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Review Article

Measures of Treatment Success in Schizophrenia, With A Focus on Brexpiprazole: A Narrative Review

Short Title: Brexpiprazole And Treatment Success

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Abstract:

Antipsychotic treatment for patients with schizophrenia is effective, but unmet needs remain. Main areas in which needs are present and treatment success can be measured are efficacy, tolerability, adherence, response, remission, life engagement, and recovery. Brexpiprazole is an atypical antipsychotic, which acts as a partial agonist on dopamine D2 receptors.

This narrative review will discuss brexpiprazole in the light of measures of treatment success. Specifically, available data on efficacy, tolerability, adherence, and response are explored. Recovery is currently not very well defined and seems hard to achieve for patients with schizophrenia with current treatments. Functional outcomes and life engagement are essential on the way to recovery. Life engagement is discussed in more detail, with an outlook of how this measure may make recovery a more concrete, tenable, and measurable process, potentially employed as an outcome in clinical trials and in clinical care.

Keywords: Schizophrenia, Brexpiprazole, Efficacy, Tolerability, Adherence, Response, Remission, Life Engagement, Recovery, Quality of Life

Background:

Schizophrenia is a disease that causes great suffering and impairment in most afflicted patients. Antipsychotic treatment is effective, but unmet needs remain [1]. The main intended effect of available antipsychotics is symptom reduction or resolution. However, there are multiple other areas of need, like psychosocial functioning and quality of life, and various measures of treatment success. Some of these measures are discussed here. Measures may be considered "basic" or "foundational", e.g., efficacy on the core symptoms of schizophrenia, or more "advanced" or "higher level", e.g., recovery, resulting in a pyramid model of outcomes (Figure 1). While tolerability is foundational, placed at the bottom of the pyramid, tolerability can be a reason for treatment discontinuation at any point on the patient journey, interfering with attainment of higher level outcomes.

Additionally, this review will focus on brexpiprazole, an antipsychotic that has been approved for the treatment of schizophrenia and as an adjunct to antidepressants for major depressive

disorder. Brexpiprazole is a partial agonist at dopamine D2 receptors [2], a property that it shares with aripiprazole [3] and cariprazine [4]. Furthermore, it is an agonist at serotonin 5-HT1A receptors and an antagonist at 5-HT2A and noradrenaline alpha1b/2C receptors [2]. Brexpiprazole has been studied in relation to foundational and higher-level outcomes in schizophrenia, and thus available data on brexpiprazole regarding these measures will be reviewed.

Efficacy:

The efficacy of antipsychotics is usually assessed by reduction of symptoms on the Positive and Negative Syndrome Scale (PANSS) [5] or the Brief Psychiatric Rating Scale (BPRS) [6]. As such, and with the exception of clozapine, the efficacy of available antipsychotics is comparable, with only subtle differences between them [7].

Pivotal studies have shown the efficacy of brexpiprazole in reducing symptoms of acute schizophrenia [8,9]. A meta-analysis of randomized controlled trials (RCTs) on the acute management of schizophrenia [10] included seven trials that compared 1618 patients on brexpiprazole with 742 patients on placebo. The mean difference was -4.48 points on the PANSS, favoring brexpiprazole.

Schizophrenia symptoms are numerous and researchers have searched for meaningful groupings, implementing factor analyses [111213]. Marder factors are a well-known example of a five-factor model [11] and brexpiprazole has demonstrated efficacy across these factors [14].

Another measure of efficacy can be the prevention of relapse. A systematic review and meta-analysis by Leucht and colleagues on antipsychotics for relapse prevention in schizophrenia calculated a number needed to treat (NNT) of 3 to prevent one relapse within one year, with oral antipsychotics showing similar efficacy for relapse prevention [15]. Relatedly, the pivotal study by Fleischhacker and colleagues showed efficacy of brexpiprazole as a maintenance treatment to prevent relapse [16].

Tolerability:

While efficacy of available antipsychotics is comparable, differences in side-effect profiles are more marked [7]. In clinical practice, the side effect profile is often the reason that one antipsychotic is chosen over another for the treatment of a given patient. Common adverse effects of antipsychotics are extrapyramidal symptoms (EPS), weight gain and other metabolic disturbances, prolactin elevation, and sedation.

