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CLINICAL EFFECTIVENESS AND SAFETY PROFILE OF LITHIUM-ANTIPSYCHOTIC AND VALPROATE-ANTIPSYCHOTIC COMBINATIONS IN BIPOLAR DISORDER: A NARRATIVE REVIEW

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ABSTRAK

Gangguan bipolar merupakan gangguan psikiatri kronis yang ditandai dengan episode perubahan suasana hati berulang, sehingga dapat mengganggu fungsi sehari-hari dan memerlukan pengobatan farmakologis jangka panjang. Kombinasi penstabil suasana hati dengan antipsikotik generasi kedua (*second-generation antipsychotics*/SGA) sering digunakan dalam penatalaksanaan gangguan bipolar, terutama kombinasi lithium-SGA dan valproat-SGA. Tinjauan naratif ini bertujuan untuk menganalisis dan membandingkan efektivitas klinis, luaran fungsional, serta aspek keamanan kedua kombinasi tersebut pada pasien gangguan bipolar. Penelusuran literatur dilakukan melalui basis data PubMed, ScienceDirect, dan Scopus terhadap artikel yang diterbitkan pada periode 2016–2026. Dari 2.482 artikel yang teridentifikasi, sebanyak 31 artikel memenuhi kriteria seleksi awal, kemudian tujuh artikel dipilih untuk dianalisis dalam tinjauan ini. Hasil menunjukkan bahwa kombinasi lithium-SGA dan valproat-SGA sama-sama memberikan manfaat klinis dalam mengendalikan gejala mania dan mencegah kekambuhan episode suasana hati, meskipun efektivitasnya dapat berbeda berdasarkan fase pengobatan. Kombinasi lithium-SGA menunjukkan manfaat pada penanganan episode mania akut dan episode campuran. Namun, bukti mengenai luaran fungsional masih terbatas dan menunjukkan hasil yang bervariasi. Kedua kombinasi juga memiliki pertimbangan keamanan yang berbeda sehingga pemilihan terapi perlu disesuaikan dengan kondisi klinis pasien, tujuan pengobatan, respons yang diharapkan, profil keamanan, serta kebutuhan pemantauan. Dengan demikian, pemilihan kombinasi lithium-SGA atau valproat-SGA harus dilakukan secara individual berdasarkan pertimbangan manfaat dan risiko terapi.

Kata Kunci: *Bipolar, Mood Stabilizers, Antipsikotik, Efektivitas, Profil Keamanan*

ABSTRACT

Bipolar disorder is a chronic psychiatric condition characterized by recurrent mood episodes that may impair daily functioning and require long-term pharmacological treatment. Combination therapy involving mood stabilizers and second-generation antipsychotics (SGAs) is commonly used in the management of bipolar disorder, particularly lithium-SGA and valproate-SGA combinations. This narrative review aimed to analyze and compare the clinical effectiveness, functional outcomes, and safety profiles of these two combinations in patients with bipolar disorder. A literature search was conducted using PubMed, ScienceDirect, and Scopus for articles published between 2016 and 2026. Of the 2,482 articles identified, 31 met the initial selection criteria, and seven were subsequently included in this review. The findings indicated that both lithium-SGA and valproate-SGA combinations provided clinical benefits in controlling manic symptoms and preventing mood episode recurrence, although their

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effectiveness varied according to the treatment phase. Lithium-SGA combinations demonstrated benefits in the management of acute manic and mixed episodes. However, evidence regarding functional outcomes remained limited and varied across studies. Both combinations also presented distinct safety considerations. Therefore, treatment selection should be individualized according to the patient's clinical condition, therapeutic goals, expected treatment response, safety profile, and monitoring requirements. In conclusion, both combinations may serve as therapeutic options for bipolar disorder, with their selection requiring careful consideration of the potential clinical benefits and associated risks.
Keywords: *Bipolar, Mood Stabilizers, Antipsychotic, Effectiveness, Safety Profile*

INTRODUCTION

Bipolar disorder is a chronic and potentially disabling psychiatric disorder characterized by recurrent episodes of mania, hypomania, and depression, which can substantially affect patients' psychological well-being and daily functioning. The recurrent nature of the disorder contributes to a considerable clinical burden, including impaired social relationships, reduced occupational productivity, increased hospitalization, and the need for long-term pharmacological treatment. Beyond acute mood disturbances, patients may experience persistent difficulties in maintaining clinical stability and achieving functional recovery between episodes. Consequently, the management of bipolar disorder requires a comprehensive approach that addresses acute symptom control, remission, prevention of recurrence, and long-term recovery. Recent developments in the understanding and management of bipolar disorder emphasize the importance of integrating clinical outcomes with patients' broader treatment needs (Oliva et al., 2025).

