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EXPERT OPINION

Brexpiprazole in the Management of Schizophrenia: A Consensus Report of Best Practices From Acute to Maintenance Treatment

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Abstract: Brexpiprazole is a second-generation antipsychotic with multiple indications, including the treatment of schizophrenia. As a partial dopamine agonist, brexpiprazole differs from most other antipsychotics, yet uncertainties about its full mechanism of action have led to some ambiguity among prescribers. To address this gap, an international panel of psychiatric experts was organized and convened with funding from Otsuka Pharmaceutical Europe Ltd and H. Lundbeck A/S to discuss the safe and effective use of brexpiprazole across different stages of schizophrenia treatment. Brexpiprazole's pharmacological profile—characterized by balanced binding affinities across norepinephrine, dopamine, and serotonin receptors—contributes to its efficacy in multiple symptom domains, including agitation and negative symptoms. Its tolerable safety profile, marked by minimal activation and minimal sedation and a relatively low risk of long-term cardiometabolic concerns, further supports its clinical utility. Brexpiprazole is a viable first-line therapy in both inpatient and outpatient settings when properly titrated and monitored. Brexpiprazole also serves as an option for different symptom domains in schizophrenia and for patients needing to switch antipsychotics due to inadequate symptom control or intolerable adverse events. Long-term maintenance therapy is essential for relapse prevention in schizophrenia, and when prescribed at appropriate doses for psychotic symptom control, brexpiprazole can provide sustained benefits with minimal long-term safety concerns. This report outlines the consensus panel's recommendations on the optimal initiation and administration of brexpiprazole in management of schizophrenia treatment, including a treatment algorithm, which is supported by a literature review.

Plain Language Summary: Brexpiprazole is a unique medication used to treat schizophrenia, a complex and often disabling disorder. Many other antipsychotic treatments have limitations, either failing to fully address symptoms or causing intolerable side effects. Brexpiprazole offers a potential solution to some of these challenges, yet its full therapeutic value in schizophrenia treatment may not be widely recognized among prescribers. To bridge this gap, a panel of psychiatric experts convened to discuss brexpiprazole's distinctive pharmacological properties and the evidence supporting its efficacy across multiple symptom domains, along with its acceptable safety profile. This report summarizes their discussions and serves as a resource for prescribers on initiating and managing brexpiprazole treatment effectively in patients with schizophrenia.

Keywords: schizophrenia, brexpiprazole, dopamine partial agonist, tolerability, efficacy

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Introduction

Schizophrenia is among the top 20 leading causes of disability worldwide, imposing significant health, financial, and social burdens on both patients and caregivers.[1,2] Schizophrenia presents with a broad spectrum of symptoms classified as positive (eg, hallucinations, delusions, disorganized speech or behavior), negative (eg, anhedonia, avolition, asociality, affective flattening, alogia), and cognitive (eg, impairments in attention, memory, language, processing speed, executive functioning, and social cognition).[3–6] Despite the availability of multiple antipsychotic treatments, challenges such as incomplete symptom control, non-adherence, intolerable side effects, cognitive impairment, and fluctuating disease characteristics remain common.[7,8] Effective treatment requires an individualized approach based on each patient's unique symptom profile and treatment goals. While treatment algorithms and clinical guidelines exist, they are not always frequently updated or specific to individual medications.[7,9–11] Antipsychotic medications remain as the preferred pharmacologic approach, but their varying efficacy and safety profiles make selecting an optimal agent for an individual patient complex.[6,8,12,13]

Brexpiprazole is approved in the United States for schizophrenia in patients aged 13 years and older, as adjunctive treatment for major depressive disorder, and for agitation associated with Alzheimer's disease-related dementia.[14] In Europe, brexpiprazole is indicated for the treatment of schizophrenia, which is the focus of this consensus report, in adults and adolescents aged 13 years and older.[15,16] Brexpiprazole is one of three partial dopamine agonists available in Europe, alongside aripiprazole and cariprazine. Prescribing decisions for schizophrenia treatment may be influenced by clinician's familiarity with established medications and varying perceptions of partial agonists. This report provides an overview of brexpiprazole's pharmacological profile and summarizes the available evidence on its efficacy and safety to support informed clinical decision-making in the management of schizophrenia.

Methods

In July 2024, a panel of international psychiatrists with expertise in the clinical treatment of schizophrenia and antipsychotic prescribing convened to develop clinical recommendations on the use of brexpiprazole for adults with schizophrenia. The panel was chaired by Christoph U. Correll, MD, and included experts from the US and Europe with experience in schizophrenia treatment and research. Panelists included Leslie Citrome, MD (US); Charlotte Emborg Mafi, MD (Denmark); Andrea Fagiolini, MD (Italy); Erich Seifritz, MD (Switzerland); Paul Seerden, MD (Netherlands); Jari Tiihonen, MD (Finland); and Antonio Vita, MD (Italy). Each panelist responded to a pre-meeting survey, and the results were reviewed during an in-person meeting with facilitated discussion. The panel analyzed publicly available clinical trial data and shared their perspectives to reach a consensus on treatment considerations for schizophrenia, including a proposed treatment algorithm. This article presents the consensus findings from the panel discussion.

Brexpiprazole: Understanding the Pharmacology

The panel recognized that brexpiprazole's pharmacological profile makes it an appealing option for schizophrenia treatment but noted that certain misconceptions about its use persist among some prescribers. Understanding brexpiprazole's pharmacology as a partial dopamine D_2 agonist is essential for appreciating its clinical effectiveness.

Partial D_2 agonists were originally classified separately from other second-generation antipsychotics due to their distinct mechanism of action, which influences efficacy across symptom domains and the likelihood of specific adverse effects. However, in clinical practice this classification has led to some misunderstandings, including the incorrect belief that "partial" agonism implies "reduced" efficacy compared to full D_2 antagonists (Table 1). In practice, therapeutic doses for schizophrenia treatment typically achieve at least 65% postsynaptic D2 receptor antagonism, with partial agonists exerting antidopaminergic effects comparable to those of full D2 antagonists.

Unlike traditional antipsychotics, partial D_2 agonists have minimal histaminergic blockade, resulting in a lower cardiometabolic burden and less sedation. This reduced sedation has sometimes been misinterpreted as lower efficacy, particularly in acute settings where sedation is used for symptom control. Additionally, the longer half-life of the partial agonists (typically three days) differs from the shorter half-life of most antidopaminergic antipsychotics, requiring careful clinical consideration. Despite these differences, partial agonists effectively manage psychotic symptoms while

Table 1 Misperceptions Vs Evidence Regarding Brexpiprazole

Misperception	Evidence
Partial agonist = partial antipsychotic efficacy	The efficacy of brexpiprazole as a treatment for schizophrenia has been proven in multiple Phase 3 clinical trials,[17–20] and systematic reviews demonstrate no significant differences in individual antipsychotic drug effect between D_2 receptor antagonists and partial agonists.[12,21,22]
Partial agonists, including brexpiprazole, are not effective for agitation and hostility	A post-hoc analysis of data from three clinical trials showed that brexpiprazole resulted in significant decreases in the excitement and hostility components of the Positive and Negative Syndrome Scale.[23]
Partial agonists/brexpiprazole should not be used in an acute setting	The use of brexpiprazole for patients with acutely exacerbated schizophrenia is effective when prescribed and monitored appropriately.[17,18,24]
Partial agonists/brexpiprazole are only effective in less severely ill patients with schizophrenia	The use of brexpiprazole for patients with more severe psychopathology is effective when prescribed and monitored appropriately.[17,18,24]

maintaining dopamine levels, reducing the risk of extrapyramidal symptoms (EPS), prolactin elevation, sexual dysfunction, and secondary negative or cognitive symptoms.[6,12,25–31]

Brexpiprazole's Balanced Receptor Binding Profile

After the discovery of aripiprazole as an antipsychotic with a novel molecular structure and mechanism that offered improved tolerability compared to many existing antipsychotics,[1,2] research efforts continued to develop a molecule that maintained antipsychotic efficacy while further enhancing tolerability. Researchers hypothesized that increasing antagonism at 5-HT_{2A} enhancing agonism potency at 5-HT_{1A} receptors and reducing intrinsic activity at D_2 receptors—compared to aripiprazole—could result in an agent with a more favorable side effect profile, including reduced akathisia and insomnia, along with broader symptom control, such as improved efficacy for anxiety and depressive symptoms. This research ultimately led to the discovery of brexpiprazole.[32]

Brexpiprazole has a well-balanced receptor profile, functioning as a partial agonist at dopaminergic D_2 and serotonergic 5-HT_{1A} receptors, while acting as an antagonist at 5-HT_{2A} and noradrenergic $\alpha_{1B/2C}$ receptors, all with similar sub-nanomolar affinity (Figure 1).[33,34] Compared to aripiprazole, brexpiprazole demonstrates a more balanced profile between dopamine and serotonin receptors, exhibits higher affinity at 5-HT_{1A}/5-HT_{2A} and $\alpha_{1B/2C}$ receptors, and has lower intrinsic activity at D_2 receptors.[33,35] Traditionally, symptoms in schizophrenia have been thought to be related to impairments in neuromodulation of dopamine, serotonin, and glutamate. It is worth noting that impairments in norepinephrine activity may also play a critical role in the schizophrenia pathophysiology, specifically in precipitating cognitive deficits, reducing motivation, and impacting arousal levels.[36]

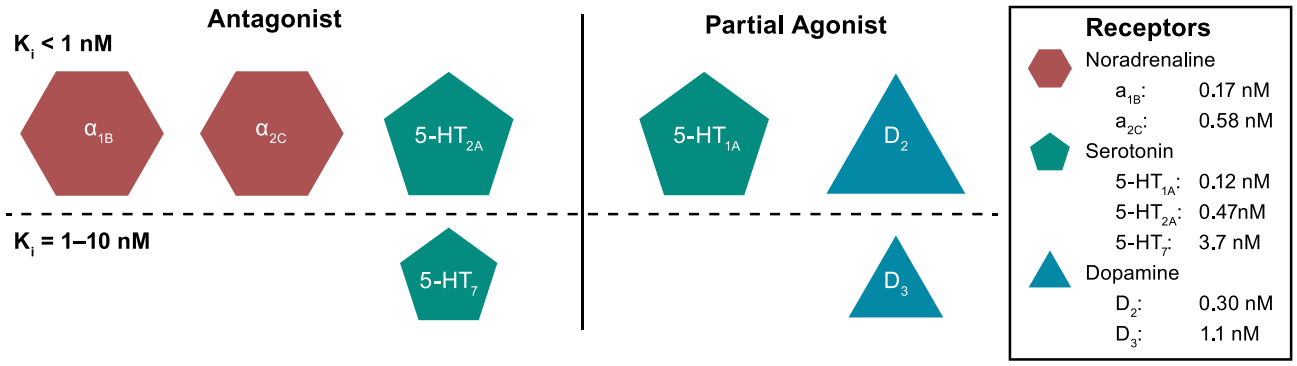

Figure 1 Pharmacologic profile for brexpiprazole as categorized by K_i binding affinity values at dopamine, serotonin, and norepinephrine receptors.[15,33,37]
Abbreviations: K_i, inhibitory constant, with lower values representing higher affinity; nM, nanomolar.