In the pivotal studies on brexpiprazole, EPS were found to be minimal [8,9,16]. In a small open-label switch study with 37 patients switching to brexpiprazole, a significant decrease on the Drug-Induced Extrapyramidal Symptoms Scale total score ($p=0.008$) was found [17]. A meta-analysis including RCTs with data on antipsychotic-induced weight gain reported an average of 0.95 kg [0.64; 1.25] ($p < .001$) for brexpiprazole, as well as a significantly higher risk by 3.11 [1.97; 4.91] for clinically relevant weight gain ($p < .001$) and a number needed to harm (NNH) of 20 compared to placebo [18]. A post-hoc analysis of pooled data on brexpiprazole reported ≥7% weight increase in 10.4% of patients, with a difference vs. placebo of 6.3% [19]. The effect of brexpiprazole on prolactin levels was studied in a post-hoc analysis [20]. Prolactin levels in patients with baseline values greater than the upper limit of normal tended to decrease over time during treatment with brexpiprazole regardless of previous treatment. In short-term studies, the incidence of prolactin-related treatment-emergent adverse events (TEAEs) was 1.8% for brexpiprazole and 0.6% for placebo. In long-term studies, the incidence of prolactin-related TEAEs was 1.7%.

Sedating properties of antipsychotics are a major concern and have to be considered in a situational context. Some might consider it desirable to have a sedating effect in an antipsychotic that is given to an acutely agitated patient, although it is imperative to emphasize that calmness and sedation are not synonymous. Indeed, calmness without sedation may be a preferable goal to foster rapport and allow timely assessment with an alert patient. Importantly,

efficacy for reduction of acute agitation in schizophrenia has been demonstrated without sedation [21]. In long-term treatment, sedation is clearly undesirable. Sedation can impair return to work or school, reintegration into society, engagement with psychosocial therapies or rehabilitation, and participation in social activities [22], thus preventing full functional recovery and potentially contributing to medication discontinuation. It is therefore preferable to decouple efficacy and sedation by initially combining a non-sedating antipsychotic with a sedating co-medication (only if sedation is necessary) in acutely agitated patients. Subsequently, the comedication can be removed, leveraging the efficacy of the antipsychotic to foster the achievement of higher-level outcomes (Figure 1) without the burden of sedation. In a meta-analysis of data on activation or sedation from the product labels of oral second-generation antipsychotics, the only agents found to be neither activating nor sedating were paliperidone and brexpiprazole [23]. For brexpiprazole, the NNH for akathisia was 112 (not significant), with a NNH for other activating adverse events of 33. The NNH for somnolence was 271

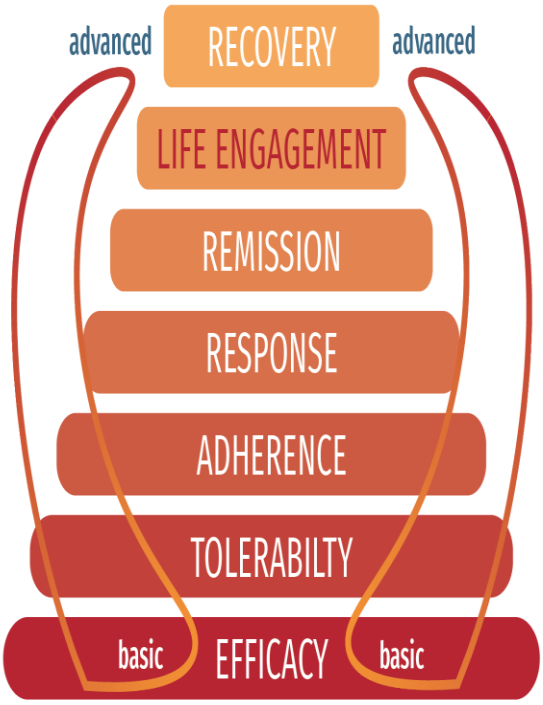

Figure 1: Pyramid model of measures of treatment success in schizophrenia.