Pharmacological treatment remains a fundamental component of bipolar disorder management, particularly among patients experiencing severe mood episodes, recurrent illness, or inadequate responses to monotherapy. Mood stabilizers and second-generation antipsychotics (SGAs) are important therapeutic agents because they provide complementary effects in managing different phases of the disorder. Lithium and valproate are widely used mood stabilizers, although their therapeutic roles, clinical indications, and safety considerations differ according to treatment phase and individual patient characteristics. Contemporary treatment recommendations emphasize the selection of pharmacological regimens based on symptom severity, previous treatment response, tolerability, and long-term therapeutic objectives. Therefore, individualized pharmacological management and the appropriate use of combination therapy are essential considerations in achieving sustained clinical improvement (Keramatian et al., 2023).

Lithium has an established role in the pharmacological management of bipolar disorder, particularly in maintenance treatment and the prevention of recurrent mood episodes. However, its relatively narrow therapeutic range requires regular serum concentration monitoring to minimize the risk of toxicity and ensure appropriate treatment exposure. In contrast, valproate is frequently used in the management of acute manic episodes and remains an important therapeutic option for selected patients requiring mood stabilization. Evidence from an overview of systematic reviews and meta-analyses indicates that valproate has demonstrated efficacy in acute mania, bipolar depression, and maintenance treatment, although the strength of evidence differs across treatment outcomes. These differences highlight the importance of considering treatment phase, expected therapeutic response, and individual safety requirements when selecting between lithium and valproate (Mari et al., 2024).

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Second-generation antipsychotics are frequently combined with mood stabilizers when monotherapy provides insufficient symptom control or additional therapeutic effects are required. The combination of lithium or valproate with an SGA represents an important pharmacological strategy because it may improve symptom management and contribute to the prevention of subsequent mood episodes. A systematic review and network meta-analysis of randomized controlled trials evaluated the comparative efficacy of mood stabilizers and antipsychotics, providing evidence regarding pharmacological strategies for preventing recurrence during the maintenance phase of bipolar disorder (Kishi et al., 2021). Nevertheless, the therapeutic benefits of combination regimens may vary according to the specific medications, treatment duration, patient characteristics, and clinical outcomes assessed. A comprehensive evaluation of these combinations is therefore necessary to understand their potential contributions to both acute symptom management and long-term disease stability (Carli et al., 2023).

Real-world treatment effectiveness is another important consideration in evaluating pharmacological strategies for bipolar disorder because outcomes observed in routine clinical practice may differ from those reported in controlled clinical trials. Evidence from a nationwide register-based cohort study demonstrated differences in the effectiveness of pharmacological treatments, emphasizing the importance of evaluating treatment outcomes under actual clinical conditions (Lähteenvuo et al., 2023). In addition to symptom stabilization and relapse prevention, long-term pharmacological management should also consider clinically significant outcomes, including suicide risk. A nationwide retrospective cohort study examining lithium, valproate, and atypical antipsychotics further highlighted the relevance of investigating the relationship between long-term pharmacological treatment and suicide risk among patients with bipolar disorder (Park et al., 2026). These findings support the need to evaluate combination therapy through a broader clinical perspective that considers treatment effectiveness, long-term outcomes, and individual patient characteristics.

Beyond symptom control and relapse prevention, functional recovery represents an essential component of successful bipolar disorder treatment. Improvement in mood symptoms does not necessarily indicate complete recovery of cognitive abilities, social relationships, occupational performance, or overall quality of life. Research investigating olanzapine combined with sodium valproate has reported improvements in clinical symptoms and cognitive function, suggesting that pharmacological combination therapy may provide benefits extending beyond mood symptom management (Wang et al., 2025). The importance of evaluating functional outcomes is also reflected in clinical research involving other neurological conditions, although findings from these populations cannot be directly extrapolated to bipolar disorder (Hidayaturrahmi et al., 2023). Therefore, functional outcomes should be considered alongside conventional clinical indicators when examining the potential benefits of lithium-SGA and valproate-SGA combinations.