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Differentiation From Other Antipsychotics

The affinities of brexpiprazole for various receptors compared to select antipsychotic medications are displayed in Table 2. The table includes the partial agonists aripiprazole, brexpiprazole, and cariprazine, select second-generation antipsychotics which have both dopamine and serotonin activity (quetiapine, risperidone), and haloperidol, a first-generation D_2 receptor antagonist, among others.[33,35] Drugs that predominantly block D_2 receptors can cause a range of side effects, such as tardive dyskinesia and akathisia, and are associated with elevated prolactin levels. Dopamine and serotonin receptor antagonists are less likely to cause EPS but do introduce cardiometabolic risks, such as weight gain, blood sugar elevation, and lipid abnormalities.[32,38]

Brexpiprazole binds with high affinity to D_2 and 5-HT_{1A} receptors, acting as a partial agonist to modulate dopamine and serotonin activity, respectively. Additionally, it serves as a high-affinity antagonist at 5-HT_{2A} serotonin receptors and α_{1B} and α_{2C} noradrenergic receptors. This receptor activity contributes to brexpiprazole's favorable antipsychotic profile, which includes improvements in cognitive performance and sleep patterns, as well as potential benefits in addressing core schizophrenia symptoms, including cognitive deficits. Increased noradrenergic activity has been linked to positive schizophrenia symptoms, such as heightened cognitive excitement, grandiosity, hypervigilance, and hostility.[36] By antagonizing α_1 and α_{2C} receptors, brexpiprazole may help alleviate these symptoms, as observed in clinical trials.[17–20] Brexpiprazole also has a low risk of common adverse effects associated with both first- and second-generation antipsychotics, such as EPS, cardiometabolic complications, weight gain, and akathisia.[12,33] Overall, brexpiprazole's balanced receptor-binding profile contributes to its distinct clinical effects across multiple symptom domains in schizophrenia while maintaining a well-tolerated safety profile.[12,30,38]

Clinical Evidence From Randomized Clinical Trials

The panel agreed that the evidence supports brexpiprazole as an efficacious treatment choice for people with acutely exacerbated schizophrenia and for both short-term and long-term treatment approaches. There are numerous first- and second-generation antipsychotics available, and systematic reviews have demonstrated minimal differences in efficacy between the available agents.[12,21,22] The efficacy of brexpiprazole was evaluated in multiple phase 3 placebo-controlled randomized clinical trials, as summarized in Table 3. These trials evaluated patients aged 18 to 65 years with a diagnosis of schizophrenia, excluding those with first-episode schizophrenia or comorbid mental health conditions, including a history of active substance abuse within the past six months. All short-term trials included patients

Table 2 Receptor Binding Affinities of Select Antipsychotics

Receptor	ARI	BRX	CAR	ASE	CLO	ILO	LUR	OLA	QTP	RIS	HAL
D_2	++++	++++	++++	++	+	+++	+++	++	+	+++	+++
D_3	+++	+++	++++	+++	+	+++	o	++	+	+++	+++
5-HT_{1A}	+++	++++	+++	+++	+	++	+++	o	++	+	o
5-HT_{2A}	+++	++++	++	++++	++	+++	+++	+++	++	++++	+
α_1	++	+++	+	+++	+++	+++	++	++	++	+++	++
α_{2C}	++	++++	o	+++	++	++	+++	++	++	+++	+
H_1	++	++	++	+++	+++	+	o	+++	+++	+++	o
M_1	o	o	o	o	++	o	o	++	+	o	o
M_3	o	o	o	o	++	o	o	++	+	o	o

Notes: Adapted with permission from Siafis et al.[38] Aripiprazole values from Solmi et al.[6] Antagonism and inverse agonism are indicated by blue whereas partial agonism is indicated by yellow. The number of crosses and color intensity are correlated to binding affinity. K_i > 100: + (weak association); K_i 11–100: ++ (moderate association); K_i 1–9: +++ (strong association) K_i < 1: ++++ (very strong association); o = no value available.

Abbreviations: ARI, aripiprazole; ASE, asenapine; BRX, brexpiprazole; CAR, cariprazine; CLO, clozapine; HAL, haloperidol; ILO, iloperidone; LUR, lurasidone; OLA, olanzapine; QTP, quetiapine; RIS, risperidone.

Table 3 Randomized Double-Blind Placebo-Controlled Phase 3 Studies of Brexpiprazole

Study Name (NCT #)	Duration	Dose	Design	Primary Endpoint
Vector (NCT01396421)[17]	6-week	Fixed-dose (0.25, 2, or 4 mg daily)	Four-arm; 14-day screening, 6-week treatment, 30-day follow-up	Change in PANSS total score from baseline to week 6 versus placebo
Beacon (NCT01393613)[18]	6-week	Fixed-dose (1, 2, or 4 mg daily)	Four-arm; 14-day screening, 6-week treatment, 30-day follow-up	Change in PANSS total score from baseline to week 6 versus placebo
Lighthouse (NCT01810380)	6-week	Flexible-dose brexpiprazole (2 to 4 mg daily)	Three-arm including active reference (quetiapine XR); 14-day screening, 6-week treatment, 30-day follow-up	Change in PANSS total score from baseline to week 6 versus placebo
Lighthouse extension (Study 14644B) (NCT01810783)	52-week	Titration to maintenance dose (1 to 4 mg daily)	14-day titration period followed by a flexible dosing period, 1–4 mg/day, from day 15 to the end of the study	Number of treatment emergent adverse events (TEAEs)
Equator (NCT01668797)[20]	52-week	Titration to maintenance dose (1 to 4 mg daily)	15-day screening, 1 to 4-week conversion phase, up to 24-week stabilization including titration from 1 to 4 mg, and 52-week placebo-controlled maintenance phase	Time from randomization to relapse versus placebo
Zenith (NCT01810783)[39]	52-week	Titration to maintenance dose (1 to 4 mg daily)	28-day titration period followed by a flexible dosing period, 1–4 mg/day to the end of the study.	Frequency and severity of TEAEs

experiencing an acute exacerbation of psychotic symptoms, and patients were hospitalized for the 6-week treatment period. In the maintenance trial, both inpatient and outpatient participants with acute symptoms of schizophrenia were included and underwent different treatment phases prior to randomization to continued treatment with brexpiprazole or placebo.

Short-Term Trials: Vector, Beacon, Lighthouse

The Vector trial,[17] one of two short-term fixed-dose, placebo-controlled studies, demonstrated significant improvements in PANSS total scores for the 2 mg and 4 mg brexpiprazole groups compared to placebo. These improvements emerged as early as week 1 for the 2 mg group and week 2 for the 4 mg group, with sustained statistical significance through the primary endpoint at week 6. As expected from preclinical studies, the 0.25 mg dose did not show significant improvement over placebo. Additionally, at week 6, both the 2 mg and 4 mg groups showed significant improvements on the Clinical Global Impressions Severity (CGI-S) and Improvement (CGI-I) scales.[17]

The Beacon trial,[18] another short-term fixed-dose study, followed a similar design but replaced the lowest 0.25 mg dose with a 1 mg arm. This study confirmed significant improvements in PANSS and CGI scores from baseline to week 6 for the 4 mg brexpiprazole group compared to placebo.[18]

The Lighthouse trial, Study 14644A,[19] which was also an acute study, randomized patients to receive brexpiprazole (2–4 mg), quetiapine XR (400–800 mg), or placebo, with quetiapine XR included as an active control to validate study sensitivity. At the 6-week primary endpoint, the mean PANSS total score change for brexpiprazole (−20.0) trended toward statistical significance versus placebo (−15.9, p=0.056), though a higher-than-expected placebo response likely influenced the results. However, a pre-specified sensitivity analysis using analysis of covariance confirmed a statistically significant treatment effect for brexpiprazole (last observation carried forward [LOCF]: p=0.025; observed cases [OC]: p=0.026). Additionally, brexpiprazole significantly improved CGI-S scores compared to placebo. In contrast, quetiapine XR demonstrated significant separation from placebo on both the PANSS total score and CGI-S at week 6.[19]

Finally, in a pooled analysis of the almost identically designed Vector and Beacon short-term studies,[40] both the 2 mg and 4 mg brexpiprazole groups showed statistically significantly greater improvements from baseline in PANSS total score compared with placebo (Figure 2), which started as early as week 1 and persisted through the end of the trial at week 6. For the key secondary efficacy endpoint, mean change from baseline at week 6 in CGI-S total score, brexpiprazole 2 mg and 4 mg consistently showed statistically significant improvement compared with placebo. The numbers-needed-to-treat to demonstrate a clinical response, defined as a ≥30% improvement in PANSS total score from baseline, for brexpiprazole 2 mg and 4 mg to were 9 and 6, respectively.

Long-Term Trials: Lighthouse Extension, Equator, and Zenith

In a long-term, open-label, flexible dose, extension trial to the Lighthouse extension study, Study 14644B,[41] which was designed to determine the safety and efficacy of brexpiprazole as a maintenance treatment for schizophrenia, results showed continued improvement at week 52 based on the PANSS total score, CGI-S, and Personal and Social Performance (PSP) scale. The mean dose at the last visit was 3.1 mg daily, with at least 50% of patients being on 4 mg brexpiprazole daily.

The Equator trial was a long-term, randomized, placebo-controlled, relapse-prevention study. The study included both inpatient and outpatient individuals experiencing acute psychotic symptoms at the time of screening. The design included a screening period, an open-label 1- to 4-week run-in phase to convert subjects from prior antipsychotic medication to brexpiprazole and a 12- to 36-week medication stabilization phase, after which subjects were randomized to the placebo-controlled maintenance phase, which was planned for 52 weeks. The study was terminated early based on significantly positive outcomes observed at a prespecified interim analysis. The final analysis, depicted in Figure 3, found a 71% relative reduction in risk for impending relapse in the group treated with brexpiprazole compared to the placebo group. The mean dose at the last visit of the maintenance phase was 3.6 mg daily.[20]

A subsequent open-label, flexible-dose extension trial, Zenith (NCT01397786), recruited participants from the Vector, Beacon, and Equator studies as well as de novo patients not previously on brexpiprazole. The design included a 2- to 28-day screening and washout period for new patients, a conversion phase to cross-titrate them from prior antipsychotic medication, and a 26- to 52-week open-label treatment phase. Flexible doses between 1 and 4 mg were allowed, and the mean daily dose at the last visit was 3 mg. While the primary intent of the study was to review the long-term safety and tolerability of brexpiprazole, efficacy was evaluated as a secondary endpoint, using scores from the PANSS and CGI scales. Through week 52, group scores showed an overall decline in mean PANSS score and mean CGI-S score (Figure 4A and 4B, respectively).[39]

Post Hoc Analyses of Short-Term and Long-Term Trial Data: Improvements Across Specific Symptom Domains and Levels of Severity

Several post hoc analyses have been conducted based on the Vector, Beacon, Lighthouse, Lighthouse extension, Equator, and Zenith trials. Overall, results from these trials supported the original positive efficacy conclusions and offered new insights into brexpiprazole's efficacy across different symptom domains of schizophrenia.