Adherence:

Adherence to medication is the most important factor in preventing relapse in schizophrenia [24]. Good tolerability of an antipsychotic may improve adherence, as side effects are known to play a major role in non-adherence [25]. Non-adherence is a common phenomenon in patients with schizophrenia [25,26]; this is a major problem because a stable patient's condition may worsen rapidly and without warning once medication intake is stopped [27]. Moreover, after subsequent relapses, patients may not regain their previous level of health [28]. The problem of adherence is, however, not specific to schizophrenia, or even psychiatry. In general medicine, there are also problems with suboptimal adherence to therapies, especially in patients with chronic conditions [29]. Therefore, how to improve adherence is a question that is of interest in almost all medical specialties.

Adherence may be influenced by both the treatment (efficacy, tolerability) and the communication about the treatment [25]. A retrospective cohort study that analyzed health insurance claims data from Japan compared 978 patients who received brexpiprazole with 4898 patients who received other second-generation oral antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone, perospirone, blonanserin, paliperidone, or asenapine) [30]. Patients who received brexpiprazole were significantly less likely to discontinue treatment than those who received other oral antipsychotics (hazard ratio 0.86, 95% CI 0.78–0.95; p = 0.0024). The cumulative treatment continuation rates after 180 days were higher in the brexpiprazole group (45.9%, 95% CI 42.5–49.2]) than in the other oral antipsychotics group (39.5%, 95% CI 38.1–41.0; log-rank test, p < 0.0001). In a retrospective study on patients with schizophrenia who were prescribed either asenapine or brexpiprazole as part of their routine medical care, the treatment continuation rates for asenapine and brexpiprazole were 19.0% and 38.6% at 52 weeks, with that of brexpiprazole found to be significantly higher than that of asenapine (p = 0.002) [31].

Response:

Once a patient has started an antipsychotic medication, which is tolerated and consistently taken, the question is whether a clinically relevant symptomatic improvement is seen, i.e., whether the patient shows a response. The exact definition of a response depends on the clinical situation. In acutely ill patients, especially those with a first episode of psychosis, a lot of improvement can be expected and thus, an improvement of 50% or more on a rating scale such as the PANSS is defined as a response [32]. In chronically ill patients who are switched to a new medication, less improvement may be expected, making improvements of 20% adequate [32]. Also, floor effects must be taken into account – if a patient already shows a low symptom burden at the start of the treatment, the percentage of improvement may be low, even if the symptoms improve.

For brexpiprazole, response rates were determined in a pooled analysis of the pivotal studies [33]. A reduction of ≥ 30% from baseline in PANSS total score or a clinical global impressions-improvement score of 1 (very much improved) or 2 (much improved) was used as the response criterion. The percentage of responders was 45.5% for brexpiprazole vs. 31.0% for placebo, yielding an NNT of 7 (95% CI 5–12). Antoun Reyad and colleagues found in their meta-analysis a relative risk of 1.31 (1.19-1.43) to respond with brexpiprazole vs. placebo [10].

Remission:

Andreasen and colleagues published criteria for remission in 2005 [34]. These criteria stipulate that core symptoms of schizophrenia are at most mild (reflected by a score of 3 on the PANSS or BPRS) for a period of at least 6 months. These criteria were found achievable and sustainable, with about 40-60% of patients being able to achieve remission, depending on the population under study [35]. Using remission to measure treatment success has the advantage of avoiding the floor effects seen in measures of response discussed above. Remission in patients treated with brexpiprazole has been studied for a sample of 347 patients from an open-label extension study of the pivotal acute studies [36]. Remission rates of 30% by week 26 and 34% by week 58 were observed.

However, patients with schizophrenia are not only affected by the symptoms of the disease. The majority of patients also show impaired psychosocial functioning and reduced quality of life [37]. Cognitive, perceptual, motor, and emotional deficits affect interpersonal contacts and occupational functioning, often leading to social withdrawal and reduced quality of life of the patients. Taking functioning and health-related quality of life into account as measures for treatment success together with symptomatic remission leads to the concept of recovery.

