2000: a population-based observational study. Br. J. Clin. Pharmacol. 56 (5), 569–575. doi:10.1046/j.1365-2125.2003.01905.x.

Højlund, M., Andersen, J.H., Andersen, K., Correll, C.U., Hallas, J., 2021. Use of antipsychotics in Denmark 1997-2018: a nation-wide drug utilisation study with focus on off-label use and associated diagnoses. Epidemiol. Psychiatr. Sci. doi:10.1017/S2045796021000159.

Wang, J., Jiang, F., Yang, Y., et al., 2021. Off-label use of antipsychotic medications in psychiatric inpatients in China: a national real-world survey. BMC Psychiatry 21 (1), 1–9. doi:10.1186/s12888-021-03374-0.

Solmi, M., Murru, A., Pacchiarotti, I., et al., 2017. Safety, tolerability, and risks associated with first- and second-generation antipsychotics: a state-of-the-art clinical review. Ther. Clin. Risk Manag. 13, 757–777. doi:10.2147/TCRM.S117321.

Stahl, S.M., 2016. Mechanism of action of brexpiprazole: comparison with aripiprazole. CNS Spectr. 21 (1), 1–6. doi:10.1017/S1092852915000954.

Orsolini, L., Tomasetti, C., Valchera, A., et al., 2016. An update of safety of clinically used atypical antipsychotics. Expert Opin. Drug Saf. 15 (10), 1329–1347. doi:10.1080/14740338.2016.1201475.

EMA. Rxulti-Epar-Product-Information_en.; 2021. https://www.ema.europa.eu/en/documents/product-information/rxulti-epar-product-information_en.pdf.

Thase, M.E., Youakim, J.M., Skuban, A., et al., 2015a. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J. Clin. Psychiatry 76 (9), 1232–1240. doi:10.4088/JCP.14m09689.

Thase, M.E., Youakim, J.M., Skuban, A., et al., 2015b. 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. J. Clin. Psychiatry 76 (9), 1224–1231. doi:10.4088/JCP.14m09688.

Hobart, M., Skuban, A., Zhang, P., et al., 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. J Clin Psychiatry 79 (4). doi:10.4088/JCP.17m12058.

Cha, D.S., Luo, X., Ahmed, J., Becirovic, L., Cha, R.H., McIntyre, R.S., 2019. Brexpiprazole as an augmentation agent to antidepressants in treatment resistant major depressive disorder. Expert Rev. Neurother. 19 (9), 777–783. doi:10.1080/14737175.2019.1653759.

FDA. Rexulti (brexpiprazole) FDA Approval History. 2021

Dold, M., Aigner, M., Lanzenberger, R., Kasper, S., 2015. Antipsychotic 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. 18 (9). doi:10.1093/ijnp/pyv047.

Thase, M.E., Weiller, E., Zhang, P., Weiss, C., McIntyre, R.S., 2019. Adjunctive brexpiprazole in patients with major depressive disorder and anxiety symptoms: post hoc analyses of three placebo-controlled studies. Neuropsychiatr. Dis. Treat. 15, 37–45. doi:10.2147/NDT.S185815.

Beyer, J.L., Weisler, R.H., 2016. Adjunctive brexpiprazole for the treatment of major depressive disorder. Expert Opin. Pharmacother. 17 (17), 2331–2339. doi:10.1080/14656566.2016.1254188.

Mulder, R., Hamilton, A., Irwin, L., et al., 2018. Treating depression with adjunctive antipsychotics. Bipolar Disord. 20, 17–24. doi:10.1111/bdi.12701.

Thase, M.E., 2016. Adverse effects of second-generation antipsychotics as adjuncts to antidepressants: are the risks worth the benefits? Psychiatr. Clin. N. Am. 39 (3), 477–486. doi:10.1016/j.psc.2016.04.008.

StahlStephen GM, 2021. Stahl's Essential Psychopharmacology : Prescriber's Guide, 6th ed. Cambridge University Press.

Marazziti, D., 2017. Understanding the role of serotonin in psychiatric diseases. F1000Res. 6, 180. doi:10.12688/f1000research.10094.1.

Lin, S.H., Lee, L.T., Yang, Y.K., 2014. Serotonin and mental disorders: a concise review on molecular neuroimaging evidence. Clin. Psychopharmacol. Neurosci. Off. Sci. J. Korean Coll. Neuropsychopharmacol. 12 (3), 196–202. doi:10.9758/cpn.2014.12.3.196.

Pae, C.U., Serretti, A., Patkar, A.A., Masand, P.S., 2008. Aripiprazole in the treatment of depressive and anxiety disorders: a review of current evidence. CNS Drugs 22 (5), 367–388. doi:10.2165/00023210-200822050-00002.

Katzman, M.A., 2011. Aripiprazole: a clinical review of its use for the treatment of anxiety disorders and anxiety as a comorbidity in mental illness. J. Affect. Disord. 128 (Suppl), S11–S20. doi:10.1016/S0165-0327(11)70004-0.

Carton, L., Cottencin, O., Lapeyre-Mestre, M., et al., 2015. Off-label prescribing of antipsychotics in adults, children and elderly individuals: a systematic review of recent prescription trends. Curr. Pharm. Des. 21 (23), 3280–3297. doi:10.2174/1381612821666150619092903.