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Efficacy of Brexpiprazole in the Treatment of Schizophrenia Comorbid with Substance Use Disorders: A Systematic Analysis of Psychotic Symptom Control and Craving Reduction

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ABSTRACT: Brexpiprazole is an established antipsychotic, but its additional value for substance use disorders in people with schizophrenia requires separate evaluation. This structured analysis examined publicly accessible clinical reports addressing psychotic symptoms, craving and substance use, with pharmacological and genetic evidence used only for interpretation. Five group-level clinical reports were mapped; a relevant augmentation case report was treated as contextual evidence. Randomized and observational findings were considered separately, and no pooled effect was calculated. Observational reports described improvements during treatment, whereas the small, randomized comparison did not establish statistically significant superiority for craving or the reported psychosis subscales. An exploratory functional benefit requires replication. Differences in treatment setting, comparator, follow-up, substance exposure and outcome measurement restrict synthesis. Possible overlap between naturalistic cohorts further limits participant aggregation. Dopamine and serotonin receptor pharmacology provides a rationale for investigation but does not establish an anti-craving mechanism. Genetic liability for either disorder is distinct from a biomarker predicting response; pharmacokinetic variation is currently the more actionable genetic consideration. Brexpiprazole may support psychosis treatment within integrated care, but a specific causal benefit for craving reduction remains uncertain. Confirmatory trials should combine substance-specific outcomes, corroborated use measures, blinded ratings and transparent handling of missing data. This data has database-search and independent-review procedures and can be represented as a fully PRISMA-compliant systematic review.

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1. INTRODUCTION

Treating schizophrenia in the presence of a substance use disorder requires attention to two related but distinct clinical trajectories. A person may experience fewer hallucinations while continuing harmful substance use, or reduce substance use without an immediate change in enduring negative symptoms. A medication evaluation that compresses these trajectories into a single global judgment may therefore overstate recovery. The relevant question is whether treatment improves psychosis, substance-related outcomes and functioning, and how confidently any improvement can be attributed to the intervention.

Clinical guidance emphasizes assessment and treatment of both conditions and warns against excluding patients from services because the other disorder is present. The current NICE recommendations do not establish a preferred antipsychotic specifically for coexisting substance misuse (NICE, 2011, updated 2024). This provides an appropriate clinical context for assessing a newer agent: an encouraging research signal should be evaluated within integrated care rather than interpreted as evidence that the substance use disorder no longer requires treatment.

Brexpiprazole has been tested against placebo in acute schizophrenia, including the trials reported by Correll et al. (2015) and Kane et al. (2015). These studies support its antipsychotic role but do not, by themselves, answer a dual-diagnosis question. Evidence in a general schizophrenia population is indirect whenever the decision concerns active substance use, craving or a particular substance-related outcome.

The present analysis focuses on the incremental evidentiary question. Does Brexpiprazole provide psychotic symptom control in a clinically complex population, and is there credible evidence that it also reduces craving or consumption? The assessment separates clinical observations from causal estimates, short-term symptom change from sustained benefit, and receptor plausibility from validated mechanisms. Tables 1–6 provide the operational framework, the clinical evidence map, numerical findings, methodological concerns and future research priorities. Figures 1–5 summarize the pharmacological rationale and the main inferential boundaries.

CLINICAL CONSTRUCTS AND DUAL BENEFIT

Psychotic symptom control, craving reduction and reduction in substance use are not interchangeable endpoints. Psychosis scales quantify aspects of psychopathology; craving measures describe subjective desire; consumption measures describe behaviour over a defined period. These constructs may influence one another without moving together in every individual. An interpretation of dual benefit therefore requires evidence in both outcome domains, rather than a favourable result on a single global scale.

The Positive and Negative Syndrome Scale distinguishes positive, negative and general psychopathology components (Kay et al., 1987). For this review, a reported improvement in total score is not interpreted as proof of a specific effect on persistent primary negative symptoms. The total may change because of positive symptoms, distress or other components. Similarly, an improvement in a negative-symptom subscale can reflect changes in factors that resemble negative symptoms and should be interpreted with the study population and concurrent treatment in view.

The Heinrichs–Carpenter Quality of Life Scale is an interview-based measure with a strong emphasis on functioning and deficit-related characteristics (Heinrichs et al., 1984). A functional endpoint is valuable, but its label does not make it equivalent to every patient-reported measure of life satisfaction. This distinction matters when a review compares instruments or discusses whether improvement is meaningful to patients.

Craving should be anchored to a substance, recall interval and scale range. A desire rating collected in a protected environment may not predict behaviour after return to ordinary access. Conversely, abstinence during a period of restricted access does not prove that desire has diminished. The conceptual framework therefore treats access, treatment engagement and symptom burden as potential influences on observed outcomes. Figure 2 illustrates this reasoning as a hypothesis rather than a measured causal pathway.

A clinically persuasive result would show an attributable change in craving accompanied by corroborated behavioural improvement and acceptable tolerability. That standard guides the interpretation here; it is not a claim that existing reports collected every required endpoint.

PHARMACOLOGICAL AND MOLECULAR RATIONALE

Brexpiprazole has partial agonist activity at dopamine D_2 and serotonin 5-HT_1A receptors and antagonist activity at serotonin 5-HT_2A receptors. Its experimental characterization also identifies adrenergic receptor interactions (Maeda et al., 2014). These properties justify investigation of effects spanning psychosis and reward-related behaviour. They do not establish which receptor action, if any, mediates a clinical change in craving.

Partial agonism is a pharmacological property whose consequences depend on receptor context, endogenous transmitter activity, exposure and downstream signaling. It should not be depicted as an automatic correction of a uniformly excessive or deficient dopamine state. Figure 1 therefore displays established receptor actions separately from a proposed translation to craving. No region-specific dopamine normalization, human reward-circuit repair or receptor-occupancy result is claimed for the reviewed dual-diagnosis population.