Recovery:

Shortly after the Andreasen criteria for remission were published in 2005, there was a call for recovery criteria [38]. The concept of recovery is broader than that of symptomatic remission. Usually, recovery criteria encompass symptomatic remission plus adequate psychosocial functioning and/or health-related quality of life (HRQOL) [39–42], which is also known as “recovery as an outcome” [43]. Ideally, a patient who has achieved recovery as an outcome would be indistinguishable from a person who has never had schizophrenia. However, precise criteria for recovery as an outcome are still not defined. Moreover, there is no consensus on what should constitute “adequate functioning”, as there are no clear standards even in the healthy population [44]. Ascher-Svanum and colleagues tried to find an empirically driven definition of “good functioning” and proposed a total score of ≥84.5 on the Quality of Life Scale (QLS), which, according to the authors, measures function rather than HRQOL [45]. Functional outcomes in patients with schizophrenia under treatment with brexpiprazole have been recorded on the Personal and Social Performance (PSP) scale. Data from 4 RCTs showed a combined PSP difference of 3.24 (95% CI: 2.22-4.25) in brexpiprazole-treated patients vs. placebo-treated patients [10]. In long-term open-label studies with 177 patients, 41.8 of the patients achieved functional remission, defined as a PSP score of ≥71 [46].

In a meta-analysis of recovery in schizophrenia with data on 8994 patients receiving various treatments in 50 studies, only 13.5% met recovery criteria [39]. From these data, it seems that recovery as an outcome is actually hard to achieve, and very few patients with schizophrenia achieve recovery. With the available treatments, there are still unmet needs in terms of improvement in negative symptoms, cognitive symptoms, and functioning [47,48]. This situation has led to a different definition of recovery that may more attainable, which is "recovery as a process" [43]. Recovery as a process is a positive attitude towards life, characterized by traits such as hope, motivation, a sense of purpose, empowerment, and the notion that life has a meaning. Various terms have been used for this concept, including "personal recovery" [49], "subjective recovery" [50], and "recovery orientation" [43]. Recovery as a process may be seen in patients despite the presence of ongoing clinical symptoms and functional impairment [49].

Life engagement:

Recently, life engagement has been proposed as a meaningful measure in schizophrenia [51]. Life engagement is strongly related to the process of recovery and may make this concept more tenable and measurable, once fully developed. Much like "recovery as a process", life engagement is separate from both symptomatic and functional remission as well as HRQOL and may be considered as an essential part of the path leading to "recovery as an outcome" (Figure 2).