A 2020 post hoc analysis by Meade et al[24] compared patients with more severe versus less severe symptoms (baseline PANSS score >95 vs ≤95) from the Vector, Beacon, Lighthouse, Lighthouse extension, and Zenith trials. Total PANSS scores for both those defined as severely ill and less severely ill significantly improved compared with placebo, with greater effects being seen in the more severely ill group in both the short-term (Figure 5A) and long-term studies (Figure 5B). PSP scores also improved similarly, with a continual decline over 26 weeks, which were maintained over the final 26 weeks of the study, indicating long-term improvement in functioning (Figure 5C).[24]

Improvements in functioning were the focus of a 2022 post hoc analysis performed by Correll et al,[42] which included all six trials previously mentioned. Patient functioning was determined by scores from the PSP and Global Assessment of Functioning (GAF) scales. The analysis showed significant improvements in all four domains of the PSP scale for patients on brexpiprazole versus placebo in the acute treatment phase (Figure 6A). In the double-blind maintenance study, GAF score improvement was maintained in the maintenance phase, whereas scores worsened in the placebo-treated group (Figure 6B). The open-label trials demonstrated that a functional response (defined as PSP/GAF increase ≥10) was

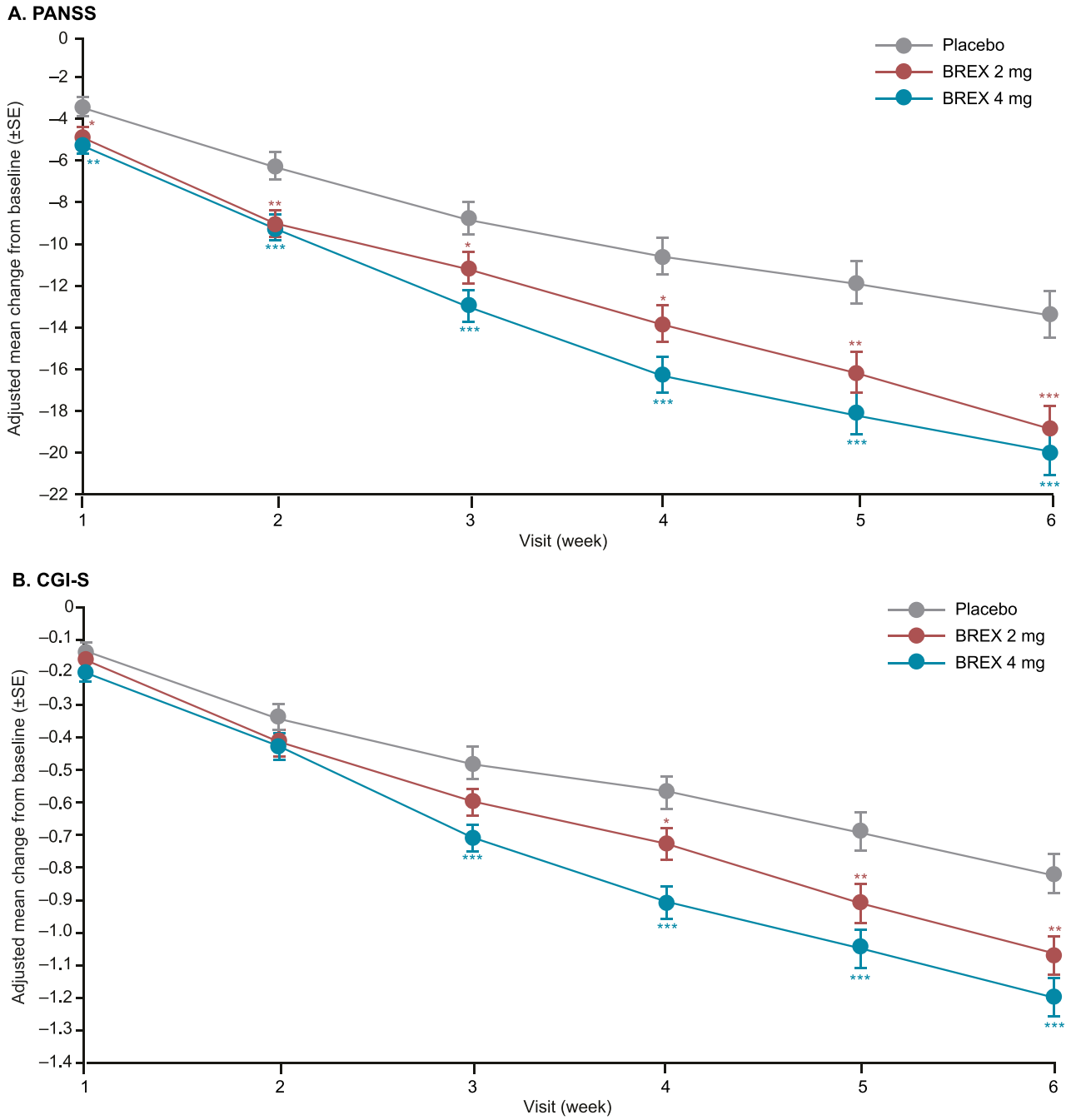

Figure 2 Change in key efficacy measures noted in phase 3 clinical studies.

Notes: Reprinted from Correll CU, Skuban A, Hobart M et al. Efficacy of brexpiprazole in patients with acute schizophrenia: Review of three randomized, double-blind, placebo-controlled studies. Schizophr Res. 2016;174(1–3):82–92. © 2016 The Authors. Published by Elsevier B.V. Creative Commons CC-BY-NC-ND license.[40] Least squares mean (standard error) change from baseline in Positive and Negative Syndrome Scale total score (**A**) and Clinical Global Impressions–Severity of Illness score (**B**) for combined brexpiprazole 2 mg and 4 mg and placebo groups (efficacy population). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$; mixed-model repeated measures analysis. Combined brexpiprazole groups are compared with the combined placebo group.

Abbreviations: BREX, brexpiprazole; CGI-S, Clinical Global Impressions – Severity of illness; PANSS, Positive and Negative Syndrome Scale; SE, standard error.

achieved by 80.9% to 86.2% of patients, and functional remission (PSP ≥71 or GAF ≥61) was achieved by 40.4% to 44.1% of patients.[42]

Furthermore, a recent pooled analysis of all three acute-phase 6-week, placebo-controlled studies and two 52-week open label extension studies (total n=1793) with brexpiprazole[43] focused on patient life engagement (PLE) as

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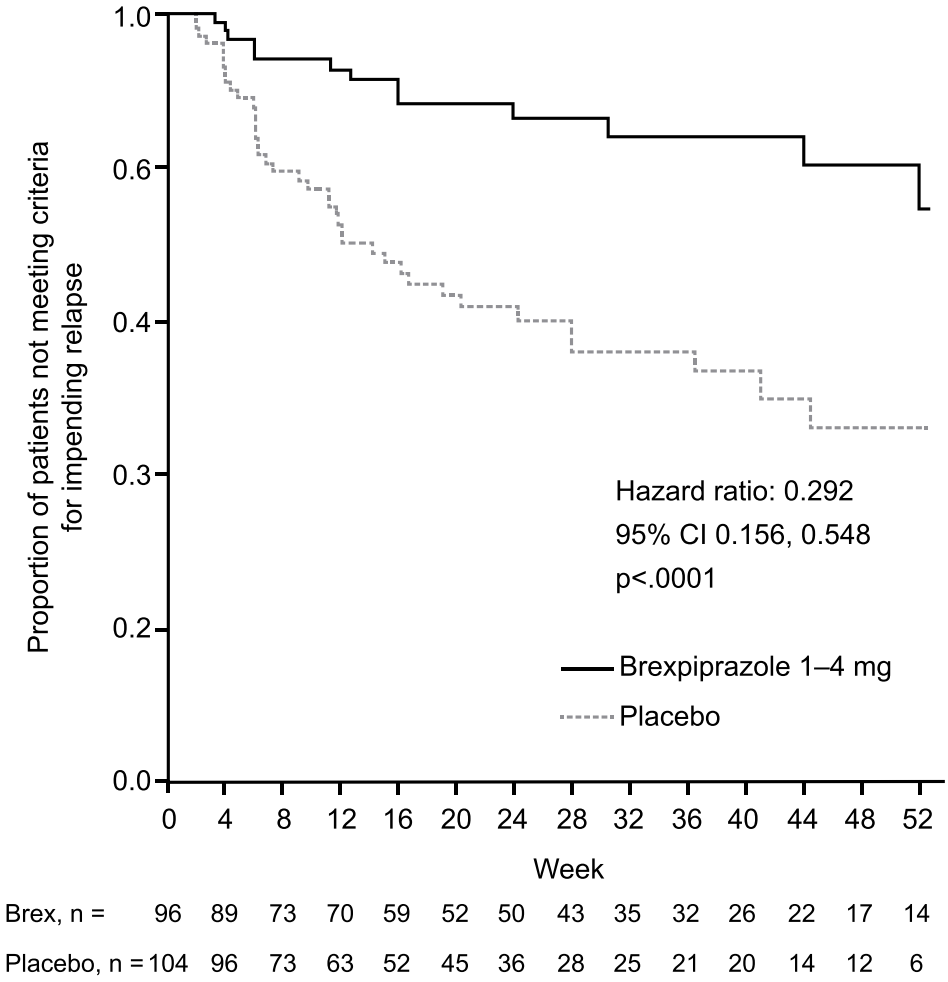

Figure 3 Time from randomization to impending relapse in the Equator trial double-blind maintenance phase.
Notes: Reprinted from Fleischhacker WW, Hobart M, Ouyang J et al. Efficacy and safety of brexpiprazole (opc-34712) as maintenance treatment in adults with schizophrenia: a randomized, double-blind, placebo-controlled study. Int J Neuropsychopharmacol. 2017;20(1):11–21. © The Author 2016. Published by Oxford University Press on behalf of CINP. This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License.[20]

a particularly patient-relevant outcome related to functionality and wellbeing.[44,45] Three approaches had been used previously to identify PANSS items that reflect patient life engagement, ie, (i) a panel discussion with expert psychiatrists; (ii) interviews with patients with schizophrenia; and (iii) a principal component analysis to explore clustering of items. This approach ultimately resulted in a composite set of 14 PANSS items that may be relevant to patient life engagement (P2, N1, N2, N3, N4, N5, N6, N7, G6, G7, G11, G13, G15, G16), with responder status being defined as difference estimates of ≥5 and ≥10 points versus placebo or baseline.[46] Applying this composite score, significantly greater improvement in patient life engagement from baseline to Week 6 was observed for brexpiprazole 2–4 mg/day (p<0.001; Cohen's d effect size: 0.28).[43] These improvements were maintained over 58 weeks on brexpiprazole 1–4 mg/day. At Week 6, response rates among patients treated with brexpiprazole versus placebo were 71.6% versus 58.0% (≥5-point improvement; p<0.001) and 43.5% versus 32.8% (≥10-point improvement; p<0.001). At Week 58, response rates in patients treated with brexpiprazole were 90.5% (≥5-point improvement) and 78.2% (≥10-point improvement).[43] Taken together, these results indicate that brexpiprazole has value not only for improving functioning but also for symptoms that are related to a concept of life engagement, in both the short-term and long-term.