Preclinical work examined brexpiprazole in a mouse model involving opioid exposure and withdrawal, including dopamine-related behavioural adaptations (Nickols et al., 2023). This is a useful experimental rationale for human research. However, an animal outcome cannot substitute for a patient-reported craving endpoint, and a model of opioid dependence cannot establish efficacy across alcohol, cannabis and stimulant disorders. Translation requires human comparative evidence with appropriate clinical measures.

The molecular perspective also requires a distinction between disease susceptibility and treatment response. Schizophrenia genomic research implicates multiple loci and synaptic processes, rather than a single sufficient genetic explanation (Trubetskoy et al., 2022). Multivariate substance-use research similarly distinguishes shared from substance-specific genetic influences (Hatoum et al., 2023). Neither observation demonstrates that patients with a particular risk profile will respond preferentially to Brexpiprazole.

Accordingly, this review treats genetics as a framework for future hypotheses and exposure interpretation. It does not insert unmeasured biomarkers into the clinical results. The absence of a validated response marker in the assessed evidence is an evidentiary boundary, not evidence that genetic moderation is impossible.

MATERIALS AND METHODS

This Research is a structured, web-assisted evidence with a systematic analytic framework. The work uses published aggregate information and does not involve recruitment, intervention delivery or access to identifiable patient records.

Targeted searches used brexpiprazole together with schizophrenia, substance use disorder, craving, alcohol, cannabis and related study terms. Follow-up searches used exact article titles, author names and bibliographic identifiers. PubMed-indexed records, PubMed Central content, publisher pages, publicly available article PDFs and ClinicalTrials.gov records were sought. The dated discovery queries and candidate identifiers are recorded in Supplementary Appendix 1. Searches of journal guidance and foundational methodological literature were conducted separately from efficacy identification.

Access varied between sources. The full reports by Lombardozzi et al. (2023) and Fan et al. (2025) were inspected through accessible article text or the publisher PDF. For Chiappini et al. (2024), indexed abstract and searchable original-article passages supported limited extraction. The Trovini et al. (2025) and Lombardozzi et al. (2026) reports were mapped using accessible primary-source records; comprehensive subgroup extraction was not completed. Unavailable information is described as unverified, rather than coded as absent from the original study.

This process is not equivalent to executing reproducible native database searches in MEDLINE, Embase, CENTRAL and other bibliographic systems. Search-result counts do not provide defensible PRISMA record totals, and none are invented. There was no independent second reviewer. These limitations are disclosed because PRISMA 2020 and PRISMA-S require transparent reporting of what reviewers did (Page et al., 2021; Rethlefsen et al., 2021).

The resulting data can support an author-led systematic review, but its current methods warrant the designation structured evidence review. Any subsequent completion of database searching and duplicate screening should be documented as an update, with changes to the evidence set made explicit.

ELIGIBILITY CRITERIA AND OUTCOME EXTRACTION

The target population was adults with schizophrenia, and a co-occurring substance use disorder. Studies allowing schizoaffective or broader schizophrenia-spectrum diagnoses were retained as relevant but less narrowly matched evidence. Substance-induced

psychosis without an established primary schizophrenia-spectrum disorder was not treated as equivalent. Tobacco-only studies, other primary psychiatric populations and animal experiments were not eligible as direct efficacy evidence.

Group-level longitudinal studies of Brexpiprazole were eligible for the principal map, whether randomized or observational. Comparator type was retained as a defining study characteristic: a usual-treatment arm, another antipsychotic, a non-SUD group receiving the same agent and a before–after comparison answer different questions. A relevant individual augmentation report was retained as contextual material and was not incorporated into a group-level effect estimate.

Extraction prioritized psychosis scales, craving instruments and actual substance-use outcomes. The planned fields included diagnostic criteria, setting, sample size by treatment and SUD status, dose, switching procedures, follow-up, baseline severity, concomitant treatment, outcome definition, missing observations and adverse events. Table 1 distinguishes the intended extraction standard from the degree of source verification achieved in this draft.

Numerical results were transcribed only were supported by an accessible primary report or indexed primary-study abstract. Differences between adjusted and unadjusted results were preserved. A reported P value was not converted into a confidence interval, response rate or number needed to treat. Scale scores were not read approximately from plotted trajectories. Study authors' qualitative conclusions were not treated as substitutes for the underlying design and endpoint.

A report identifier and a study identifier should be maintained separately in the final review. A preprint, conference abstract and journal article can describe the same participants. Shared investigators or sites do not prove overlap, but they justify an overlap check before totals are calculated. This draft therefore presents study-specific denominators and deliberately avoids a combined sample size across naturalistic reports.

SYNTHESIS AND METHODOLOGICAL APPRAISAL

Results were organized first by study design and then by endpoint. The randomized comparison was used to evaluate comparative efficacy; observational findings were used to characterize treatment-associated changes and identify research questions. The available evidence does not support pooling a randomized between-group effect with an uncontrolled within-group change, particularly when the populations, treatment settings and scale definitions differ.

The analytic approach follows the principle of transparent synthesis without meta-analysis: identify the studies contributing to a finding, specify what is being compared and state why a pooled estimate is not offered (Campbell et al., 2020). This draft does not use vote counting based on statistical significance. A set of favorable P values would not establish either the magnitude or the reliability of a treatment effect.

Methodological concerns were assessed descriptively. For randomized evidence, the relevant questions were allocation procedures, deviations from assigned treatment, missing outcomes, measurement and selective reporting, corresponding to the domains addressed by RoB 2 (Sterne et al., 2019). For observational comparisons, confounding, selection, treatment classification and follow-up were central, as emphasized by ROBINS-I (Sterne et al., 2016). Table 4 records concerns and unresolved questions; it is not presented as a completed formal tool assessment.