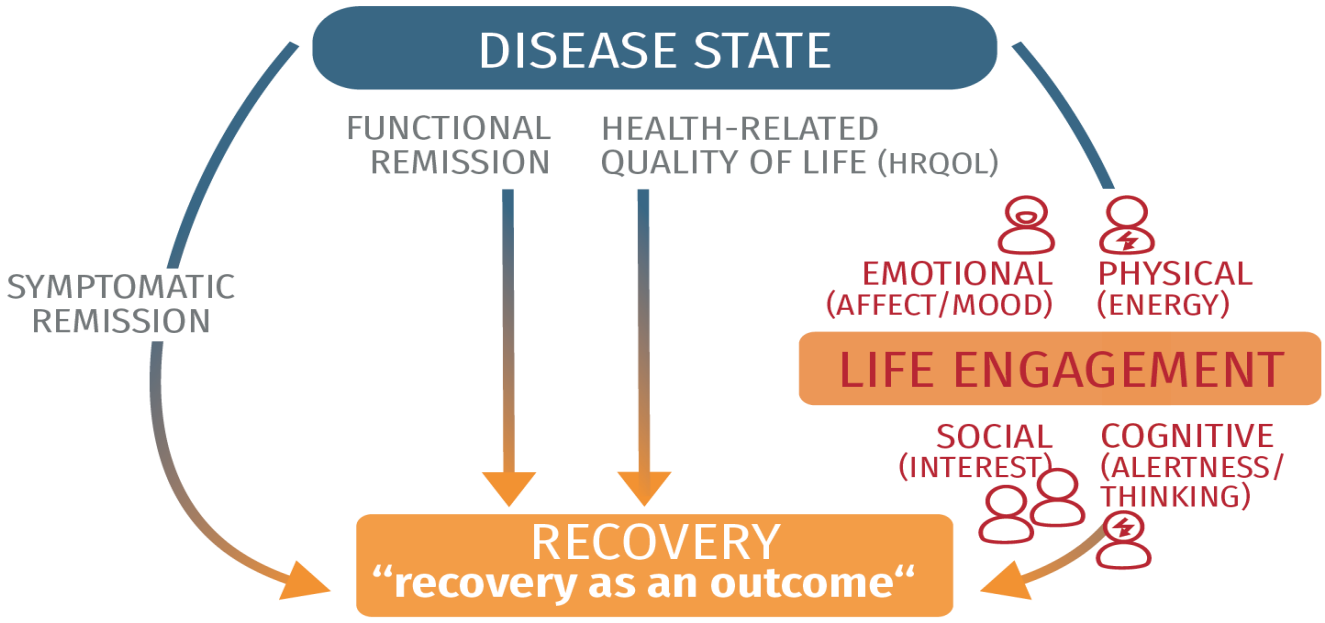

Figure 2: Relation of symptomatic remission, functional remission, and life engagement as factors leading to recovery. Based on Chan et al., 2018 [49].

Life engagement has been described to interact with symptomatic as well as functional outcomes [52], but is distinct from both (Figure 2). The essence of life engagement is for the patient to connect with the world and others and to regain a sense of self that often becomes eroded by mental illness and its symptoms [52]. Symptom improvement must happen first, or at least concurrently, in order to make engagement with life possible. The relationship between functioning and life engagement is more complex; while functioning describes role fulfillment and performance of activities in a social context, life engagement is more closely related to quality of life and grounded in a subjective sense of connection with others, as well as the ability to experience pleasure [52]. Life Engagement and functioning have a bidirectional relationship: enhanced engagement (in the form of alertness, energy, interest in social activities) enables better functioning, and better functioning creates more opportunities for life engagement [52].

Table 1. IDS-SR items used to capture life engagement

(8) Response of your mood to good or desired events	(19) General interest	(23) Feeling slowed down
(15) Concentration/decision making	(20) Energy level	(29) Interpersonal sensitivity
(16) View of myself	(21) Capacity for pleasure of enjoyment (excluding sex)	
(17) View of my future	(22) Interest in sex (please rate interest, not activity)	

Table 2. PANSS items used to capture life engagement in schizophrenia

N1 Blunted affect	N5 Difficulty in abstract thinking	G13 Disturbance of volition
N2 Emotional withdrawal	N6 Lack of spontaneity & flow of conversation	G 15 Preoccupation
N3 Poor rapport	G6 Depression	G 16 Active social avoidance
N4 Passive/apathetic social withdrawal	G7 Motor retardation	

A 10-item subscale of the Inventory of Depressive Symptomatology Self-Report (IDS-SR) scale [53] has been proposed as a possible measure of life engagement (Table 1) [54]. The IDS-SR is a scale used in major depressive disorder (MDD) to evaluate core symptoms of MDD as well as atypical and melancholic symptoms [53]. For the life engagement construct, the 10 items were identified using a modified Delphi process, based on relevance for capturing patient well-being and engagement with life beyond the core symptoms of MDD [54].

In schizophrenia, life engagement may be captured using select PANSS items (Table 2) [55]. These PANSS items were identified using a similar modified Delphi process by a group of specialists in the treatment of patients with schizophrenia as relevant to capture patient engagement and well-being beyond an improvement of the core symptoms of schizophrenia.

Using these measures, post-hoc analyses have shown that brexpiprazole may have a direct effect on life engagement in patients with MDD or schizophrenia, separate from effects on PSP-measured functioning and PANSS score [56]. Additional patient validations and psychometric analyses are ongoing, and concurrent with evolution of the life engagement construct, specific PANSS items may change slightly.

Furthermore, a four-domain framework of life engagement has been proposed [57], based on semi-structured exit interviews of MDD trials in which patients were asked qualitative questions about improvements they had experienced during treatment. Their answers were coded and served as a basis for the development of the four domains, emotional (affect/mood), physical (energy), social (interest), and cognitive (alertness/thinking) (Figure 3). In online interviews, patients with

schizophrenia reported that life engagement was meaningful to them, and confirmed that they found the four-domain framework relevant to life engagement [51].