Safety considerations also play a central role in determining the appropriateness of long-term combination therapy for bipolar disorder. Lithium requires regular serum concentration monitoring because its narrow therapeutic range increases the risk of toxicity, while valproate presents different safety considerations, including metabolic, hepatic, and reproductive concerns. Furthermore, the addition of SGAs may increase the overall adverse-effect burden through metabolic disturbances, weight gain, and other agent-specific complications. Evaluating combination pharmacotherapy also requires attention to the effectiveness and safety of individual drug regimens, as demonstrated in literature examining combination treatment strategies in other chronic diseases, although such findings should not be interpreted as direct

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evidence for bipolar disorder (Pagedongan & Astuti, 2025). Consequently, treatment selection should involve an individualized assessment of the potential therapeutic benefits, adverse effects, patient characteristics, and monitoring requirements associated with the complete combination regimen.

Despite the growing body of evidence concerning mood stabilizers and SGAs, the comparative therapeutic roles of lithium-SGA and valproate-SGA combinations remain insufficiently characterized across different treatment outcomes. Existing research has investigated pharmacological effectiveness, maintenance treatment, recurrence prevention, and long-term clinical outcomes, but differences in study populations, treatment regimens, follow-up periods, and outcome measures limit direct comparisons between these strategies. Furthermore, previous research examining structured care pathways in mood disorders has highlighted the importance of comprehensive treatment approaches, but it does not establish the comparative effectiveness of these specific pharmacological combinations (Kim et al., 2023). This narrative review therefore provides an integrated synthesis of the available evidence by examining the clinical effectiveness, functional outcomes, and safety profiles of lithium-SGA and valproate-SGA combinations across different treatment phases. Specifically, this review aims to identify the therapeutic benefits, limitations, and safety considerations of both combination strategies to support more individualized and evidence-informed pharmacological management of patients with bipolar disorder.

METHOD

This study employed a narrative review approach to synthesize evidence regarding the clinical effectiveness, functional outcomes, and safety of lithium combined with second-generation antipsychotics (SGAs) and valproate combined with SGAs in patients with bipolar disorder. Literature searches were conducted using three electronic databases: PubMed, ScienceDirect, and Scopus. The search strategy was developed based on the review objectives and the PICO framework using combinations of the keywords “bipolar disorder,” “lithium,” “valproate,” “antipsychotic,” “effectiveness,” “efficacy,” “safety,” “adverse effects,” and “combination therapy.” The search was restricted to English-language articles published between 2016 and 2026. Studies were considered eligible if they involved patients diagnosed with bipolar disorder, evaluated lithium-SGA or valproate-SGA combination therapy, and reported outcomes related to clinical effectiveness, functional outcomes, or safety. Eligible study designs included randomized controlled trials, cohort studies, and comparative observational studies. Articles were excluded if they did not evaluate the relevant treatment combinations, were unrelated to the review objectives, or did not report the specified clinical outcomes. A total of 2,482 articles were identified across the three databases. Following initial screening of titles and abstracts, 31 articles were considered relevant for further assessment. Of these, 24 articles were excluded because they did not sufficiently meet the review objectives or eligibility criteria, leaving seven articles for the final narrative synthesis. The selected studies were reviewed descriptively by examining their study characteristics, patient populations, treatment regimens, treatment phases, and reported clinical, functional, and safety outcomes. The findings were then compared and synthesized narratively to identify similarities, differences, and clinically relevant patterns concerning the therapeutic roles of lithium-SGA and valproate-SGA combinations across different phases of bipolar disorder.

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RESULTS AND DISCUSSION

Results

The literature search strategy was developed using the Population, Intervention, Comparison, and Outcome (PICO) framework to establish the scope and focus of the review. The framework was used to identify the relevant population, treatment combinations, comparative interventions, and clinical outcomes associated with bipolar disorder. The population consisted of adult patients diagnosed with bipolar disorder, while the interventions focused on lithium combined with second-generation antipsychotics (SGAs). The comparison involved valproate combined with SGAs, with particular attention to clinical effectiveness, functional outcomes, and safety. The PICO framework used to formulate the literature search strategy is presented in Table 1.