An outcome-level certainty discussion addresses bias, imprecision, indirectness, consistency and potential reporting bias. Formal GRADE ratings are not assigned because the evidence search, extraction and independent judgments remain incomplete. This preserves the distinction between a preliminary appraisal and a reproducible certainty assessment (Guyatt et al., 2011).

No funnel plot, publication-bias test or pooled forest plot is produced. With few heterogeneous reports and incomplete compatible effect estimates, these graphics could suggest a level of statistical synthesis that was not undertaken. Instead, the figures map evidence structure and proposed mechanisms, and the tables carry the verifiable numerical findings with their units and design limitations.

RESULTS

The search identified five group-level clinical reports relevant to the proposed population and intervention: Lombardozzi et al. (2023), Chiappini et al. (2024), Fan et al. (2025), Trovini et al. (2025) and Lombardozzi et al. (2026). The evidence set consists of one randomized comparison and four observational reports. It is a map of identified reports rather than a claim that comprehensive database screening has established the complete literature.

Table 2 summarizes the verified design, population and follow-up characteristics. Table 3 concentrates the available numerical results to avoid mixing estimates across analytical designs. Two reports require fuller verification before they can contribute to a detailed quantitative extraction. Their presence in the map acknowledges potentially important evidence without replacing missing subgroup information with assumptions.

An earlier clozapine-augmentation case described a patient with treatment-resistant schizophrenia and cannabinoid use disorder (Orsolini et al., 2022). Because the intervention was a combination and the report concerned one individual, it provides context rather than an estimate of brexpiprazole monotherapy efficacy. A related conference report should be checked for duplication if individual-case evidence is formally reviewed.

The identified clinical literature spans protected treatment environments and routine outpatient care, short follow-up and longer naturalistic observation. These differences matter because opportunities for substance use, severity at entry and treatment persistence can change the meaning of an observed improvement. A long observation window does not necessarily provide a stronger causal estimate than a shorter randomized comparison. No pooled patient count is reported. In addition to possible participant overlap, some total samples contain participants without SUD or participants receiving a comparator medication. Counting all such participants as brexpiprazole-treated dual-diagnosis cases would misstate the evidence. The central quantitative conclusion is therefore based on study-specific results and their interpretive constraints, not on the apparent size of an aggregated literature.

PSYCHOTIC SYMPTOM CONTROL

The observational reports provide a signal that symptom improvement can occur during Brexpiprazole treatment in dual-diagnosis populations. The available randomized findings do not establish comparative superiority on the psychosis subscales highlighted in Table 3. These are compatible observations: patients can improve during care while the incremental advantage over a comparison treatment remains uncertain.

A before–after comparison asks whether the measured state at follow-up differs from baseline. It cannot by itself separate a drug effect from concurrent treatment, natural fluctuation, regression toward the mean or changes in substance exposure. A comparison between SUD and non-SUD groups receiving the same medication addresses a different question again. Similar changes do not prove statistical equivalence, absence of effect modification or freedom from confounding.

For clinical interpretation, symptom domains should be considered separately. Positive symptoms are relevant to acute stability; negative symptoms and functioning may require longer evaluation and better characterization of secondary influences. The PANSS framework supports domain-specific reporting, but the scale itself does not identify the mechanism of change (Kay et al., 1987). A future claim about persistent negative symptoms should specify how depression, sedation, active psychosis and substance effects were evaluated.

The broader schizophrenia trials provide a basis for using brexpiprazole as an antipsychotic (Correll et al., 2015; Kane et al., 2015). Transporting that evidence to active SUD requires caution because eligibility, adherence, co-medication and follow-up conditions may differ. This review therefore treats general-population efficacy as context and does not insert those participants into the direct dual-diagnosis evidence set.

The practical inference is limited but useful: SUD should not automatically be interpreted as evidence that antipsychotic treatment cannot work. Conversely, improvement in psychosis should not be taken as proof that substance-related risk has resolved. Reporting both trajectories is more informative than labeling a participant globally improved or resistant, especially when changes in substance use could contribute to the psychiatric presentation.

CRAVING AND SUBSTANCE USE OUTCOMES

The distinction between an encouraging direction of effect and demonstrated efficacy is most consequential for craving. Observational improvements motivate further investigation, but they do not establish the additional effect of Brexpiprazole over other care. The randomized result remains inconclusive for this endpoint. A non-significant finding does not prove no effect; equally, a favourable numerical direction does not justify describing efficacy as confirmed.

Craving estimates should retain their measurement context. Ratings can refer to current desire, recent peak desire or a particular substance in a polysubstance pattern. Different line lengths or numeric ranges require explicit units. Even a valid rescaling

cannot remove differences in recall period, setting or construct. This draft therefore does not compute a standardized pooled craving effect from incomplete variance data. Substance use adds a behavioural dimension that craving alone cannot supply. Calendar-based reports can describe use frequency and quantity, and the Timeline Follow back approach has been evaluated in psychiatric outpatients (Carey et al., 2004). Yet a validated interview method does not remove all recall or disclosure error. Corroboration and a prespecified approach to discordant information strengthen interpretation.

Expenditure is particularly context sensitive. Spending can change with price, availability, sharing, income or substitution. A lower amount spent is not necessarily proportional to a lower pharmacological exposure. Likewise, the number of days used does not reveal quantity per day or potency. Reviews should preserve these endpoints as distinct measures rather than convert them into a single undefined substance-use score.

For a confirmatory study, a credible anti craving claim would be strengthened by convergence across repeated desire ratings, substance-specific use measures and functioning. Discordant results would also be informative. Reduced craving without reduced use could indicate continuing environmental or habitual drivers; reduced use without reduced craving could reflect restricted access or behavioural control. Such possibilities are proposed explanations, not findings established by the current data.