Finally, a post hoc analysis that included all six previously mentioned randomized and open-label extension trials was completed to evaluate short- and long-term effects of brexpiprazole based on subsets of scores within the PANSS, referred to as the "Marder factors": positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/

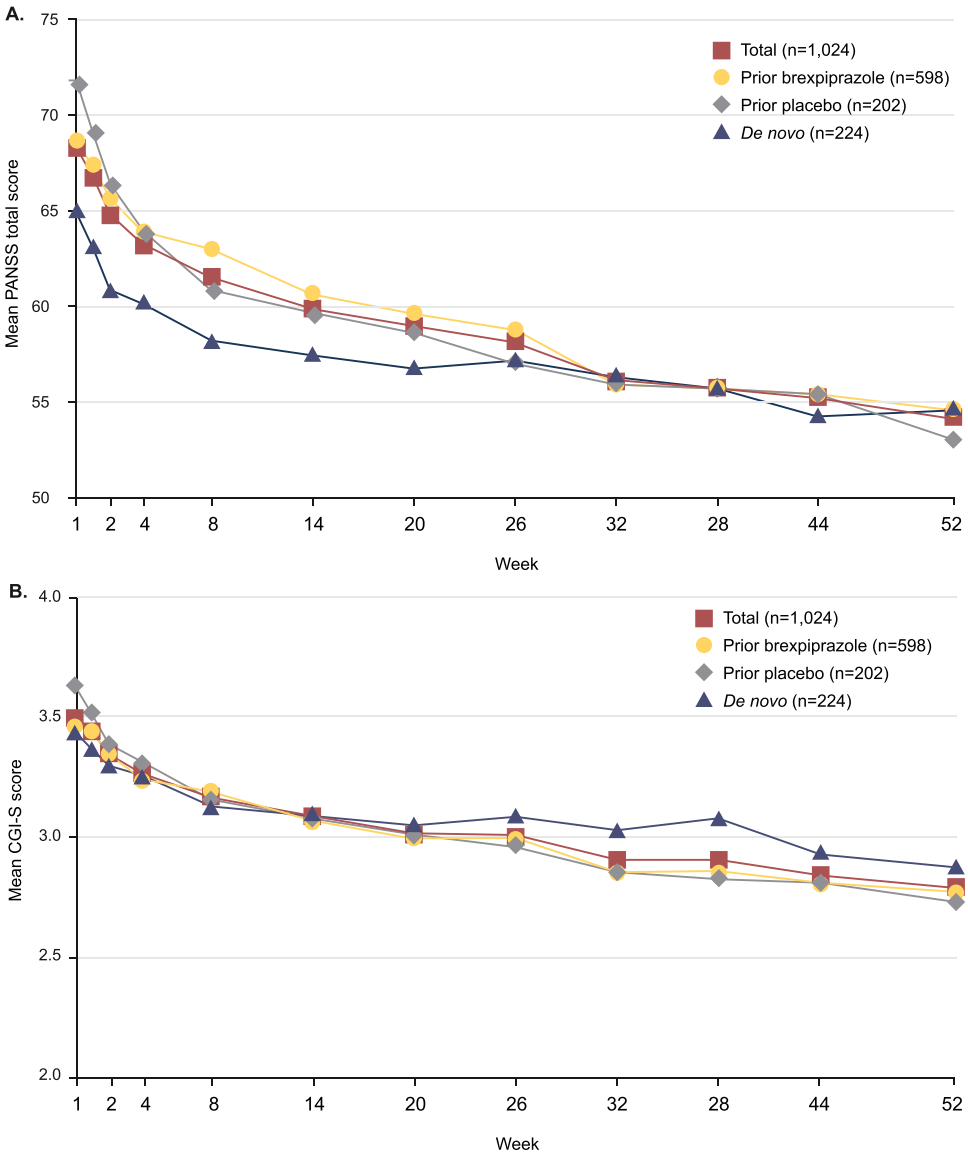

Figure 4 Sustained changes in key efficacy measures noted in a long-term observational study.
Notes: Reprinted from Forbes A, Hobart M, Ouyang J, Shi L, Pfister S, Hakala M. a long-term, open-label study to evaluate the safety and tolerability of brexpiprazole as maintenance treatment in adults with schizophrenia. Int J Neuropsychopharmacol. 2018;21(5):433–441. Copyright © 2018, © The Author(s) 2018. Published by Oxford University Press on behalf of CINP. Creative Commons CC-BY-NC license.[39] Mean change in key efficacy measures over 52 weeks for patients with schizophrenia receiving open-label brexpiprazole 1–4 mg/d, stratified by treatment prior to entering the study (observed cases). **(A)**: Mean PANSS score over 52 weeks in the Zenith study in patients receiving brexpiprazole dosed 1 to 4 mg/day. **(B)**: Mean CGI-S over 52 weeks in the Zenith study in patients receiving brexpiprazole dose 1 to 4 mg/day.
Abbreviations: CGI-S, Clinical Global Impressions – Severity of illness; PANSS, Positive and Negative Syndrome Scale.

excitement, and anxiety/depression. In the short-term studies, brexpiprazole was associated with significant improvement in each of the PANSS Marder factors compared to placebo at week 6. The analysis demonstrated that positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression were all significantly improved. In the 52-week double-blind trial, the interpretation is limited due to a small proportion of patients completing the full 52-week period; however, improvement was generally maintained versus worsening in the placebo group, with statistical significance noted for positive symptoms, disorganized thought, and uncontrolled hostility/excitement. In the open-label extension trials, improvements on all five PANSS Marder factors were maintained for up to 58 weeks of treatment. At the time of their analysis, study authors noted brexpiprazole was the only oral antipsychotic shown to benefit all five factors for a one-year duration.[47]

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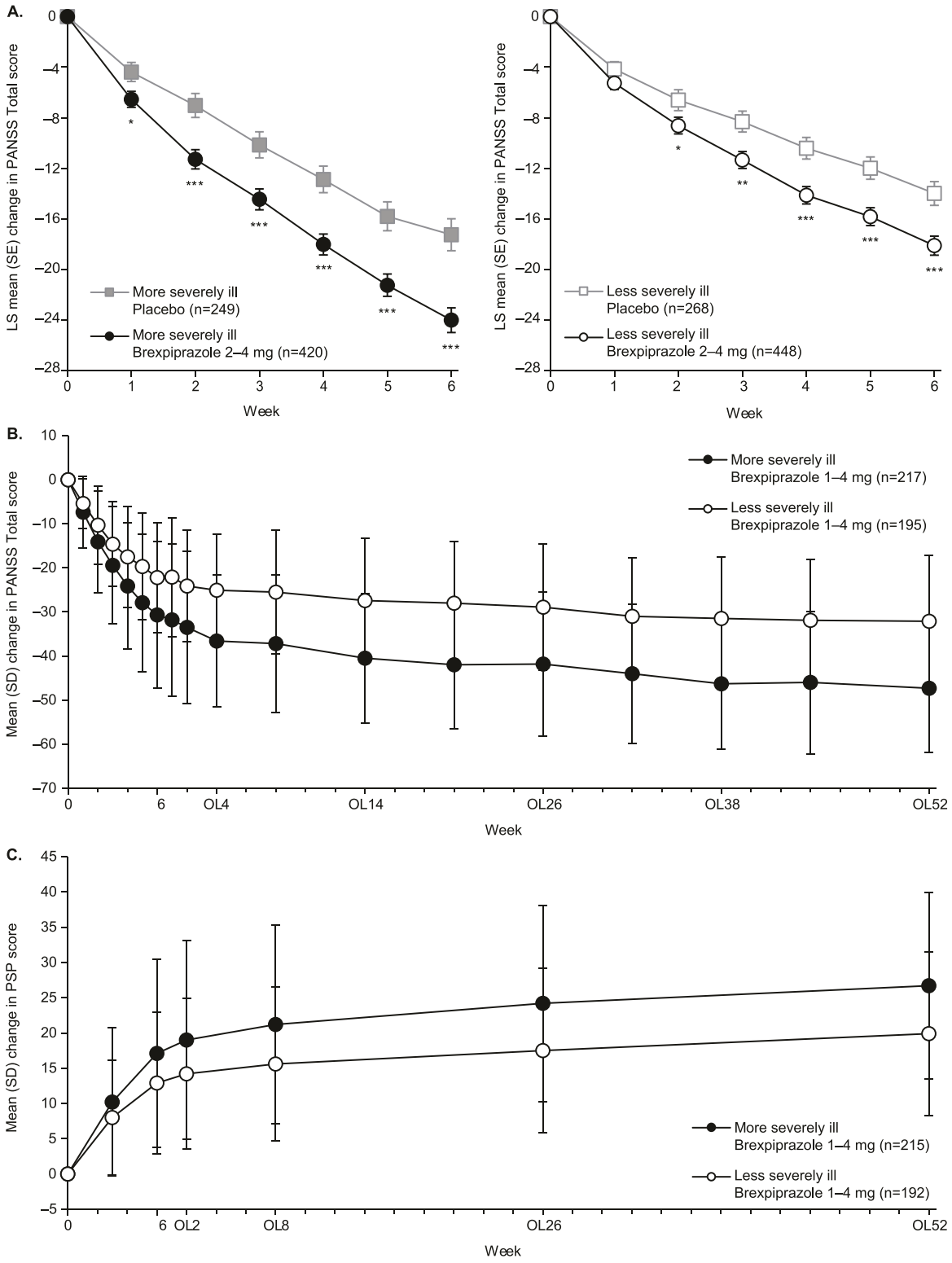

Figure 5 Short and long-term changes in key measures by baseline severity level.

Notes: Reprinted from Meade N, Shi L, Meehan SR, Weiss C, Ismail Z. Efficacy and safety of brexpiprazole in patients with schizophrenia presenting with severe symptoms: Post-hoc analysis of short- and long-term studies. J Psychopharmacol. 2020;34(8):829–838. © The Author(s) 2020. This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License.[24] **(A)** Positive and Negative Syndrome Scale (PANSS) Total score change during short-term and **(B)** long-term treatment with brexpiprazole, and **(C)** Personal and Social Performance scale (PSP) score change during long-term treatment, stratified by baseline illness severity (efficacy sample). Baseline PANSS Total score: (**A**) more severely ill placebo, 105.6; more severely ill brexpiprazole, 105.8; less severely ill placebo, 87.4; less severely ill brexpiprazole, 86.6; (**B**) more severely ill, 106.3; less severely ill, 86.0. Baseline PSP score: (**C**) more severely ill, 40.5; less severely ill, 48.6. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo.

Abbreviations: LS, least squares; MMRM, mixed model for repeated measures; OL, open-label; SD, standard deviation; SE, standard error.