Table 1. PICO Framework for Keyword Formulation

PICO element	Description
Population (P)	Adult male and female patients (≥18 years) diagnosed with bipolar disorder
Intervention (I)	Combination therapy of lithium and second-generation antipsychotics (SGAs)
Comparison (C)	Combination therapy of valproate and second-generation antipsychotics (SGAs)
Outcome (O)	Clinical effectiveness, functional outcomes, and safety of lithium-SGA and valproate-SGA combination therapies in patients with bipolar disorder

The PICO framework provided the basis for developing the search terms and identifying relevant publications across the selected databases. The literature search was conducted using PubMed, ScienceDirect, and Scopus, with keywords related to bipolar disorder, lithium, valproate, antipsychotics, effectiveness, efficacy, safety, and adverse effects. The search was restricted to English-language publications from 2016 to 2026 to obtain recent and clinically relevant evidence. Boolean operators were applied according to the search requirements of each database. The distribution of articles retrieved from the three databases is presented in Table 2.

Table 2. Results of the Literature Search Based on PICO-Derived Keywords

Database	Search keywords	Search results
PubMed	("bipolar disorder") AND (lithium AND antipsychotic) AND (valproate AND antipsychotic) AND (effectiveness OR efficacy OR safety OR adverse effects)	438
ScienceDirect	("bipolar disorder") AND (lithium OR valproate) AND antipsychotic AND ("combination therapy") AND (effectiveness OR safety OR adverse events)	667
Scopus	("bipolar disorder") AND (lithium OR valproate) AND (antipsychotic* OR "second-generation antipsychotic") AND (effectiveness OR "length of stay" OR safety OR "adverse events")	1,377
Total		**2,482**

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The retrieved articles were subsequently screened based on their titles and abstracts to identify studies relevant to the review objectives. Articles considered potentially eligible underwent further assessment according to the predefined inclusion and exclusion criteria, particularly regarding the study population, treatment combinations, and reported clinical outcomes. Following this process, 31 articles were considered relevant for further assessment, while 24 articles were excluded because they did not sufficiently meet the eligibility criteria. The remaining studies were included in the final narrative synthesis. The complete article selection process is illustrated in Figure 1.