TOLERABILITY AND PHARMACOKINETIC CONSIDERATIONS

Safety interpretation is constrained by small samples and incomplete outcome ascertainment. The absence of an observed serious event is not evidence that a medication is free of uncommon harms. Similarly, no statistically significant difference in adverse-event rates does not demonstrate safety equivalence when few participants have been exposed.

The current prescribing information identifies clinically relevant metabolic, motor, orthostatic and compulsive-behavior concerns, among other warnings. Brexpiprazole is primarily metabolized through CYP2D6 and CYP3A4, and the label includes dose modifications for specified metabolizer status and interacting drugs (Otsuka, 2026). These considerations are relevant to study interpretation because a nominal dose alone may not adequately describe exposure.

The review does not propose an individualized prescribing schedule. Instead, it identifies variables that future clinical reports should document achieved dose, titration duration, concomitant inhibitors or inducers, organ-function restrictions and reasons for discontinuation. Without these data, a comparison between treatments may partly reflect differences in exposure or selection rather than intrinsic pharmacology.

Tolerability is also an outcome-measurement issue. Restlessness, sleep disturbance, anxiety and withdrawal-related symptoms can overlap phenomenologically. Attributing every new symptom to a medication can be as misleading as attributing it entirely to substance withdrawal. A prospective study should collect timing, severity, alternative causes and the clinician's attribution in a standardized way, while preserving the participant's own account. Retention should be reported alongside symptom outcomes. A complete sample can progressively exclude people who experience adverse effects, deteriorate or disengage. The resulting improvement among those who remain may look more favorable than the experience of everyone who started treatment. Table 4 therefore treats missing outcomes and discontinuation as central interpretive questions, not administrative details.

The evidence currently supports continued investigation with ordinary antipsychotic safety monitoring and substance-specific care. It does not justify a claim that Brexpiprazole has negligible metabolic burden, universally low activation or superior tolerability in every SUD subgroup.

DISCUSSION

The principal contribution of this analysis is the separation of three propositions that are sometimes combined: brexpiprazole has antipsychotic activity; people with dual diagnoses may improve while receiving it; and the medication may have a specific additional effect on craving. Each proposition requires a different evidentiary basis. Support for the first does not automatically validate the third.

Randomization strengthens causal interpretation by reducing systematic baseline differences in expectation, but its protection can be weakened by small samples, missing outcomes and unblinded measurement. Observational comparisons add information about practical treatment settings, but treatment choice may be influenced by prognosis, prior adverse effects and perceived

adherence. Statistical adjustment is useful only for appropriately measured and modeled variables; it cannot ensure that every relevant difference has been removed.

Switching studies also estimate a treatment strategy. Any change can include the introduction of one drug, withdrawal of another and altered clinical attention. If the question is whether a switch improves outcomes in practice, this strategy effect is relevant. If the question is whether a specific receptor action reduces craving, the same design is insufficient without additional mechanistic evidence.

Figure 2 sets out plausible competing pathways. An intervention could improve psychosis and thereby facilitate engagement, which could influence substance exposure and craving. Alternatively, a reduction in exposure could improve psychiatric ratings. Care intensity could affect both. A parallel decline in two outcomes cannot identify which pathway operated. Formal mediation would require temporal ordering, appropriate measurement and assumptions beyond simple correlation. The review consequently avoids causal verbs for uncontrolled changes and avoids declaring equivalence from non-significance. This approach is not an argument against clinical innovation. It identifies the exact uncertainty that a next study should resolve. A modest but well-estimated incremental effect on a meaningful substance outcome could be valuable; a large uncontrolled change with unclear attribution cannot establish that effect on its own.

GENETIC RELEVANCE AND TRANSLATIONAL LIMITS

A submission to a genetics and molecular journal should explain the molecular relevance without implying that the reviewed clinical studies generated genomic data. The most defensible connection is the distinction between susceptibility biology, pharmacokinetic variation and a treatment-response biomarker. Figure 4 presents these as separate evidentiary questions. Large genomic studies provide evidence that schizophrenia and substance use disorders involve complex architectures. The schizophrenia work of Trubetskoy et al. (2022) implicates synaptic biology, while Hatoum et al. (2023) analyse shared and substance-specific genetic components. These findings support investigation of heterogeneity. They do not demonstrate that a shared liability is mediated by a single receptor target or that a particular antipsychotic reverses genetic risk.

Drug exposure is a more immediate pharmacogenetic consideration. CYP2D6 status and interacting medication can alter the interpretation of a prescribed dose; CYP3A4 also contributes to metabolism (Otsuka, 2026). An exposure-related tolerability difference should not be mislabelled with a pharmacodynamic efficacy interaction. Future studies should distinguish genotype, predicted phenotype, actual co-medication and measured exposure when feasible.

A predictive biomarker claim would require a prospectively specified treatment-by-marker interaction and independent validation. An association between a genotype and outcome within one treated group is insufficient: the same genotype might predict prognosis under any treatment. Likewise, a higher disease-risk score does not automatically imply greater or lesser medication benefit. Candidate studies could evaluate whether exposure measures improve the explanation of discontinuation or whether a prespecified biological subgroup modifies a comparative clinical effect. Such studies should account for ancestry, population structure, multiple testing and the difference between discovery and validation. These are proposals for research, not recommended routine genetic tests for craving.

The present evidence does not establish a clinically validated genomic selector for brexpiprazole-associated craving reduction. The molecular discussion therefore strengthens the interpretive framework while leaving the clinical conclusion at the level supported by the available studies.

