

BREXPIRAZOLE 2 mg STARTING DOSE: A CASE SERIES

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INTRODUCTION

Brexiprazole (Rexulti package insert, 2015) is a third generation, serotonin-dopamine activity modulator, approved on July 2015 in the USA for the treatment of schizophrenia and for adjunctive therapy to antidepressant treatment in patients with major depressive disorder. The FDA-recommended target dosage for the treatment of schizophrenia in adults is 2 mg to 4 mg once daily. The approved starting dose of brexpiprazole for the treatment of schizophrenia in adults is 1 mg once daily on days 1 to 4, 2 mg once daily on day 5 through day 7, then to 4 mg on day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg. The brexpiprazole titration period could delay the adequate control of symptoms and prolong the duration of disease leading to an apparent poor response to treatment and preclude some antipsychotic switching strategies such as abrupt switch and descending taper switch (Crapanzano et al. 2021). To our knowledge, there is no previous report on the use of brexpiprazole at starting dose of 2 mg in an adult sample affected by Schizophrenia Spectrum and Other Psychotic Disorders. We briefly present 3 patients with severe psychosis, followed on January-February by 2 different Psychiatry Outpatient Units of the Italian National Health Service located in Agrigento and Florence, Italy. All patients were treated with brexpiprazole 2 mg/d without titration. The approved starting dose is 1 mg daily, thus the off-label use was discussed with, and approved by, each of the patients treated, who signed an informed consent.

CASES

Case 1

A 22-year-old Latin American male drug-naive patient (approximately two weeks after the onset of initial symptoms) presenting a first episode of psychosis characterized by persecutory and referential delusions, anguish, inner tension, insomnia and impaired working performance was treated with lorazepam 2.5 mg in the evening and brexpiprazole 2 mg/d on day 1, 3 mg/d on day 3, 4 mg on day 8. Two weeks

later the patient showed a partial improvement in psychotic symptoms and a notable absence of adverse effects except mild transient sedation.

Case 2

A 48-year-old Caucasian woman presented to our Outpatient Units due to relapse of psychotic symptoms including persecutory, referential and passivity delusions, anxiety, inner tension and perplexity. She had a single previous analogous psychotic episode one year earlier, treated with paliperidone 6 mg/d with complete remission that she discontinued prematurely without consultation with the prescribing doctor. We prescribed a starting dose of brexpiprazole 2 mg/d with a subsequent marked reduction of anxiety/inner tension/perplexity and a partial improvement of delusion symptoms during the first 10 days of treatment. Higher doses were not required. No side effects were observed.

Case 3

A 50-years-old Caucasian man was evaluated 3 days after a single hospitalization (January 2022) due to a first psychotic episode characterized by auditory hallucinations, mental disorganization, delusions, and psychomotor agitation. A polypharmacy was prescribed at hospital discharge: valproate 1000 mg/d, quetiapine 75 mg/d, delorazepam 3 mg/d. The patient achieved a remission of delusions, hallucinations, agitation but persistence of confusion, blunted affect, avolition, alogia, anhedonia, suspicious behavior and perplexity. He immediately discontinued the pharmacological treatment without consultation with the prescribing doctor due to excessive sedation. A starting dose of brexpiprazole 2 mg/d was prescribed with a subsequent reduction of confusion and perplexity and without relapse of delusion symptoms and hallucinations during the first 2 weeks of treatment. Sedation or other side effects were not observed.

DISCUSSION

Use of a subtherapeutic dose of brexpiprazole (4 days are required to reach a therapeutic dose of 2 mg) may be unsuitable without the advantage of frequent

clinical observations provided in psychiatric inpatient units, furthermore acute symptoms if untreated can develop into a more severe psychotic episode. Finally the importance of reducing the duration of untreated psychosis is well recognized (Agius et al. 2010, Mees et al. 2011, Ostojčić et al. 2018). Results of pooled safety data from short term studies showed that there were no reports of adverse events with an incidence \geq 5% and twice that of placebo in patients treated with brexpiprazole within the recommended dose. The incidence of adverse events at least two-fold higher in the >4 mg brexpiprazole group than 2-4 mg brexpiprazole group were: akathisia, anxiety, somnolence, dizziness, extrapyramidal symptoms. Of note, in the high dose group brexpiprazole was started without any titration (Kane et al. 2016). In line with these data and with meta-analysis assessing efficacy of brexpiprazole 2-4 mg/d (Kane et al. 2016, Marder et al. 2017), this case series suggests that a 2 mg starting dose of brexpiprazole may be safe, provide adequate and rapid control of symptoms, shorten the treatment duration with a suboptimal dose, and reduce the need for comedication (such benzodiazepines to treat severely excited patients) or antipsychotic switching. Larger, prospective and randomized trials should be conducted to confirm our preliminary observations and better define selected clinical features that may justify a rapid dose titration.

Contribution of individual authors:

Calogero Crapanzano: conceptualization, writing original draft, writing review, editing.

Ilaria Casolaro & Bruno Beccarini Crescenzi: writing review, editing.

Chiara Amendola: supervision.

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