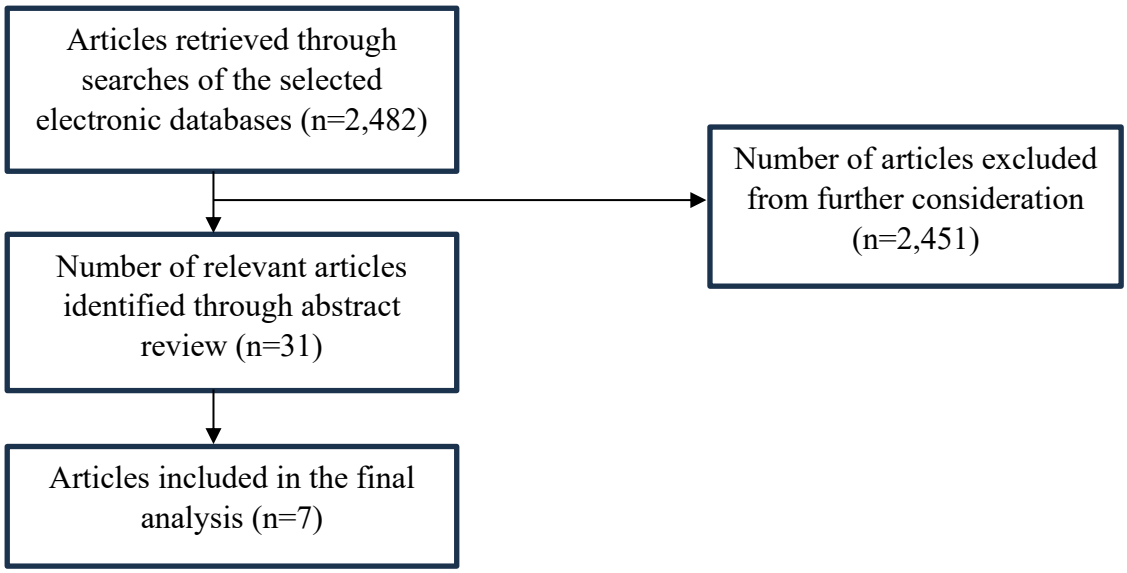


Figure 1. Flowchart Illustrating the Process of Article Selection

The selected studies were then examined to identify their research designs, patient characteristics, treatment regimens, and reported outcomes. The included literature comprised randomized controlled trials, post-hoc analyses, observational studies, and population-based cohort studies conducted in different clinical settings. The studies investigated several aspects of pharmacological treatment, including acute symptom control, maintenance treatment, mood episode recurrence, psychiatric hospitalization, suicide risk, cognitive function, and treatment tolerability. Although the studies shared a common focus on mood stabilizers and SGAs, their treatment combinations, study populations, and outcome measures varied. The characteristics and principal findings of the included studies are summarized in Table 3.

Table 3. Characteristics and Main Findings of Included Studies on Lithium-SGA and Valproate-SGA Combinations in Bipolar Disorder

Author(s) and year	Research design	Study characteristics	Main findings
Calabrese et al. (2017)	Randomized, double-blind, placebo-controlled trial	496 patients with bipolar I disorder receiving lurasidone combined with lithium or valproate	Adjunctive lurasidone reduced the risk of mood episode recurrence and was generally well tolerated, with minimal effects on

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		during maintenance treatment.	weight and metabolic parameters.
Kang et al. (2019)	Post-hoc analysis of a randomized, double-blind, placebo-controlled trial	Patients with bipolar I disorder receiving lithium or valproate combined with an atypical antipsychotic during maintenance treatment.	No significant difference was observed between lithium and valproate in preventing mood episode recurrence. Continued antipsychotic treatment provided additional protection against recurrence.
Lähteenvuo et al. (2023)	Register-based national cohort study	60,045 patients with bipolar disorder identified through Finnish national registers.	Lithium treatment was associated with a lower risk of psychiatric hospitalization, supporting its effectiveness in real-world clinical practice.
Liu et al. (2020)	Naturalistic observational study	182 patients with bipolar disorder experiencing manic episodes and receiving lithium combined with an SGA.	Lithium-SGA combinations improved manic symptoms, although differences in adverse-effect profiles were observed among treatment combinations.
Park et al. (2026)	Nationwide retrospective cohort study	Patients with bipolar disorder identified through Korean national healthcare claims data and receiving lithium, valproate, and/or atypical antipsychotics.	Lithium- and valproate-based treatment regimens were associated with lower suicide risk.
Tournier et al. (2019)	Population-based cohort study	20,086 patients with bipolar disorder receiving mood stabilizers, SGAs, or their combinations.	Mood stabilizer-SGA combinations were associated with a lower risk of treatment failure compared with monotherapy.
Wang et al. (2025)	Observational study	80 patients with bipolar disorder receiving olanzapine alone or in combination with sodium valproate.	Combination treatment improved manic and depressive symptoms, with reported improvements in cognitive function and favorable tolerability.

Overall, the findings indicate that combination therapy involving lithium or valproate with SGAs may provide clinical benefits in the management of bipolar disorder, although the observed effects vary according to treatment phase and individual treatment regimens. Lithium-SGA combinations demonstrated benefits in controlling manic symptoms and potentially

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preventing mood episode recurrence, while lithium treatment was also associated with favorable real-world outcomes regarding psychiatric hospitalization. Similarly, valproate-SGA combinations showed improvements in manic and depressive symptoms, with additional evidence of improvements in cognitive function. Maintenance studies further suggested that adjunctive antipsychotic treatment may contribute to reducing the risk of mood episode recurrence, although the available evidence does not establish the superiority of lithium over valproate or vice versa.