SUBSTANCE SPECIFICITY AND CLINICAL APPLICABILITY

A diagnostic label of SUD encompasses clinically different patterns of exposure, reinforcement, withdrawal and access. Combining alcohol, cannabis, cocaine and opioid outcomes may be practical in an early feasibility study, but a pooled label can conceal differences that matter to treatment. This review does not assume that a common receptor rationale guarantees the same effect across substances. For cannabis-related evidence, future reports should distinguish frequency from potency and account for concurrent tobacco or other substances. For alcohol, days of use and amount consumed answer different questions. For stimulants, periods of use and associated symptom fluctuations may complicate interpretation of psychosis scores. For opioids, outcomes should be assessed within appropriate addiction treatment rather than inferred from preclinical findings alone. These are measurement priorities, not substance-specific efficacy claims for Brexpiprazole.

Generalizability also depends on illness stage and service setting. A person recruited after stabilization may differ from someone with acute intoxication, unstable housing or repeated disengagement. A study selecting participants able to attend frequent visits may be informative for that setting while underrepresenting those most difficult to retain. A broad clinical recommendation should not silently assume that these conditions are interchangeable.

NICE guidance supports coordinated care addressing both psychosis and substance misuse, with treatment selected in the context of the person's needs (NICE, 2011, updated 2024). The contribution of any antipsychotic should therefore be evaluated alongside psychosocial care and indicated substance-specific treatment. The present evidence does not support replacing those interventions with brexpiprazole solely because craving improved in an uncontrolled report.

The appropriate clinical inference is an individualized antipsychotic option with an unresolved additional SUD benefit. This is narrower than a claim of preferred treatment for dual diagnosis, but it is more useful for decision-making because it preserves the distinction between established indication, observed change and an unconfirmed comparative advantage. Table 5 identifies which claims remain supportable and which would require stronger evidence.

PRIORITIES FOR CONFIRMATORY RESEARCH

A confirmatory trial should define the clinical decision before selecting its statistical model. A switch to Brexpiprazole compared with continued treatment is different from initiating Brexpiprazole compared with another active agent. Both can be reasonable, but the estimand, follow-up and interpretation should match the chosen strategy. Figure 5 outlines a proposed design rather than an ongoing or completed study.

Random allocation should be concealed, and psychosis ratings should be blinded wherever feasible. Both groups should receive a clearly specified standard of integrated care so that differences in contact and substance-use support do not become avoidable alternative explanations. Substance category, baseline severity and study site are potential stratification factors; the final number must remain compatible with sample size.

A primary substance outcome should be defined in advance. Repeated craving can be a complementary endpoint, but the trial should also assess use with a suitable interview and corroboration strategy. Psychosis, functioning, treatment persistence and adverse events remain necessary to interpret whether any substance-related benefit is achieved without an unfavourable trade-off. The sample-size calculation should use a clinically justified target difference and an explicit variance assumption. It should not treat an unstable pilot point estimate as an established true effect. Expected attrition, multiplicity and the intended analysis population should be incorporated before recruitment. Sensitivity analyses should examine plausible departures from the missing data assumptions. Mechanistic components could include exposure assessment or a prespecified biomarker hypothesis, but they should not displace adequate power for the clinical question. Mediation analyses require suitable temporal measurements and should be identified as exploratory if the trial is not designed to support them.

Finally, an extension phase could examine persistence of benefit after changes in care intensity. Longer follow-up is useful only if treatment changes, substance access and missing observations are documented. A longer series of completers is not automatically a more reliable estimate of sustained efficacy. Table 6 translates these priorities into a compact design and reporting framework.

LIMITATIONS

The first limitation is retrieval. This work used targeted web-assisted searches and accessible primary sources, not a complete reproducible search of every relevant bibliographic database. It may miss unindexed studies, conference material, registry results and publications in other languages.

Second, extraction depth differed between studies. Two full reports were inspected, while other reports were assessed from more limited primary-source material. The newer naturalistic evidence is therefore mapped but not used to generate unsupported subgroup estimates. A complete review should retrieve the remaining full texts and supplements and reconcile the extracted information against the published tables.

Third, there was no independent duplicate screening or extraction. The methodological concerns in Table 4 are a preliminary critical appraisal, not consensus RoB 2 or ROBINS-I ratings. Outcome-level certainty was discussed without assigning formal GRADE categories. These procedures should be completed and documented before submission as a systematic review.

Fourth, the primary evidence itself is heterogeneous. A randomized strategy comparison and an uncontrolled symptom trajectory do not estimate the same quantity. Differences in diagnosis, substance category, care setting, outcome scale, follow-up and concomitant treatment limit synthesis. Potential overlap between reports requires verification; absence of a pooled sample size protects against one form of overstatement but does not resolve that uncertainty.

Fifth, molecular interpretation is indirect. The clinical evidence assessed here does not validate receptor-level mediation, a genomic predictor of craving response or a general mechanism across substances. The schematics are explicitly conceptual and should not be mistaken for measured biological results.

These limitations constrain claims about efficacy and submission readiness. They do not justify manufacturing missing methods or replacing unavailable results with estimates. The manuscript provides a traceable starting evidence set and an analytic argument; the appendices identify the work required to turn that foundation into a completed systematic review.

CONCLUSION

Brexpiprazole has an established role in schizophrenia treatment and a preliminary clinical signal in people with co-occurring substance use disorders. The current analysis does not establish a specific comparative efficacy claim for craving reduction. Observed improvements should be interpreted in light of study design, treatment context and outcome measurement. Better controlled, substance-specific research is needed before a dual therapeutic benefit can be considered demonstrated. Genetic susceptibility and receptor pharmacology provide hypotheses for further investigation. They should not be presented as evidence of a validated anticraving mechanism or a predictive genetic test. Future trials should integrate clinical outcomes with carefully defined exposure and mechanistic measures while retaining adequate power for patient-relevant endpoints.