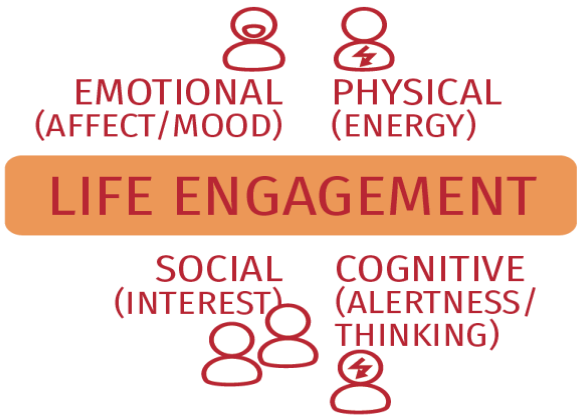

Figure 3: Four-domain model of life engagement.

A post-hoc analysis of 3 randomized controlled trials of brexpiprazole in the treatment of schizophrenia used PANSS items to measure life engagement. In this analysis, changes in the selected PANSS items for life engagement clustered together in a principal component analysis, confirming the selection of these specific items [55]. An improvement of the engagement items in patients receiving brexpiprazole vs. placebo was seen in 10 out of 11 items at week 6 ($p < 0.05$) [55].

Life engagement may be used as a framework to make recovery as a process more concrete, tenable, and measurable, so that it can be employed as an outcome in clinical studies. Life engagement may also be incorporated into the outcome of recovery. This outcome may require symptomatic remission, functional remission, adequate HRQOL, and life engagement. As a definition of symptomatic remission is available, and various measures of functioning are in routine use – although a consensus definition of functional remission is still lacking – the addition of an outcome measure for recovery as a process, which could be framed as life engagement, will be helpful in the development of treatments that aim towards recovery. Moreover, for patients, framing the broad outcome as one of life engagement may provide reassurance that outcomes are patient-centered and individually-tailored, potentially increasing a patient's involvement in their treatment.

Conclusion:

Brexpiprazole has shown some promising properties on various measures of treatment success in schizophrenia, beyond basic goals of symptom reduction. Further development of life engagement as both a process and as an additional outcome can promote the attainment of higher-level outcomes in schizophrenia treatment. Further studies and work in the field of life engagement could potentially help pave the road towards patient recovery.

Transparency & Ethical requirements:

Declaration of funding

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Declaration of financial/other relationships

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Author contributions

ZI conceptualized and wrote the manuscript.

References:

1. Correll CU. What are we looking for in new antipsychotics? J Clin Psychiatry. 2011;72 Suppl 1:9–13.

2. Maeda K, Sugino H, Akazawa H, et al. Brexpiprazole I: in vitro and in vivo characterization of a novel serotonin-dopamine activity modulator. J Pharmacol Exp Ther. 2014;350:589–604.

3. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther. 2002;302:381–389.

4. Kiss B, Horváth A, Némethy Z, et al. Cariprazine (RGH-188), a dopamine D(3)

receptor-preferring, D(3)/D(2) dopamine receptor antagonist-partial agonist antipsychotic candidate: in vitro and neurochemical profile. J Pharmacol Exp Ther. 2010;333:328–340.

5. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261–276.

6. Overall JE, Gorham DR. The brief psychiatric rating scale. Psychol Rep. 1962;10:799–812.

7. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939–951.

8. Correll CU, Skuban A, Ouyang J, et al. 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.

9. Kane JM, Skuban A, Ouyang J, et al. 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.

10. 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;35:119–128.

11. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry. 1997;58:538–546.

12. Lindenmayer J-P, Czobor P, Volavka J, et al. Effects of atypical antipsychotics on the syndromal profile in treatment-resistant schizophrenia. J Clin Psychiatry. 2004;65:551–556.

13. Wallwork RS, Fortgang R, Hashimoto R, et al. Searching for a consensus five-factor model of the Positive and Negative Syndrome Scale for schizophrenia. Schizophr Res. 2012;137:246–250.