Despite these clinical benefits, evidence concerning functional outcomes remains relatively limited compared with evidence on symptom control and recurrence prevention. Improvements in cognitive function were reported in studies evaluating olanzapine combined with sodium valproate, suggesting that combination therapy may provide benefits beyond the reduction of mood symptoms. However, most included studies primarily assessed clinical outcomes, such as symptom improvement, hospitalization, recurrence, and treatment failure, rather than comprehensive functional recovery. Consequently, the available evidence remains insufficient to determine the extent to which lithium-SGA and valproate-SGA combinations improve social functioning, occupational performance, and overall quality of life. These findings highlight the importance of distinguishing clinical symptom improvement from broader functional recovery when evaluating treatment outcomes in bipolar disorder.

In addition to clinical effectiveness and functional outcomes, safety represents an important consideration in the use of combination therapy. The included studies generally reported favorable tolerability for some combination regimens, although adverse-effect profiles differed according to the specific mood stabilizer and SGA used. Adjunctive lurasidone with lithium or valproate demonstrated minimal effects on weight and metabolic parameters in maintenance treatment, while observational findings involving lithium-SGA combinations indicated differences in adverse effects among individual regimens. Nevertheless, the available studies provided limited direct comparisons of long-term safety between lithium-SGA and valproate-SGA combinations. Therefore, the overall findings suggest that treatment selection should consider clinical effectiveness, functional needs, individual safety profiles, and the monitoring requirements associated with each combination.

Discussion

Bipolar disorder requires a pharmacological treatment strategy that considers acute symptom control, relapse prevention, and long-term clinical stability. The combination of mood stabilizers and second-generation antipsychotics (SGAs) represents an important therapeutic approach, particularly in patients who do not achieve an adequate response to monotherapy. Carli et al. (2023) explained that lithium, valproate, and atypical antipsychotics have different roles in the management of acute and maintenance phases of bipolar disorder, indicating that treatment selection should be tailored to individual clinical conditions. In clinical practice, the effectiveness of lithium-SGA and valproate-SGA combinations is influenced not only by the choice of mood stabilizer but also by the specific antipsychotic agent, symptom severity, and treatment phase. These findings suggest that an individualized treatment approach is more appropriate than assuming that a single pharmacological combination is superior for all patients with bipolar disorder.

The different pharmacological characteristics of lithium and valproate are among the factors contributing to variations in treatment response. Lithium plays an important role in maintenance treatment and relapse prevention, whereas valproate is commonly used to manage acute manic episodes and maintain mood stability in selected patients. Yee et al. (2021)

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demonstrated that valproate has evidence supporting its effectiveness in the long-term management of bipolar disorder, although its benefits may vary according to patient characteristics and the treatment outcomes being evaluated. Meanwhile, Sofwatussuba et al. (2025) provided an overview of antipsychotic use in patients with bipolar disorder in clinical practice, highlighting the importance of rational prescribing and appropriate treatment indications. Therefore, the selection of lithium-SGA or valproate-SGA combinations should consider treatment objectives, previous treatment responses, tolerability, and individual patient needs during different phases of the disorder.

Regarding the comparative effectiveness of the two treatment combinations, the study by Li et al. (2026) provides particularly relevant evidence because it specifically evaluated the effectiveness of lithium- and valproate-based combinations with atypical antipsychotics in preventing rehospitalization following a first manic episode in patients with bipolar I disorder. This study is directly relevant to the present review because it uses a long-term clinical outcome to evaluate the effectiveness of pharmacological treatment strategies. Its findings should be interpreted in the context that rehospitalization is an important indicator of clinical stability but does not fully represent patients' recovery in everyday life. Furthermore, differences in patient characteristics, antipsychotic selection, and treatment duration may influence the comparative outcomes of the two combinations. Therefore, treatment superiority should not be determined solely by a single clinical outcome but should also consider symptom control, relapse prevention, cognitive functioning, and treatment safety.

The effectiveness of bipolar disorder treatment should also be understood in relation to patients' cognitive functioning and quality of life. Improvement in manic or depressive symptoms does not necessarily indicate complete functional recovery, as bipolar disorder may be accompanied by difficulties in memory, attention, information-processing speed, and the ability to perform social and occupational activities. Ponsoni et al. (2023) highlighted the importance of longitudinally evaluating changes in cognition, functional outcomes, and quality of life in individuals with bipolar disorder and major depressive disorder. These findings support the view that treatment success should not be assessed exclusively through changes in psychiatric symptoms but also through patients' ability to resume their daily activities. Accordingly, the evaluation of lithium-SGA and valproate-SGA combinations should incorporate functional outcomes as an important component in determining the overall clinical benefits of treatment.