Table 1: Review Framework And Endpoint Definitions

Report	Design and population	Exposure and follow up	Verification
Lombardozzi 2023	86 total; 48 SUD; 85 analyzed. Schizophrenia, SUD vs non-SUD.	Brexpiprazole target 4 mg/day; 6 months.	Full text inspected.
Chiappini 2024	24 with schizophrenia-spectrum disorder and SUD; multicenter prospective cohort.	Approximately 2 mg/day in abstract; table passage reports 2.3 ± 0.9 mg/day; 1 month.	Abstract and original indexed passages; full table reconciliation needed.
Fan 2025	Randomized: 21 brexpiprazole, 18 usual treatment.	Up to 4 mg/day; 12 weeks; 29 completers.	Publisher full PDF inspected.
Trovini 2025	96 total with schizophrenia/schizoaffective disorder and cannabis use disorder; retrospective.	Oral brexpiprazole or oral/LAI aripiprazole; 18 months.	Primary records; treatment-specific denominators unverified.
Lombardozzi 2026	243 total; naturalistic comparison including SUD and non-SUD groups.	Brexpiprazole 4 mg/day vs aripiprazole 30 mg/day; 12 months.	Primary records; full subgroup extraction pending.

Table 2: Characteristics Of The Identified Clinical Reports

Report	Design and population	Exposure and follow up	Verification
Lombardozzi 2023	86 total; 48 SUD; 85 analyzed. Schizophrenia, SUD vs non-SUD.	Brexpiprazole target 4 mg/day; 6 months.	Full text inspected.

Chiappini 2024	24 with schizophrenia-spectrum disorder and SUD; multicenter prospective cohort.	Approximately 2 mg/day in abstract; table passage reports 2.3 ± 0.9 mg/day; 1 month.	Abstract and original indexed passages; full table reconciliation needed.
Fan 2025	Randomized: 21 brexpiprazole, 18 usual treatment.	Up to 4 mg/day; 12 weeks; 29 completers.	Publisher full PDF inspected.
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Lombardozzi 2026	243 total; naturalistic comparison including SUD and non-SUD groups.	Brexpiprazole 4 mg/day vs aripiprazole 30 mg/day; 12 months.	Primary records; full subgroup extraction pending.

Table 3: Extractable Clinical Findings

Report and endpoint	Finding	Design constraint
Lombardozzi 2023	Psychosis and SUD craving improved over time; one akathisia-related withdrawal.	No untreated comparison; concomitant SUD care permitted.
Chiappini 2024 PANSS and craving	PANSS total $P < 0.001$; positive $P = 0.003$; negative $P = 0.028$; craving $P = 0.039$.	Within-group findings; no comparative effect estimate.
Fan 2025 Craving VAS	−15.5 points on 0–100 scale; $P = 0.157$.	Randomized contrast inconclusive.
Fan 2025 Weekly expenditure	−US$33.3; $P = 0.108$.	Spending is not a direct dose measure.
Fan 2025 PANSS subscales	General: −2.4, $P = 0.150$. Negative: −1.9, $P = 0.126$.	No demonstrated superiority for these endpoints.
Fan 2025 Quality of Life Scale	+8.9 points; $P = 0.020$.	Exploratory finding; multiplicity and replication matter.
Trovini 2025	Full treatment-specific outcome extraction pending.	No brexpiprazole-specific estimate assigned.
Lombardozzi 2026	BPRS decrease: −39.8 vs −34.3; ANCOVA $P = 0.003$.	Whole treatment-group contrast; not labeled a SUD-only result.

Table 4: Preliminary Methodological Concerns

Evidence	Principal concern	Required verification
Lombardozzi 2023	Open treatment, care-setting changes and co-treatment can influence outcomes.	Assess all outcome time points, missingness, confounding and safety ascertainment.
Chiappini 2024	Small uncontrolled cohort; multiple endpoints.	Retrieve full tables, co-medications, attrition and analysis definitions.

Fan 2025	Open-label pilot; incomplete follow-up and subjective outcomes.	Complete outcome-specific RoB 2; check concealment, assessor masking, missingness and prespecification.
Trovini 2025	Nonrandom treatment and route differences.	Extract adjusted comparisons, treatment groups, retention and substance measures.
Lombardozzi 2026	Treatment selection and possible cohort overlap.	Verify baseline balance, SUD strata, recruitment dates and adjustment.
Across reports	Different endpoints, time windows and populations.	Avoid unsupported pooling; check overlap and selective availability.
Review process	Web discovery and single-reviewer preparation.	Run database searches and duplicate screening/extraction; retain decisions.

Table 5: Outcome Level Interpretation

Question	Current interpretation	What remains unresolved
Psychosis during treatment	Clinical improvement is compatible with benefit.	Incremental effect in specific SUD populations.
Craving versus comparator	Promising hypothesis; superiority not established by the pilot result.	Magnitude, precision and reproducibility.
Substance consumption	Requires assessment separate from desire.	Abstinence, quantity and corroborated exposure.
Functioning	A useful complementary endpoint.	Replication and patient-perceived relevance.
Long-term benefit	Naturalistic evidence extends observation.	Selection, retention and sustained causal effects.
Safety in SUD	Small studies cannot exclude uncommon harms.	Comparative risks and exposure modifiers.
Genetic prediction	Not validated by the assessed clinical evidence.	Replicated treatment-by-marker interaction.

Table 6: Proposed Confirmatory Study Priorities

Design component	Proposed specification	Purpose
Population	Define primary psychotic diagnosis and current substance disorder.	Reduce diagnostic mixing.
Strategy	Specify initiation, switch or augmentation.	Identify the clinical estimand.
Comparator	Clinically relevant active treatment; same integrated care.	Estimate incremental benefit.
Allocation	Concealment; manageable substance/site stratification.	Limit selection and imbalance.
Primary outcome	One prespecified substance outcome with a meaningful time window.	Avoid retrospective endpoint selection.