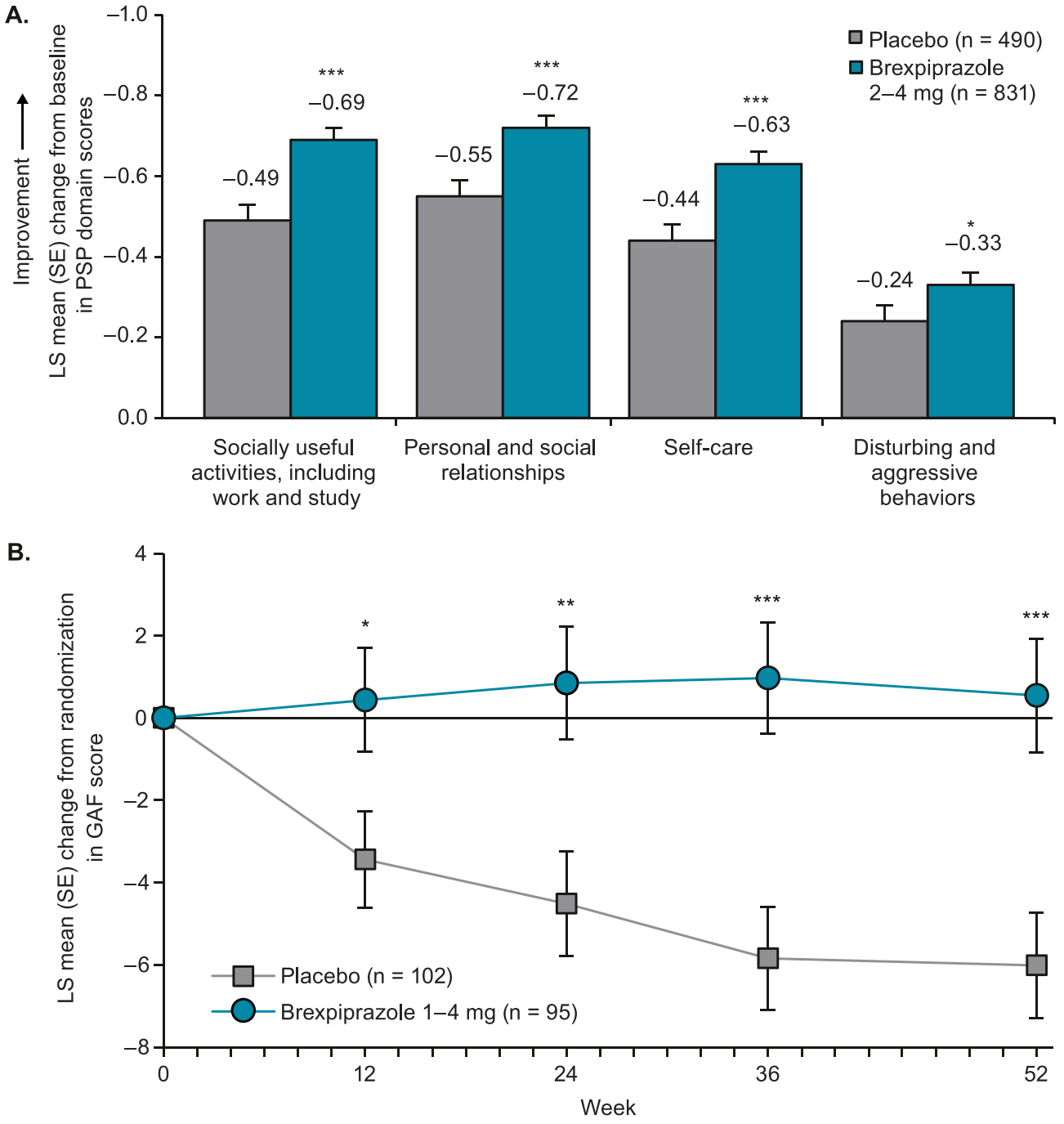

Figure 6 Short and long-term changes in functional measures.

Notes: Reprinted with permission from 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(2):20m13793. © Copyright 2022 Physicians Postgraduate Press, Inc.[42] (**A**) Mean change in PSP domain scores from baseline to week 6. PSP domains were scored from 0 (absent) to 5 (very severe), where a decrease in score signifies improvement; overall PSP score ranges from 1 (worst functioning) to 100 (best functioning), where an increase in score signifies improvement. Mean scores at baseline (placebo, brexpiprazole): PSP: 44.3, 44.4; Activities: 3.5, 3.3; Relationships: 3.1, 3.0; Self-care: 1.9, 1.7; Behaviors: 1.2, 1.0. *P <0.05. ***P <0.001 vs placebo, MMRM. (**B**) Change in GAF score over 52 weeks in the double-blind maintenance phase *P < 0.05. **P <0.01. ***P < 0.001 vs placebo, LOCF, ANCOVA.

Abbreviations: ANCOVA, analysis of covariance; GAF, Global Assessment of Functioning; LOCF, last observation carried forward; LS, least squares; MMRM, mixed model for repeated measures; PSP, Personal and Social Performance scale; SD, standard deviation; SE, standard error.

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Based on the 2019 network meta-analysis by Huhn et al,[12] brexpiprazole demonstrated efficacy across multiple symptom domains in schizophrenia, including overall symptom reduction, improvement in positive and negative symptoms, depressive symptoms, and social functioning. Although brexpiprazole was not among the most highly ranked agents in terms of effect size for overall symptom change, it demonstrated statistically significant benefit over placebo, with consistent, small effect size efficacy compared to placebo across all symptom domains reported. In the primary outcome of overall symptom reduction, all antipsychotic drugs outperformed placebo, with mean effect sizes ranging from –0.89 to –0.03 (median –0.42), but the differences between most individual agents were not statistically significant due to overlapping credible intervals. Only a few antipsychotics (clozapine, amisulpride, zotepine, olanzapine, and risperidone) demonstrated statistically superior efficacy compared to other antipsychotics. While safety and tolerability will be explored subsequently, it is noteworthy that brexpiprazole exhibited a favorable tolerability profile, with relatively low rates of all-cause discontinuation. This aligns with the authors' broader conclusions that while efficacy differences among antipsychotics tend to be gradual rather than sharply distinct, differences in tolerability and side-effect profiles are more pronounced and clinically differentiating.[12]

Real-World Evidence

Several studies have evaluated the use of brexpiprazole in the real-world setting. Healthcare costs associated with schizophrenia were evaluated by Yan et al in a 2020 retrospective cohort study of patients with schizophrenia on one of eight oral antipsychotics, including brexpiprazole.[48] Patients on brexpiprazole had the lowest annual costs of psychiatric care and lowest psychiatric inpatient costs compared to those using the other oral antipsychotics. Patients on brexpiprazole also had significantly fewer psychiatric hospitalizations per year than those on paliperidone or quetiapine.[48] A study by Aigbogun et al also emphasized the potential for brexpiprazole to be cost-effective in terms of avoidance of relapses and hospitalizations when compared to cariprazine and lurasidone.[49] Caveats to the interpretation of these results include the lack of randomization and potential for selection bias.

A component that can substantially contribute to healthcare costs is treatment discontinuation, which can result in negative and costly outcomes like relapses. In a retrospective observational cohort study utilizing a health insurance claims database of working individuals in Japan who were taking second-generation antipsychotics, patients using brexpiprazole were significantly less likely to discontinue their medication than those on other antipsychotics analyzed, which included aripiprazole, olanzapine, quetiapine, risperidone, perospirone, blonanserin, paliperidone, and asenapine. While the study did not detail the causes for treatment discontinuation, the authors suggested the favorable tolerability of brexpiprazole versus other agents may have contributed to patients' willingness to continue treatment.[50]

Clinical Trial Evidence: Safety and Tolerability

In both short-term, long-term, controlled clinical trials, and real-world evidence studies, brexpiprazole is associated with an acceptable safety profile. The panel agreed that the evidence supports brexpiprazole as a well-tolerated choice in most patients and that its tolerable profile can be helpful when discussing with patients how adhering to antipsychotic treatment could help them achieve their personal goals.

Short-Term Trials: Safety/Tolerability Findings

In the Vector trial, discontinuation rates due to treatment-emergent adverse events (TEAEs) were lower in the brexpiprazole groups (8.2%–13.3%) compared to placebo (17.4%). The most commonly reported TEAE was akathisia, occurring more frequently in the 2 mg and 4 mg groups (4.4% and 7.2%, respectively) compared to placebo (2.2%). However, reported akathisia was generally mild, with no cases leading to discontinuation. Regarding cardiometabolic effects, the 4 mg brexpiprazole group had an average weight gain of 1.28 kg compared to 0.42 kg in the placebo group. No significant changes were observed in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, glucose, or prolactin levels.[17] In Beacon, insomnia, agitation, and headache were the most frequently reported TEAEs. Notably, akathisia was more common in the placebo group (7.1%) than in the brexpiprazole groups (4.2%–6.5%). Weight gain was higher in the brexpiprazole groups (1.23 kg–1.89 kg) compared to placebo (0.35 kg), but there were no significant differences in metabolic laboratory values between treatment groups.[18] In the Lighthouse trial, the overall incidence of

TEAEs was similar between brexpiprazole and placebo. The most common TEAEs were insomnia (8.7% in the brexpiprazole 2–4 mg group vs 6.2% in the placebo group) and akathisia (6.0% vs 2.5%, respectively). Weight gain at week 6 was comparable between brexpiprazole and placebo (1.6 kg vs 0.5 kg, respectively).[19] Across all three short-term studies, the incidence of TEAEs leading to discontinuation was lower in the brexpiprazole groups than placebo, and there were no clinically relevant differences between the brexpiprazole arms and placebo in terms of EPS, prolactin changes, or cardiometabolic parameters.[51]

Long-Term Trials: Continued Tolerability

The Lighthouse extension trial assessed the long-term safety of brexpiprazole in patients rolled over from the acute, short-term trial. Most TEAEs were mild or moderate, with worsening of schizophrenia being reported as the most frequent adverse effect.[41] In the long-term Equator trial, TEAEs were generally similarly to those reported in the short-term trials, with most resolving in the maintenance phase of the study.[20] In the Zenith trial, results again aligned with the original trials indicating that brexpiprazole was generally well-tolerated. The majority of patients experienced at least one TEAE, only 8.0% of which were severe. The most frequent TEAE was worsening of schizophrenia (11.6%).[39]

Meta-Analyses Evidence: Favorable Safety Vs Other Antipsychotics

Recent meta-analyses by Huhn et al[12] and Pillinger et al[52] ranked various antipsychotics based on side effects observed in placebo-controlled clinical trials. Evaluating brexpiprazole's position in these rankings helps quantify its relative tolerability compared to other antipsychotic medications.

Table 4 presents the rank orders of select antipsychotics from these meta-analyses, where a lower number indicates a more favorable ranking in terms of side effect profile. According to the Huhn et al meta-analysis, which evaluated 32 oral antipsychotics, placebo generally ranked lower across the eight evaluated side effect domains. Older medications tended to score worse in EPS and prolactin elevation, while newer agents were more frequently associated with sedation and weight gain. Brexpiprazole had an overall ranking of 7.0, which was similar to aripiprazole (6.9) and more favorable than cariprazine (10.0), lurasidone (10.9), olanzapine (13.9), risperidone (14.6), and quetiapine (14.7). Notably, among the 32 antipsychotics analyzed, brexpiprazole was the only medication that did not show a statistically significant difference from placebo in any reported side effect category.

The meta-analysis by Pillinger et al[52] analyzed 18 antipsychotic medications based on their cardiometabolic side profiles and revealed significant differences among agents. Clozapine and olanzapine were associated with the most

Table 4 Analysis of Antipsychotic Rankings by Side Effect per Huhn Et al[12]

Side Effect ***(Total no. of Drugs Ranked)***	**Rank Order Based on MD or RR Value (95% CrI)**										
	ARI	**BRX**	**CAR**	**ASE**	**CLO**	**ILO**	**LUR**	**OLA**	**QTP**	**RIS**	**HAL**
Weight gain *(26)*	3	5	6	14*	20*	22*	2	25*	21*	17*	4†
Extrapyramidal symptoms (EPS) as indicated by use of antiparkinsonian medication *(32)*	8	12	18*	6	1†	11	16*	4	5	15*	29*
Akathisia *(30)*	10*	7	18*	13*	1	4	22*	5	6	16*	21*
Prolactin elevation *(20)*	3	8	6	13*	1†	12	15*	11*	7	19*	17*
QTc prolongation *(14)*	4	2	3	10	NR	11*	1	8*	7*	9*	6
Sedation *(32)*	11*	14	4	20*	31*	8	15*	22*	25*	16*	18*
At least one anticholinergic side effect *(32)*	9	1	15	3	25*	26*	5	22*	32*	10*	20*

Notes: †Indicates MD or RR value significantly more favorable than placebo per 95% CI; *indicates MD or RR value significantly less favorable than placebo per 95% CrI; higher ranking indicates lower side effect propensity.