The relationship between cognitive functioning and quality of life is also an important consideration when evaluating long-term treatment outcomes. Zazula et al. (2022) described the association between cognitive profiles, quality of life, and psychosocial functioning in mood disorders, emphasizing the importance of considering cognitive impairment in patient assessments. In the context of bipolar disorder, these findings indicate that patients who experience symptomatic improvement may not necessarily achieve optimal social, occupational, or daily functioning. Therefore, the use of mood stabilizer-SGA combinations should be evaluated not only according to symptomatic response but also according to their potential effects on cognitive and psychosocial functioning. The use of standardized functional assessment instruments is necessary to provide a more comprehensive evaluation of the benefits associated with both treatment combinations.

In addition to clinical effectiveness, safety is an essential consideration in determining the suitability of lithium-SGA and valproate-SGA combinations, particularly during long-term treatment. Lithium has a relatively narrow therapeutic range and therefore requires regular serum concentration monitoring to minimize the risk of toxicity. Rahmi et al. (2025) highlighted

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various cardiovascular adverse effects and toxicity associated with lithium use in adults, emphasizing the importance of clinical monitoring during treatment. Furthermore, Greil et al. (2023) examined the controversy surrounding lithium-associated weight gain using real-world drug safety data. These findings indicate that the therapeutic benefits of lithium should be considered alongside potential cardiovascular risks, weight changes, and other adverse effects, particularly when lithium is combined with antipsychotics that may also affect patients' metabolic profiles.

These safety considerations emphasize that treatment selection should be individualized according to patients' physical conditions, clinical needs, and ability to undergo regular monitoring. Gitlin and Bauer (2024) discussed the current understanding of lithium treatment, including its effectiveness, monitoring requirements, clinical challenges, and future directions. Evidence regarding collaborative care approaches may also provide additional perspectives on the importance of continuous patient monitoring, although the study by Lesmana and Wirawan (2023) focused on schizophrenia and therefore cannot be considered direct evidence of pharmacological combination effectiveness in bipolar disorder. Similarly, the case report by Pratiwi et al. (2026) and the cost-effectiveness study by Afitriyani et al. (2023), which examined schizoaffective disorder and schizophrenia, respectively, provide only contextual information regarding antipsychotic combination use and pharmacoeconomic considerations rather than direct comparative evidence for lithium-SGA and valproate-SGA combinations in bipolar disorder. Overall, the available evidence suggests that both combinations offer potential clinical benefits, but current findings remain insufficient to establish the universal superiority of either treatment strategy. Therefore, future comparative studies should employ stronger research designs, longer follow-up periods, standardized assessments of cognitive and psychosocial functioning, and comprehensive evaluations of treatment safety and costs to determine the most appropriate therapeutic strategy for different patient populations with bipolar disorder.

CONCLUSIONS

This review highlights that lithium-SGA and valproate-SGA combinations represent relevant pharmacological strategies for the management of bipolar disorder, with their therapeutic benefits varying according to the treatment phase and individual clinical characteristics. Lithium-SGA combinations appear to be particularly relevant for maintenance treatment and relapse prevention, whereas valproate-SGA combinations demonstrate potential benefits in managing acute manic and mixed episodes. Nevertheless, the available evidence does not establish the consistent superiority of either combination, indicating that treatment selection should be individualized according to clinical presentation, previous treatment response, therapeutic objectives, and patient-specific safety considerations. Furthermore, clinical symptom improvement should not be considered sufficient evidence of complete recovery, as functional and cognitive outcomes remain inadequately investigated in the available literature. Therefore, the clinical application of these combination strategies should incorporate comprehensive monitoring of treatment effectiveness, functional recovery, and potential adverse effects. Future research should prioritize well-designed comparative studies involving larger patient populations, longer follow-up periods, and standardized measures of clinical effectiveness, functional outcomes, and long-term safety. Such investigations are expected to strengthen the evidence base and support more precise, individualized treatment decisions for patients with bipolar disorder.

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