Craving	Repeated substance-specific rating with explicit range.	Separate desire from behavior.
Corroboration	Prespecified interview and biological-assessment strategy.	Address discordant exposure information.
Psychosis and function	Blinded ratings when feasible; instrument-specific interpretation.	Measure benefit and trade-offs.
Safety and retention	Record all initiators, events and discontinuation reasons.	Limit completer bias.
Mechanisms	Exposure measures and prespecified biomarker interaction.	Test rather than assume biological explanations.
Analysis	Intention-to-treat strategy, missing-data sensitivity, multiplicity plan.	Make inference reproducible.

LIST OF FIGURES

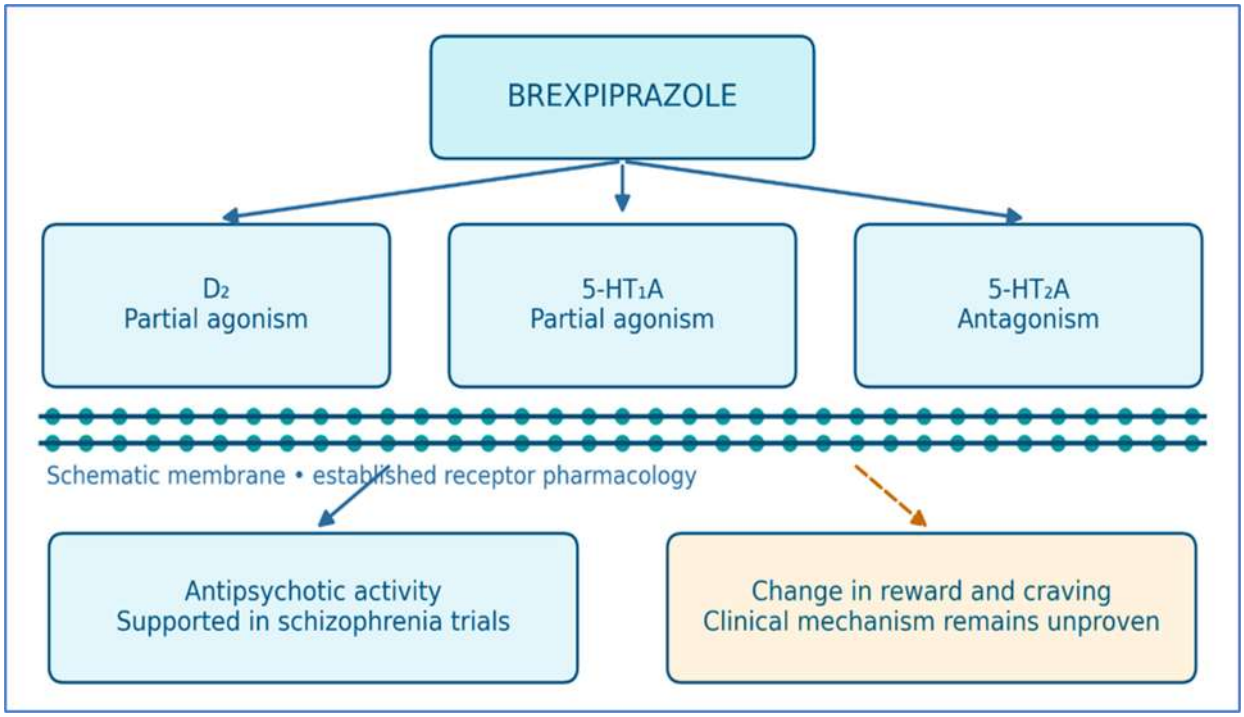

Figure 1: Receptor Actions And Clinical Translation

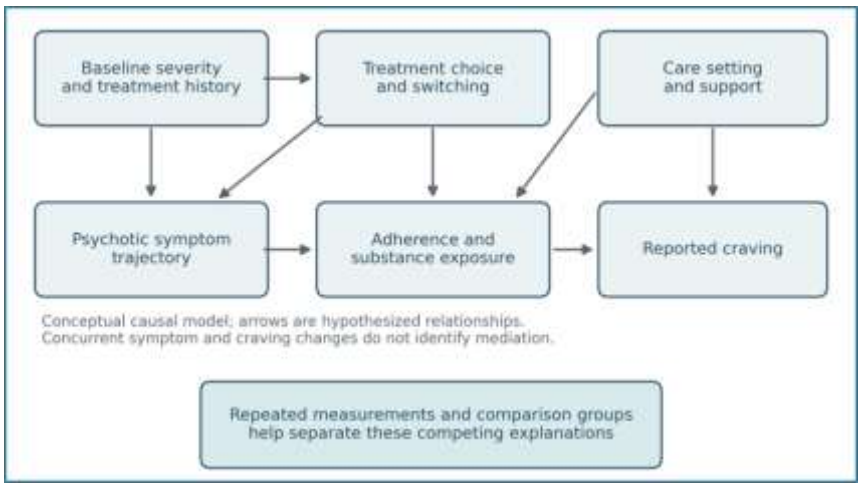