Abbreviations: ARI, aripiprazole; ASE, asenapine; BRX, brexpiprazole; CAR, cariprazine; CLO, clozapine; CrI, credible interval; HAL, haloperidol; ILO, iloperidone; LUR, lurasidone; MD, mean difference; OLA, olanzapine; QTP, quetiapine; RR, relative risk; RIS, risperidone.

unfavorable cardiometabolic effects, while others, including brexpiprazole, demonstrated more favorable cardiometabolic parameters in certain areas. When comparing rank orders across cardiometabolic categories, brexpiprazole had an average ranking of 4.8 the same as cariprazine (4.8) and similar to aripiprazole (5.7). In contrast, risperidone/paliperidone (7.3), quetiapine (9.2), and olanzapine (11.0) had less favorable rankings relative to placebo. Brexpiprazole did not show significantly worse cardiometabolic effects than placebo in any category except for weight gain, where the increase (0.88 kg) was minimal. Among the antipsychotics analyzed, lurasidone had the most favorable average ranking (3.7) for cardiometabolic side effects. Conversely, olanzapine and quetiapine had the least favorable cardiometabolic profiles, with significantly worse outcomes than placebo across multiple measures, including weight gain, total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Clinical Application: Patient Selection

Brexpiprazole's balanced receptor-binding profile contributes to a distinct clinical profile across various symptom domains of schizophrenia while maintaining a well-tolerated side effect profile, as demonstrated in previous sections. This makes brexpiprazole a valuable antipsychotic choice for most patients with schizophrenia, including those with varying disease severity. Phase 3 randomized clinical trials have shown brexpiprazole's efficacy in patients with schizophrenia, regardless of severity.[17–19] Additionally, a 2016 exploratory study by Malla et al[53] examined brexpiprazole in adult outpatients with early-episode, relatively stable schizophrenia, who had a lower average baseline PANSS total score of 70.6. After 16 weeks of treatment, the PANSS total score decreased by an average of 10.2 points, with notable improvements in social functioning. The panel agreed that brexpiprazole's efficacy across a broad range of schizophrenia symptoms, along with its well-balanced side effect profile—supported by phase 3 trial data[47,51]—makes it a favorable choice for patients whose illness is characterized by problems with daily functioning and life engagement. Additionally, its tolerability profile makes it a suitable option for individuals at risk for cardiometabolic complications, prolactin-related effects, parkinsonian symptoms, and either activating or sedating side effects.

Residual Negative and Depressive Symptoms

Negative symptoms of schizophrenia, as defined by the PANSS, include blunted affect, emotional and social withdrawal, difficulty with abstract thinking, lack of spontaneity and conversational flow, and stereotyped thinking.[3,54] These symptoms affect an estimated 50% to 90% of patients and significantly impair quality of life and overall functioning.[55] Negative symptoms often overlap with depressive symptoms, which can be either intrinsic to schizophrenia or secondary to comorbid depression—another indication in which brexpiprazole has demonstrated efficacy.[56] Notably, however, the approved brexpiprazole doses to treat depression are lower (2–3 mg/d) than for schizophrenia (2–4 mg/d), with higher doses of brexpiprazole being particularly beneficial for positive symptom control. The prevalence of depressive symptoms in schizophrenia ranges from 25% to 81%,[57] and a prospective observational study tracking patients over three years found that 39% exhibited depressive symptoms at enrollment.[58] These patients had greater reliance on relapse-related mental health resources, more safety concerns, and lower life satisfaction compared to those without depressive symptoms. While antipsychotics are well-established for treating positive symptoms, residual negative and cognitive symptoms can persist in a subset of patients, impairing daily functioning and life engagement.[42] Antipsychotics with minimal extrapyramidal and sedative effects, such as brexpiprazole, may help avoid secondary negative and cognitive symptoms.[29] Post-hoc analyses suggest that brexpiprazole offers both short- and long-term benefits for negative symptoms and overall functioning,[42,47] leading the expert panel to consider it a strong option for patients with residual negative symptoms, which can manifest as a lack of motivation or engagement in life. However, further research specifically examining brexpiprazole's impact on negative symptoms and functional outcomes would help strengthen the evidence for its use in this population.

Cardiometabolic Concerns

Metabolic syndrome is commonly associated with schizophrenia, partly due to lifestyle factors, such as smoking and physical inactivity. Given the link between metabolic syndrome, hypertension, diabetes, and cognitive decline in schizophrenia,[59] brexpiprazole's low cardiometabolic risk profile makes it a suitable option in patients with cardiometabolic comorbidities. Additionally, many second-generation antipsychotics can negatively affect weight, lipid levels, glucose metabolism, and prolactin levels.[60] Approximately one-third of patients with schizophrenia develop metabolic syndrome, with higher risks observed in those with multi-episode schizophrenia and those receiving long-term antipsychotic treatment.[59,60] Although regular body weight monitoring is still recommended, brexpiprazole has a low risk of significant weight gain, as demonstrated in phase 3 studies. Moreover, no safety concerns related to laboratory tests or vital signs have been reported.[51] The favorable ranking of brexpiprazole in the Pillinger et al meta-analysis[52] (Table 4) further supports its minimal cardiometabolic adverse impact, which has also been confirmed in long-term studies.[20,61,62] Given its low cardiometabolic risk, the panel consensus is that brexpiprazole is a suitable option both for treatment-naïve patients as a preventive measure against metabolic syndrome and for those needing to switch from other antipsychotics due to adverse cardiometabolic effects.

Cognitive Functioning

Cognitive functioning plays a crucial role in maintaining life engagement, particularly for younger patients aiming to reintegrate into school or work environments,[44,45] and the European Psychiatric Association has emphasized the need for better treatment of cognitive impairment in schizophrenia. However, while their guidance recommends second-generation antipsychotics over first-generation agents, it does not specify preferred medications.[11] Preclinical studies suggest that brexpiprazole may be more effective than aripiprazole in reversing cognitive impairment, possibly due to its balanced receptor profile.[37] Additionally, improving negative symptoms while maintaining a well-tolerated safety profile —such as minimal activation or sedation—enhances opportunities to combine treatment with cognitive remediation or cognitive-behavioral therapy, both of which are widely recommended for schizophrenia.[7,11,63] A head-to-head phase 3b study comparing brexpiprazole, aripiprazole, and placebo found no significant cognitive decline in patients receiving brexpiprazole on any cognitive test. The cognitive test battery composite score at week 6 was 0.045 with brexpiprazole, indicating no overall change in cognitive functions. However, among the eight tasks assessed, brexpiprazole showed a significantly greater improvement than aripiprazole on the One-Back Memory Task.[64] Cognitive impairment has also been linked to cardiometabolic dysregulation,[59] and brexpiprazole's low cardiometabolic risk compared to other antipsychotics may provide additional cognitive benefits. Furthermore, several antipsychotics with central anticholinergic activity have been shown to impair cognition,[65] but brexpiprazole poses minimal risk in this regard due to its low affinity for cholinergic receptors (Table 2).

Functioning and Patient Life Engagement Considerations

Brexpiprazole's favorable safety profile and ability to address multiple symptom domains of schizophrenia make it a strong option for long-term maintenance therapy. Side effects not only impact physical health but also affect overall functioning and quality of life. Therefore, a patient's perception of side effects is a key consideration in long-term treatment decisions.[66] Schizophrenia presents with a broad spectrum of symptoms, requiring clinicians to assess all domains when evaluating treatment goals, including long-term functioning and life engagement.[44,45,67] For example, even if a patient's positive symptoms are well-controlled, they may still struggle with workplace integration or accessing creative aspects of their personality. As previously discussed, brexpiprazole has been shown to improve negative and residual symptoms that affect functioning and overall life satisfaction, supporting its use as a long-term therapy. Notably, a post-hoc analysis of three acute 6-week studies and two 52-week studies examined brexpiprazole's impact on PANSS-score-based life engagement changes.[46] The findings suggest that brexpiprazole can enhance patient life engagement,[43] a critical patient-centered outcome in schizophrenia that reflects functional and personal well-being.

Agitation

Agitation is a common and challenging symptom in schizophrenia, though prevalence estimates vary depending on the definition and population studied. A study in Spain found that 25% of patients with schizophrenia experience at least one episode of agitation per year.[68] Further, a retrospective analysis of inpatients with schizophrenia in Italy reported moderate agitation in 40.5% of patients and severe agitation in 23.7%.[69] Agitation that escalates into hostility or violence can lead to emergency department visits, where traditional management strategies such as restraint and sedation pose safety risks to healthcare staff and may damage a patient's trust in the healthcare system.[23,70]

A post hoc analysis of both short- and long-term brexpiprazole studies examined its effects on agitation and hostility, as measured by the PANSS-EC (excited component) and the hostility item (P7). Results showed that patients receiving brexpiprazole at doses of 2 mg to 4 mg daily had significantly greater improvements in agitation scores compared to placebo (Figure 7).[23] The effect was statistically significant at six weeks for both doses, with the greatest improvement observed in the 4 mg group. Based on these findings, the consensus panel recommends the 4 mg daily dose for patients with multi-episode schizophrenia.

Activating and Sedating Side Effects Experienced with Other Agents

Brexpiprazole strikes a balance between two common side effect domains of antipsychotic medications: activating effects (such as akathisia, restlessness, and insomnia) and sedating effects (including sedation, somnolence, and hypersomnia). While individual responses and tolerability vary, brexpiprazole is generally not strongly associated with either activating

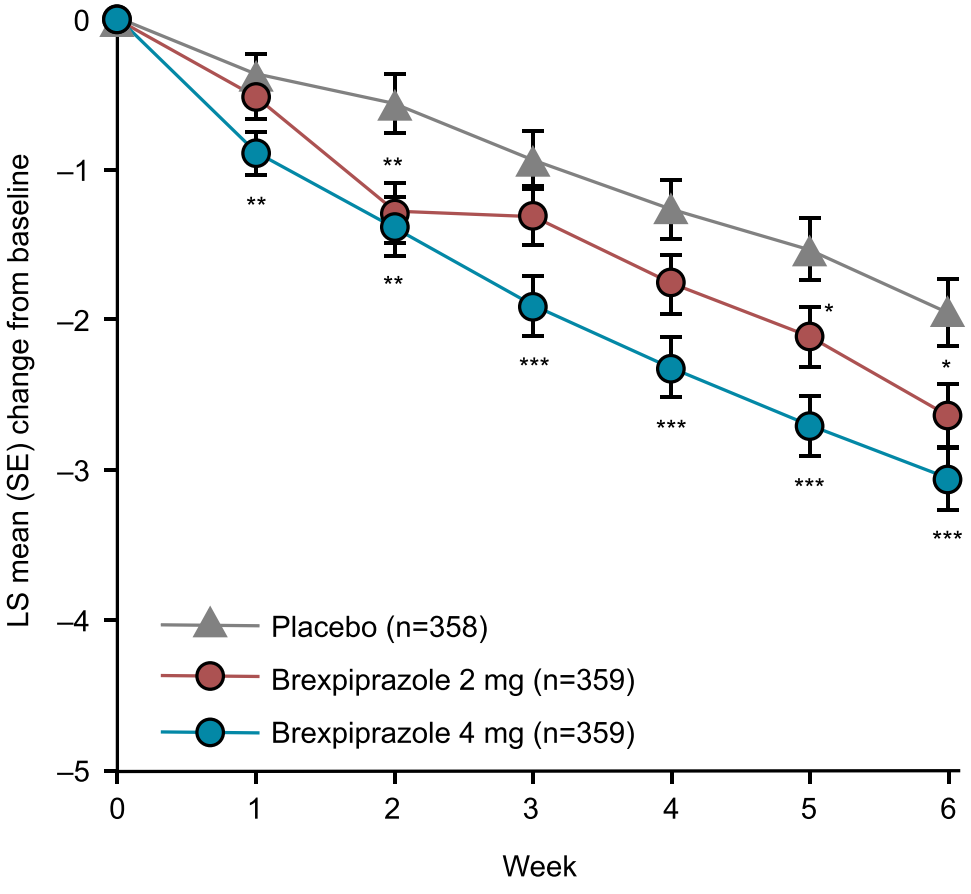

Figure 7 Mean change in PANSS-EC score from baseline to week 6.