14. Marder SR, Meehan SR, Weiss C, et al. Effects of Brexpiprazole Across Symptom Domains in Patients With Schizophrenia: Post Hoc Analysis of Short- and Long-Term Studies. Schizophr Bull Open. 2021;2:sgab014.

15. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012;379:2063–2071.

16. Fleischhacker WW, Hobart M, Ouyang J, et al. Efficacy and Safety of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults with Schizophrenia: a Randomized, Double-Blind, Placebo-Controlled Study. Int J Neuropsychopharmacol. 2017;20:11–21.

17. Ichinose M, Miura I, Horikoshi S, et al. Effect of Switching to Brexpiprazole on Plasma Homovanillic Acid Levels and Antipsychotic-Related Side Effects in Patients with Schizophrenia or Schizoaffective Disorder. Neuropsychiatr Dis Treat. 2021;17:1047–1053.

18. Barton BB, Segger F, Fischer K, et al. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. Expert Opin Drug Saf. 2020;19:295–314.

19. Weiss C, Weiller E, Baker RA, et al. The effects of brexpiprazole and aripiprazole on body weight as monotherapy in patients with schizophrenia and as adjunctive treatment in patients with major depressive disorder: an analysis of short-term and long-term studies. Int Clin Psychopharmacol. 2018;33:255–260.

20. Ivkovic J, Lindsten A, George V, et al. Effect of Brexpiprazole on Prolactin: An Analysis of Short- and Long-Term Studies in Schizophrenia. J Clin Psychopharmacol. 2019;39:13–19.

21. Ismail Z, Peters-Strickland T, Miguelez M, et al. Aripiprazole Once-Monthly in the Treatment of Acute Psychotic Episodes in Schizophrenia: Post Hoc Analysis of Positive and Negative Syndrome Scale Marder Factor Scores. J Clin Psychopharmacol. 2017;37:347–350.

22. Miller DD. Atypical antipsychotics: sleep, sedation, and efficacy. Prim Care Companion J Clin Psychiatry. 2004;6:3–7.

23. Citrome L. Activating and Sedating Adverse Effects of Second-Generation Antipsychotics in the Treatment of Schizophrenia and Major Depressive Disorder: Absolute Risk Increase and Number Needed to Harm. J Clin Psychopharmacol. 2017;37:138–147.

24. Alvarez-Jimenez M, Priede A, Hetrick SE, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies. Schizophr Res. 2012;139:116–128.

25. Kikkert MJ, Dekker J. Medication adherence decisions in patients with schizophrenia. Prim Care Companion CNS Disord. 2017;19.

26. Tiihonen J, Haukka J, Taylor M, et al. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011;168:603–609.

27. Emsley R, Chiliza B, Asmal L, et al. The nature of relapse in schizophrenia. BMC Psychiatry. 2013;13:50.

28. Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. Schizophr Res. 2013;148:117–121.

29. Brown MT, Bussell J, Dutta S, et al. Medication adherence: truth and consequences. Am J Med Sci. 2016;351:387–399.

30. Hishimoto A, Yasui-Furukori N, Sekine D, et al. Treatment Discontinuation Among Patients with Schizophrenia Treated with Brexpiprazole and Other Oral Atypical Antipsychotics in Japan: A Retrospective Observational Study. Adv Ther. 2022;

31. Inoue Y, Suzuki H, Hibino H, et al. Continuation rate for asenapine and brexpiprazole treatment in patients with schizophrenia. Brain Behav. 2021;11:e02109.

32. Leucht S, Kane JM, Kissling W, et al. What does the PANSS mean? Schizophr Res. 2005;79:231–238.

33. 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.

34. Andreasen NC, Carpenter WT, Kane JM, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. Am J Psychiatry. 2005;162:441–449.

35. Lambert M, Karow A, Leucht S, et al. Remission in schizophrenia: validity, frequency, predictors, and patients' perspective 5 years later. Dialogues Clin Neurosci. 2010;12:393–407.