Figure 2: Competing Explanations For Concurrent Improvement

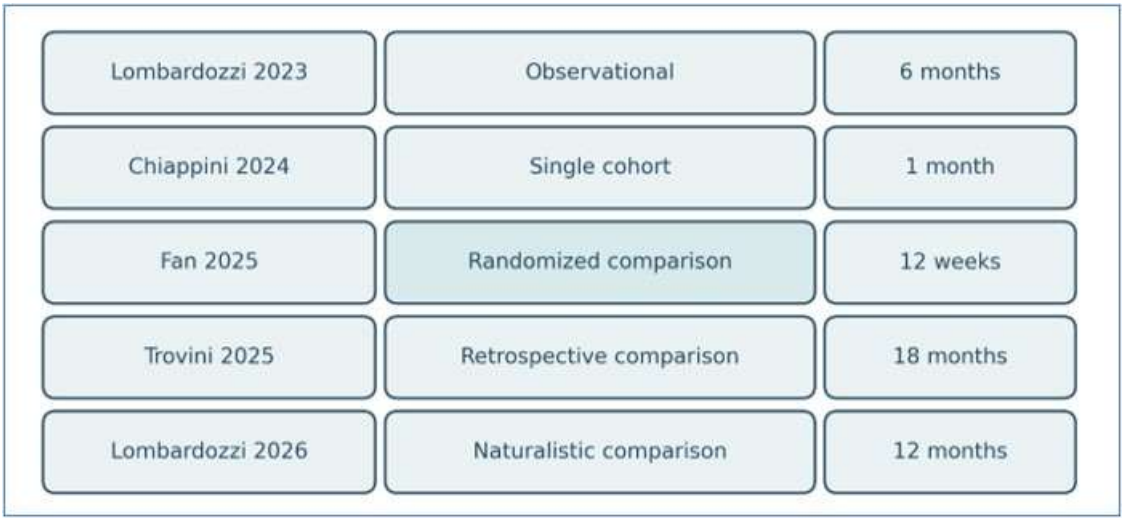

Figure 3: Evidence Map Of Identified Clinical Reports

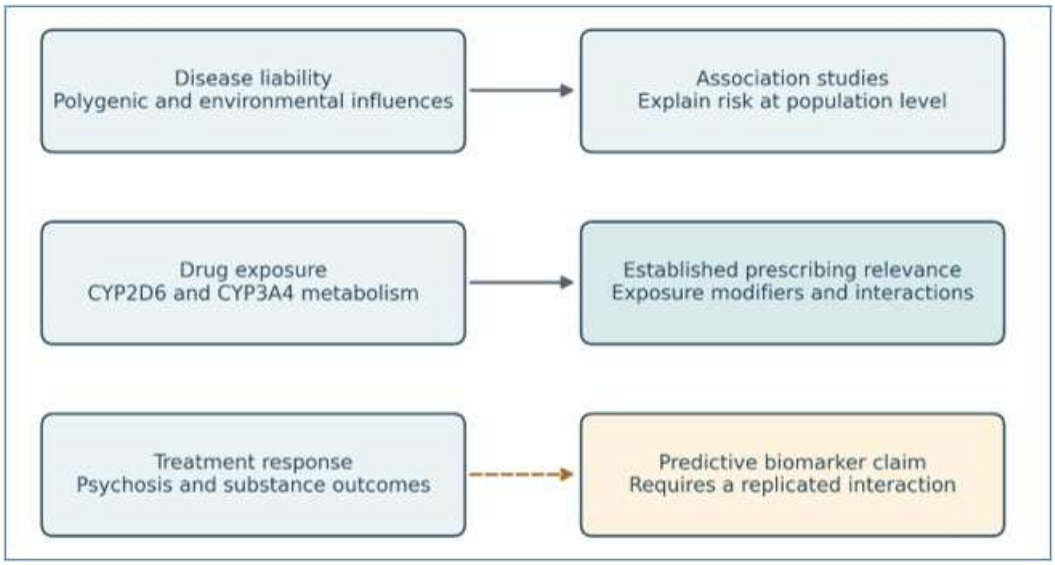

Figure 4: Genetic Interpretation Framework

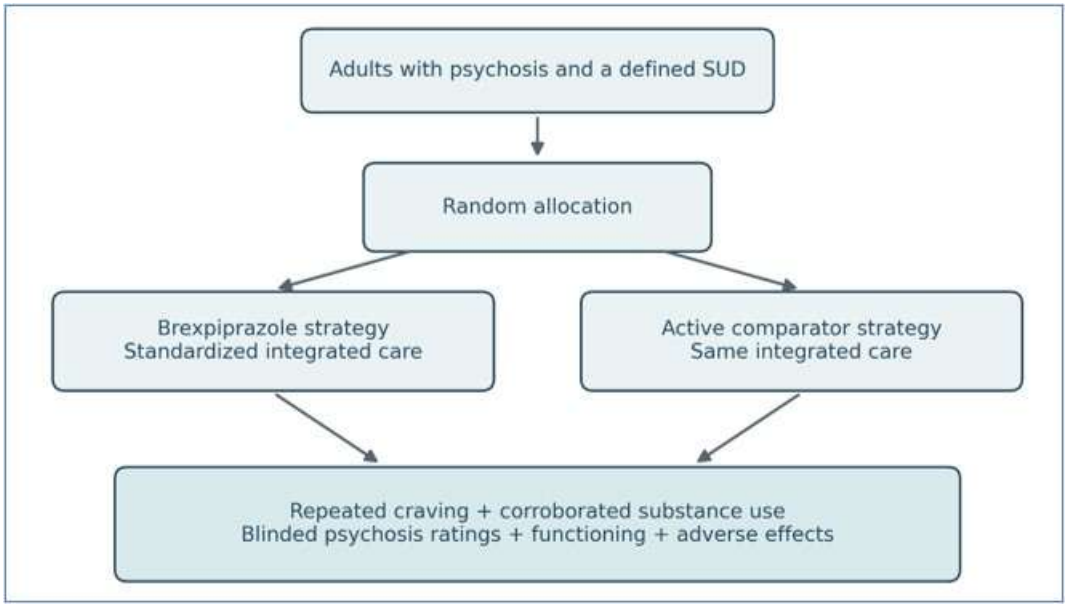

Figure 5: Proposed Confirmatory Trial Structure

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AUTHOR CONTRIBUTIONS

Shaik Sanjuda & Rama Krishna Garlapati: Conceptualization, Investigation.

Anusha Kota: Literature Review and Data Curation.

Madhuri Latha Thadanki: Review and Editing of Data.

Siddabathuni Kalyan Venkata Narayana: Review and Editing of Data

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS STATEMENT

Ethical approval was not required for this study.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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