Notes: Reprinted from Citrome L, Ouyang J, Shi L, Meehan SR, Baker RA, Weiss C. Effect of brexpiprazole on agitation and hostility in patients with schizophrenia: post hoc analysis of short- and long-term studies. J Clin Psychopharmacol. 2019;39(6):597–603. Copyright © 2019, Copyright © 2019 The Author(s). Published by Wolters Kluwer Health, Inc.[23] *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ versus placebo; pooled analysis; MMRM (short-term); observed cases (long-term). Mean (SD) PANSS-EC scores at baseline: placebo, 12.6 (3.8); brexpiprazole 2 mg, 12.8 (3.8); brexpiprazole 4 mg, 12.9 (3.7).

Abbreviations: MMRM, mixed model repeated measures; PANSS-EC, Positive and Negative Syndrome Scale excited component.

or sedating side effects. A 2017 study assessed the frequency of these side effects as reported in product labeling for several second-generation antipsychotics, including brexpiprazole, and calculated the number needed to harm (NNH) for each.[71] The findings categorized brexpiprazole as one of only two medications reviewed that fell into the "neither activating nor sedating" classification, as illustrated in Figure 8.

Additional Patient Characteristics

Brexpiprazole may be particularly beneficial for patients with multiple psychiatric and/or medical comorbidities, those experiencing symptoms across multiple schizophrenia domains, and individuals in the early stages of schizophrenia, including first-episode patients. Starting treatment with a well-tolerated antipsychotic in early-stage patients can foster a positive perception of medication, improving adherence to long-term therapy while minimizing adverse outcomes from side effects, and increase a patient's insight into their disease.[72,73] Brexpiprazole's advantages include a low risk of cardiometabolic, prolactin-related, parkinsonian, activating, or sedating side effects, as well as minimal anticholinergic effects. Notably, antipsychotics with significant anticholinergic activity have been linked to increased risks of pneumonia and choking-related mortality.[74,75]

Substance use disorder (SUD), including nicotine, alcohol, and other substances, is a common comorbidity in schizophrenia and worsens patient outcomes.[76,77] Some studies have explored brexpiprazole's role in this context. A 2023 observational study found that coexisting SUD did not reduce brexpiprazole's efficacy in managing schizophrenia symptoms and that it had a positive impact on cravings.[78] Similarly, a 2024 prospective study with a small sample size of patients with schizophrenia and SUD reported reduced cravings.[79] Given that schizophrenia involves dysregulation of the reward system and full dopamine antagonists can further suppress the reward system, a partial D_2 receptor agonist, like brexpiprazole, may help reduce drug cravings and self-medication behaviors.[80,81] However,

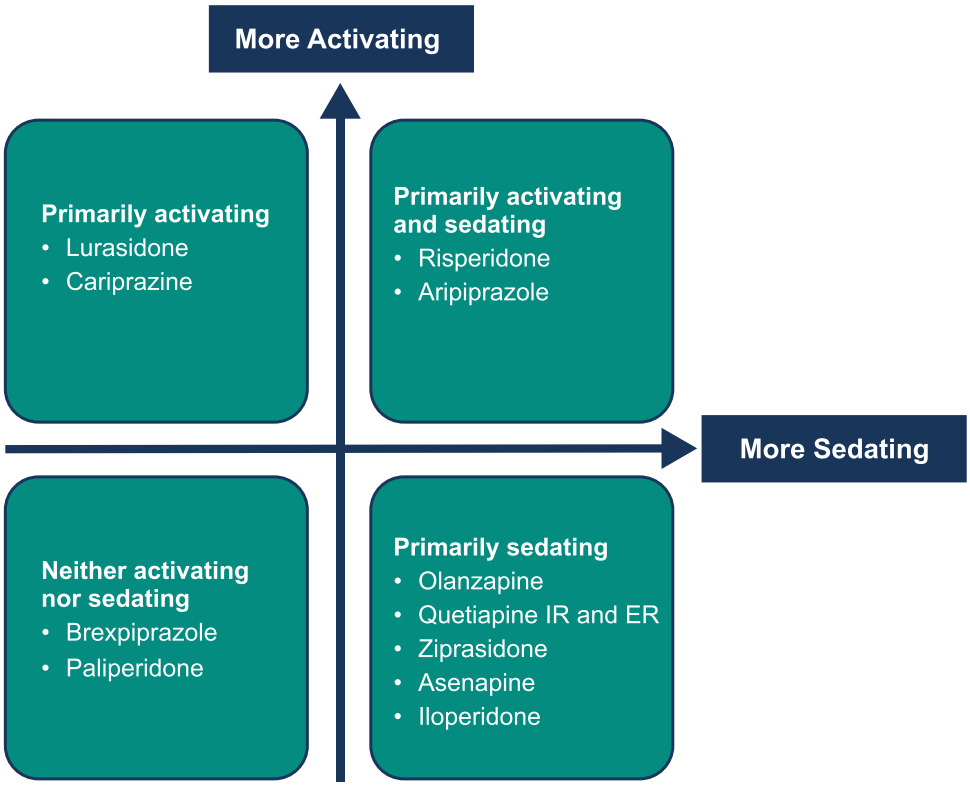

Figure 8 Data from Citrome et al.[71] Categorization of antipsychotic medications based on numbers needed to harm (NNHs) for activating and sedating side effects.
Notes: "Primarily activating" defined as NNH for akathisia statistically significant and lower than NNH for sedation/somnolence; "Primarily activating and sedating" defined as NNH for akathisia statistically significant and similar to NNH for sedation/somnolence; "Primarily sedating" defined as NNH for sedation/somnolence statistically significant and lower than NNH for akathisia; "Neither activating nor sedating" defined as NNH values for either akathisia or sedation/somnolence not significant.

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randomized controlled trials comparing brexpiprazole with other antipsychotics are needed to further evaluate potential benefits in this high-risk population.

Long-term tolerability is another key factor to consider when initiating an antipsychotic in adolescent patients. Recently, brexpiprazole was approved in Europe for the treatment of adolescents aged 13 years and older with schizophrenia. This approval was based on adult studies, pharmacokinetic data, and interim safety findings from a long-term trial, as well as a randomized, double-blind, placebo-controlled study in adolescents.[16,82,83]

Data on the use of brexpiprazole in pregnancy remain limited primarily to animal studies. If used during the third trimester, it may cause EPS or withdrawal in the newborn.[19] In the clinical development program for aripiprazole, a single participant, in the Zenith long-term trial, became pregnant after discontinuing brexpiprazole and delivered a baby with normal APGAR scores approximately eight months after her last dose.[39]

Initiation of Therapy Across Care Settings

Barriers to Initiating Brexpiprazole

In some countries, general practitioners either choose not to initiate antipsychotic therapy or are prohibited from doing so. As a result, primary care physicians often refer patients to emergency services, which may be the only available option until the patient can see a specialist, such as a psychiatrist, nurse practitioner, or physician assistant. The National Institute for Health and Care Excellence (NICE) guidelines advise against initiating antipsychotic treatment in primary care settings without psychiatric consultation;[63] however, broad and simple access to such consultations is limited to certain countries. Additionally, financial constraints such as hospital budgets or health plan formularies can create barriers to prescribing branded antipsychotics, especially in early-stage illness when multiple generic alternatives are available. In these cases, previously mentioned cost-effectiveness data can support the consideration of brexpiprazole.[48,49]

The panel also discussed common misconceptions about brexpiprazole in inpatient settings. Some clinicians mistakenly believe brexpiprazole cannot be used for first-episode schizophrenia or for inpatients requiring sedation due to agitation. However, initiating a well-tolerated agent early in the disease course can help establish a positive perception of pharmacologic therapy, and brexpiprazole is unlikely to introduce the long-term cardiometabolic risks associated with many other treatments. Due to its long half-life and non-sedating properties that are desirable in the long run, it is appropriate to co-administer a short-term sedating agent, such as a benzodiazepine, until brexpiprazole effectively controls symptoms and agitation has resolved. Moreover, an appropriate dose for symptom control needs to be achieved, exploiting the entire available dose range up to 4 mg/d.

The panel identified key strategies to address inpatient barriers and optimize brexpiprazole use:

1. Co-administer a sedating drug during the first week to manage agitation.
2. Follow the recommended titration schedule: Start with 1 mg for four days, increase to 2 mg until day 7, and reach 4 mg by day 8. If clinically appropriate, consider a more rapid titration (1 mg to 4 mg by day 4) as done in the Lighthouse study.[19]
3. 4 mg is the target dose for patients with multi-episode schizophrenia; 2–3 mg for first-episode schizophrenia. Get to this dose as quickly as possible in patients with acute schizophrenia exacerbations, as this dose provides the most robust efficacy.

The panel also emphasized the need for greater education among all members of the inpatient care team regarding brexpiprazole's benefits, suitability for inpatient care, and role in long-term maintenance therapy.

Dosing and Titration

Prescribers in both inpatient and outpatient settings should understand the long-term treatment plan, target doses, and unique characteristics of brexpiprazole, including its recommended titration schedule. The EMA's Summary of Product Characteristics (SmPC)[15] recommends an initial titration schedule that mirrors the one utilized in the Vector study to

achieve a 4 mg target maintenance dose for schizophrenia in adults.[17] This schedule consists of 1 mg daily on days 1 to 4, increasing to 2 mg daily on days 5 to 7, and reaching 4 mg on day 8 based on patient response and tolerability. The Lighthouse study, on the other hand, employed a more rapid titration approach, starting with 1 mg on day 1, increasing to 2 mg on day 2, 3 mg on day 3, and reaching a range of 2 mg to 4 mg from day 4 onward.[19] Titration strategies may need to be adjusted depending on clinical circumstances. In acute settings, a faster titration approach may be appropriate.[84] For outpatients switching from another antipsychotic, a weekly up-titration of brexpiprazole, along with a delayed taper and discontinuation of the baseline medication ("plateau cross-titration"), may be preferred. However, if switching from another partial D_2 dopamine agonist, a direct cross-titration can be utilized.[85,86]

In patients with moderate to severe hepatic or renal impairment or when co-administered with strong CYP3A4 or CYP2D6 inhibitors, the maximum daily dose of brexpiprazole is 3 mg.[15] Outside of these conditions, the panel agreed that 4 mg daily is the optimal maintenance dose for adult patients with schizophrenia. This recommendation is supported by data from the Equator trial's maintenance phase, where the mean daily dose at the last visit was 3.6 mg, as well as by additional clinical trial data showing a dose-response relationship, where 4 mg was the most effective dose for managing positive symptoms and agitation in people with multi-episode schizophrenia.[20] A meta-analysis of acute trials also found that while a 2 mg dose was effective in addressing negative symptoms, a 4 mg dose provided superior efficacy for positive symptoms and agitation without an increase in side effects.[87]

Half-Life Considerations

The terminal elimination half-life of brexpiprazole is relatively long (91.4 hours),[88] meaning it takes approximately two weeks to reach full steady-state blood concentration. Clinicians must be aware of the time required to reach steady state when initiating brexpiprazole, especially in an antipsychotic-naïve or currently drug-free patient, or when switching from another antipsychotic to brexpiprazole, as appropriate dose titration is necessary in both situations (see below). Once a patient is stabilized on a maintenance dose of brexpiprazole, the long half-life is advantageous in the case of a missed dose, as overall exposure to brexpiprazole will not significantly fluctuate.