36. Baker RA, Jin N, Weiller E, et al. Effect of Brexpiprazole on Long-term Remission in Adults with Schizophrenia: Results of an Open-label, Long-term Study. 2017.

37. Dziwota E, Stepulak MZ, Włoszczak-Szubzda A, et al. Social functioning and the quality of life of patients diagnosed with schizophrenia. Ann Agric Environ Med. 2018;25:50–55.

38. Emsley R, Chiliza B, Asmal L, et al. The concepts of remission and recovery in schizophrenia. Curr Opin Psychiatry. 2011;24:114–121.

39. Jääskeläinen E, Juola P, Hirvonen N, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39:1296–1306.

40. Correll CU, Kishimoto T, Nielsen J, et al. Quantifying clinical relevance in the treatment of schizophrenia. Clin Ther. 2011;33:B16-39.

41. Phahladira L, Luckhoff HK, Asmal L, et al. Early recovery in the first 24 months of treatment in first-episode schizophrenia-spectrum disorders. NPJ Schizophr. 2020;6:2.

42. Brissos S, Dias VV, Balanzá-Martinez V, et al. Symptomatic remission in schizophrenia patients: relationship with social functioning, quality of life, and neurocognitive performance. Schizophr Res. 2011;129:133–136.

43. Resnick SG, Fontana A, Lehman AF, et al. An empirical conceptualization of the recovery orientation. Schizophr Res. 2005;75:119–128.

44. Harvey PD, Bellack AS. Toward a terminology for functional recovery in schizophrenia: is functional remission a viable concept? Schizophr Bull. 2009;35:300–306.

45. Ascher-Svanum H, Novick D, Haro JM, et al. Empirically driven definitions of "good," "moderate," and "poor" levels of functioning in the treatment of schizophrenia. Qual Life Res. 2013;22:2085–2094.

46. Correll CU, He Y, Therrien F, et al. Effects of Brexpiprazole on Functioning in Patients With Schizophrenia: Post Hoc Analysis of Short- and Long-Term Studies. J Clin Psychiatry. 2022;83.

47. Carbon M, Correll CU. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. CNS Spectr. 2014;19 Suppl 1:38–52; quiz 35.

48. Giuliani L, Giordano GM, Bucci P, et al. Improving knowledge on pathways to functional outcome in schizophrenia: main results from the italian network for research on psychoses. Front Psychiatry. 2021;12:791117.

49. Chan RCH, Mak WWS, Chio FHN, et al. Flourishing With Psychosis: A Prospective Examination on the Interactions Between Clinical, Functional, and Personal Recovery Processes on Well-being Among Individuals with Schizophrenia Spectrum Disorders. Schizophr Bull. 2018;44:778–786.

50. Vita A, Barlati S. Recovery from schizophrenia: is it possible? Curr Opin Psychiatry. 2018;31:246–255.

51. Meehan SR, Weiss C, Adair M, et al. Exploring the concept of life engagement from the perspective of patients with

schizophrenia: A study using patient interviews. 2021.

52. Correll CU, Ismail Z, McIntyre RS, et al. Patient functioning and life engagement: unmet needs in major depressive disorder and schizophrenia. J Clin Psychiatry. 2022;83.

53. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol Med. 1996;26:477–486.

54. Thase ME, Pedersen AM, Ismail Z, et al. Efficacy of Adjunctive Brexpiprazole in Adults with MDD: Improvement of Patient Engagement Based on Selected Items from the Inventory of Depressive Symptomatology Self-Report (IDS-SR) Scale. 2019.

55. Ismail Z, Pedersen AM, Thase ME, et al. Effect of brexpiprazole on engagement in patients with schizophrenia: post-hoc analysis of three studies. 2020.

56. Meehan SR, He Y, de Jong-Laird A, et al. Path analyses to explore the direct and indirect effects of brexpiprazole on life engagement: *Post hoc* anaysis of six clinical studies in depression and schizophrenia. 2021.

57. Weiss C, Meehan SR, Brown TM, et al. Effects of adjunctive brexpiprazole on calmness and life engagement in major depressive disorder: post hoc analysis of patient-reported outcomes from clinical trial exit interviews. J Patient Rep Outcomes. 2021;5:128.