Switching From "X" to "Brex"

Switching between antipsychotic medications can be challenging due to the risk of rebound symptoms, withdrawal effects, differing side effect profiles, and variations in half-lives. Given these complexities, careful coordination between prescribers and upfront patient counseling are essential in setting appropriate expectations. Several switching strategies exist with cross-titration—gradually discontinuing the current agent while initiating the new one being the most commonly recommended approach.[89–91] This is the method included in the EMA's SmPC for brexpiprazole.[15] Although randomized controlled evidence suggests minimal differences between switching strategies,[92–94] careful monitoring and an individualized approach remain essential in clinical care settings. This procedure is particularly important when switching from an antipsychotic with a shorter half-life to one with a longer half-life or when switching from a strong antagonist to a weaker antagonist or partial agonist, where standard cross-titration may not be adequate. In these cases, receptors previously upregulated by the initial antipsychotic may become exposed to endogenous neurotransmitters or the partial agonist, leading to rebound and withdrawal symptoms.[85,95] This risk is especially pronounced when switching from potent dopamine-blocking "-done" antipsychotics or from "-pine" antipsychotics with strong antihistaminic or anticholinergic properties, potentially resulting in agitation, psychosis, akathisia, restlessness, insomnia, or anxiety.[85]

Switching between partial agonists ("-pips") tends to be less complex, making a cross-titration very viable, as their receptor profiles and half-lives are more comparable.[95] A post-hoc analysis of a long-term, open-label study in Japanese outpatients evaluated the safety and efficacy of switching to brexpiprazole from aripiprazole versus other antipsychotics over a four-week period. By week 56, the incidence of treatment-emergent adverse events (TEAEs) was comparable between the two groups: 84.1% of patients switching from aripiprazole and 88.5% of those switching from other antipsychotics reported at least one TEAE. Discontinuation rates were lower among those previously treated with aripiprazole (32.9% vs 54.8%), likely due to its pharmacological similarity as a partial D_2 dopamine agonist.[61]

Regarding cross-titration duration, a slower approach is generally more conservative but may not always be necessary. In the Equator study, clinicians cross-titrated patients from their existing antipsychotic to brexpiprazole over 1 to 4 weeks.[20] A post-hoc analysis found that 72% of participants took more than three weeks to complete the transition, with lower TEAE incidence in those with conversion times of 22–33 days compared to shorter transitions (44.4% vs 62.5%–84.2%). However, discontinuation rates at 8 weeks due to adverse events or lack of efficacy showed only minor differences across conversion groups.[84]

The consensus panel notes that, based on available data, the pharmacological properties of brexpiprazole, and clinical experience, switching to brexpiprazole can be successfully achieved using various strategies and durations tailored to individual patient needs.

Long-Term Continuation

Maintenance therapy with antipsychotics is recommended in most clinical practice guidelines to reduce the risk of relapse.[9] However, adherence remains a significant challenge, with fewer than half of patients estimated to consistently take their prescribed long-term antipsychotic medications.[5] Non-adherence can result from various factors, including patient-related reasons, medication efficacy and safety profiles, and access to resources and support.[5] Alternatively, long-acting injectable antipsychotic may also need to be considered,[96,97] which is not available for brexpiprazole.

However, patients who are satisfied with a medication's effectiveness and experience minimal side effects are generally more likely to continue therapy, reducing the risk of partial adherence or relapse. A 2022 meta-analysis identified long-acting injectable (LAI) antipsychotics as preferred options for maintenance therapy. However, in randomized controlled trials—where adherence is typically higher—brexpiprazole showed a similar relative risk for relapse as aripiprazole LAI.[22,98] Additionally, real-world evidence suggests that brexpiprazole may be associated with lower discontinuation rates compared to other oral second-generation antipsychotics.[50]

Treatment Algorithm

While specific circumstances varied across countries, all panelists agreed that more clinical guidance is needed to educate prescribers on the appropriate use of brexpiprazole. Based on clinical practice guidelines, a review of

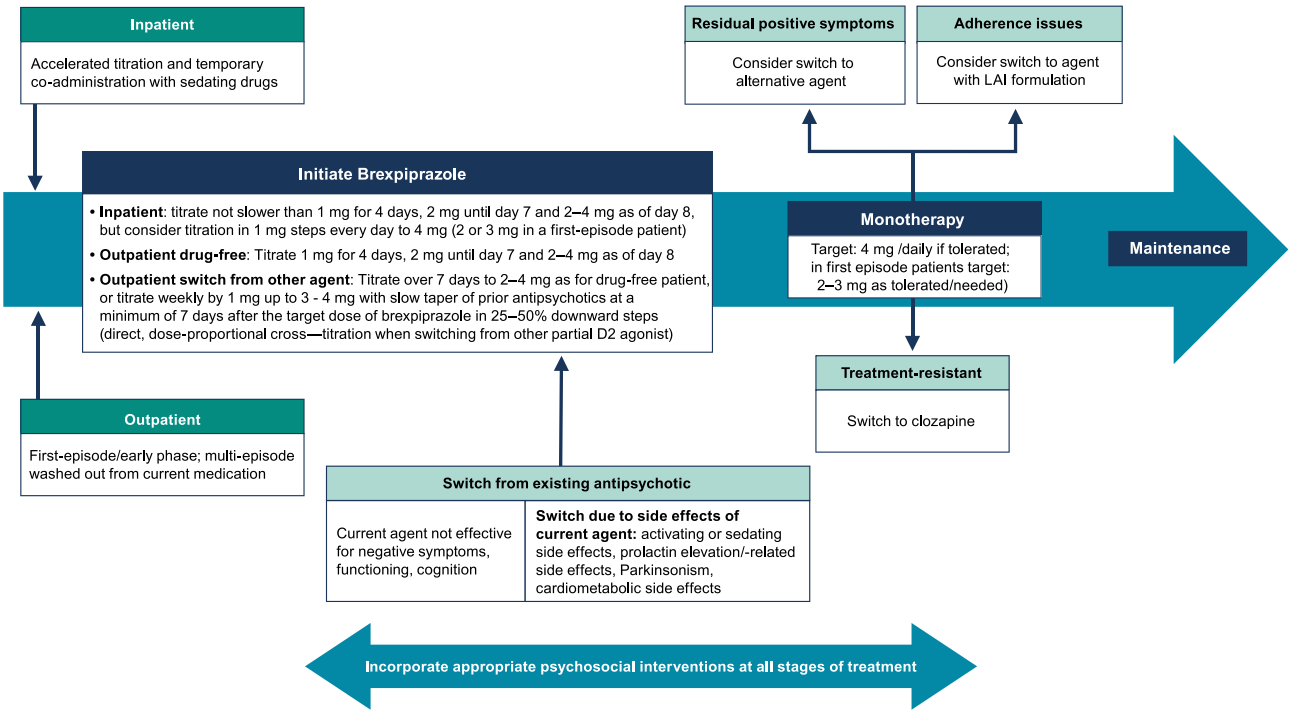

Figure 9 Recommended treatment algorithm for brexpiprazole's place in therapy for schizophrenia.

published literature, and the panelists' clinical experience, an algorithm was developed to illustrate pathways to long-term maintenance therapy with brexpiprazole (Figure 9). Patients may be initiated on brexpiprazole in an inpatient or outpatient setting as new therapy or a switch from an ineffective or intolerable agent. Brexpiprazole is acceptable as a first-line antipsychotic agent in most situations, other than as monotherapy for treatment-resistant patients, those with residual positive symptoms, or patients with adherence issues to oral medications that require a long-acting injectable formulation. Long-term maintenance treatment should be the end goal, regardless of the entry point into the treatment pathway.

Limitations

This review and consensus report of best practice regarding the use of brexpiprazole in patients living with schizophrenia has several limitations. First, all reported evidence in this manuscript (as well as in similar clinical pharmacological studies and reports) is based on either self-reported or clinician-reported rating scales. Although these rating scales have been validated and are widely used, many of which are also required by regulatory bodies to achieve approval for use of medications in clinical care, the outcomes are subjective and susceptible to recall and other biases. Second, there still is a limited number of active-controlled randomized trials for patients with schizophrenia and an acute illness exacerbation and no head-to-head trials comparing brexpiprazole with other antipsychotics for the maintenance treatment and relapse prevention. Third, available acute trials were limited to 6 weeks. Fourth, doses of brexpiprazole beyond 4 mg/day have not been explored systematically in phase 3 or Phase 4 studies. However, since there seems to be more robust efficacy with 4 mg/day than with 2 mg/day for people with schizophrenia and limited adverse effects at the maximum approved dose of 4 mg/day, exploration of the potential utility of doses higher than 4 mg/day would likely have been unfeasible for people with insufficient response to 4 mg/day and without dose-related tolerability issues. Fifth, data on functioning and quality of life were limited. Finally, real-world database studies that can complement randomized controlled data were limited.

Areas for Additional Research

More active controlled trials involving brexpiprazole should be conducted in acutely exacerbated and stabilized people with schizophrenia. In certain acute situations, titration to the 4 mg dose over a condensed timeframe may be recommended, as was highlighted in the Lighthouse study previously.[99] This approach is utilized in clinical practice today. As antipsychotic polypharmacy is a common clinical practice in the treatment of schizophrenia,[100] brexpiprazole may be considered as an adjunctive agent to enhance functionality while preserving the therapeutic effects of dopamine blockade. However, efficacy data for such combinations are insufficient, possibly except for reduced negative symptoms when adding a partial D_2 agonist to ongoing treatment with a D_2 antagonist antipsychotic.[101] Nevertheless, adjunctive brexpiprazole could, for example, be considered in patients experiencing hyperprolactinemia from potent antidopaminergic antipsychotics that are desired to be continued, as demonstrated for aripiprazole augmentation[102,103] or in a patient who requires a higher dose of their current medication but cannot increase it due to tolerability. In these cases, brexpiprazole may have a place as an agent that can provide additional incremental efficacy with more favorable tolerability, yet more data are needed in this regard. Augmentation of clozapine therapy with brexpiprazole is another possible scenario requiring more research. Studies have shown aripiprazole[104–106] and cariprazine[107,108] used as an augmentation to clozapine as an effective strategy, so additional trials would be helpful to determine if brexpiprazole could be utilized similarly. In addition, controlled trials focused on brexpiprazole's beneficial impact on negative and depressive symptoms, cognitive and functional status, and quality of life would be helpful to further support its use in addressing a wide range of symptoms and comorbidities in patients living with schizophrenia. Finally, more data on functioning and quality of life as well as service utilization and other real-world outcomes should be collected, including in larger database studies.

Conclusions

Brexpiprazole offers a promising option for improving the long-term care of patients with schizophrenia. Brexpiprazole not only effectively addresses positive symptoms, it also provides a well-tolerated treatment that targets multiple

symptom domains and enhances overall patient functioning. With brexpiprazole being a partial agonist, adequate dosing is particularly relevant, and the entire dose range up to 4 mg/day needs to be explored before concluding that there may be insufficient efficacy. With numerous antipsychotic options available, it is essential for clinicians to understand the unique attributes of each medication, including dose-dependent differences in efficacy, for example improved depressive symptom efficacy at lower doses and antipsychotic efficacy at higher doses. This review highlights the key differentiating characteristics of brexpiprazole, reinforcing its role as a valuable treatment option for individuals living with schizophrenia targeting goals within and beyond symptom improvement.

Consent Statement

All expert panelists provided consent regarding the use of their opinions and the publication of this article.

Author Contributions

The article is based on the discussions from the panel meeting. The opinions expressed in the article are the independent views of the authors and have not been influenced by third-party sponsorship.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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