Annals of General Psychiatry

REVIEW Open Access

What is the effect of lithium use on the amygdalar volume of adult patients diagnosed with bipolar disorder: a scoping review

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Abstract

Introduction Bipolar disorder is a psychiatric condition commonly treated with lithium. This treatment has various biological effects on the brain; however, variability in the areas and types of changes as a result of lithium treatment has resulted in discourse over lithium's effect. As a result, a comprehensive synthesis is needed to understand lithium's true neurological effect. This review aims to identify a common result of lithium use in the neurobiology of bipolar patients, specifically in the amygdala, to determine whether volumetric changes in the amygdala are a common effect.

Methods We conducted a preliminary search to identify key search terms across electronic databases, including Google Scholar and PubMed. After screening and application of inclusion and exclusion criteria, 9 cross-sectional studies were identified.

Results The evidence from these cross-sectional studies showed either an increase or no change in amygdalar volume. While this fails to identify a definite pattern in amygdalar volume changes, it highlights a need for further research to identify sources of heterogeneity and minimize them to ascertain accurate results.

Conclusions The present review may be used to influence future work concerning neurobiological changes in the amygdala as a result of lithium treatment for bipolar patients by summarizing patterns in the current literature.

Keywords Bipolar disorder, Lithium, Amygdala, Psychiatry

Introduction

Bipolar disorder (BD) is a psychiatric disorder that is associated with dramatic mood swings between depressive and manic episodes, as well as changes in energy and connectivity levels, which affect daily life [1]. Patients with bipolar disorder (BDP) are severely affected by the disorder and, as a result, are more susceptible to chronic stressors and interpersonal stress due to acute stressful life events [2]. Combined with cognitive impairments in attention, verbal processing, and verbal fluency, BD severely affects the day-to-day lives of people who have it. When looking at the quality of life (QOL), compared to control individuals, BDP score lower on health related QOL measures, specifically social functioning and mental health [2]. BD is also associated with a high mortality risk. These factors—along with the effects of unstable mood states, difficulty with treatment adherence due to

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the need for combined treatment approaches, and BD's comorbidity with other psychiatric disorders—all play a role in the difficulty of treating BD [3].

Lithium, a mood-stabilizing drug, is a common treatment for bipolar disorder. Lithium, in tandem with antidepressants, is used to reduce the intensity and frequency of manic episodes to regulate mood abnormalities [1]. However, the mechanism of action of lithium on the brain of BDP remains unclear [4]. The amygdala, a region of the brain associated with memory of emotional information and mood regulation, has been identified as a region of interest [5]. Abnormal amygdala volumes may be connected to atypical emotional perception and mood regulation [6]. As a result, after treatment, amygdalar volume may act as a neural marker for improved emotion processing [7, 11].

Similar reviews have evaluated the effects of lithium on different regions of interest, including the hippocampus [8] and the connectivity of the amygdala [9], in BDP, but none have focused solely on the effect on amygdalar volume. This scoping review aims to further clarify the impact of lithium treatment on the amygdalar volume of adult patients diagnosed with bipolar disorder. Our goal is to determine whether the amygdala can act as a consistent region of interest for determining the effect of lithium treatment on BDP.

Methods

This study is written in a scoping review format. This paper follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis Protocols (PRISMA-ScR) guidelines [10].

Eligibility criteria

Both empirical studies and review articles were included in the initial search, and each review article and its citations were assessed to locate any overlooked empirical studies. Ultimately, only primary empirical studies were included in the analysis for easy comparison of study methodology, findings, and conclusions. All empirical studies evaluated the amygdala in conjunction with lithium treatment for bipolar disorder. Empirical studies were required to include more than 10 BDP treated with only lithium and were excluded if participants were under 18 years of age or were nonhuman. Given the heterogeneity of treatment regimens in the articles, no restrictions were made if other treatments were used in concurrence with lithium.

Search process

The Google Scholar, PubMed, and Directory of Open-Access Journals databases were searched with a limitation for publication in the last 5 years. The following search terms were used: "bipolar AND amygdala AND 'lithium treatment'" and "(bipolar OR manic depression OR manic depressive illness) AND amygdala AND 'lithium treatment'". All the researchers reviewed the titles and abstracts. Citations from all review articles, meta-analyses, and mega-analyses were also individually investigated and were included if the empirical study met the inclusion criteria. After the investigation, secondary research articles were removed as they contained information from included studies, and all empirical studies were checked against the inclusion and exclusion criteria.

Data charting process

A data chart of relevant study characteristics, including study type, cohort size, and overall findings, was created. Both reviewers independently extracted the study data.

Synthesis

Among the final pool of sources, we summarized each study's methods and evaluated their results. Each study was categorized based on their results: whether an increase, decrease, or no change in amygdalar volume occurred throughout lithium treatment on BDP.

Results

Our database search yielded 1,830 results; all types of papers were accepted at this point. After reviewing the titles and abstracts, and removing duplicates from all searches, 98 papers–35 empirical studies and 63 review articles– were included in the full-text review. The empirical studies were individually investigated, resulting in 8 remaining studies, while the review articles were reviewed for primary empirical studies. A total of 31 relevant empirical studies were added, and all review articles were removed. All 39 empirical studies were checked against the inclusion criteria, and duplicates were removed. 32 empirical studies remained. The remaining empirical studies were reviewed to ensure that they fit the scope of our paper. After review, the 13 remaining empirical studies were checked against the exclusion criteria and 9 remained.

Table 1 summarizes the sample size, scanning technique, and study focus, including limitations, in separate columns and synthesizes the results and conclusions of each trial in an organized manner. Most of the study results include p-values to show the overall change in mass in a straightforward and uniform manner.

All the studies in this review were cross-sectional studies. Similarly, all studies primarily used magnetic resonance imaging (MRI) to identify and determine changes in the amygdala. The sample sizes, however, varied, with 4 studies including 10–19 BDP using lithium [11, 12, 14, 19], 1 study including 20–29 BDP using lithium [15], 2 studies including 30–39 BDP using lithium [13, 17], and 2 studies including 40+BDP using lithium [16, 18].

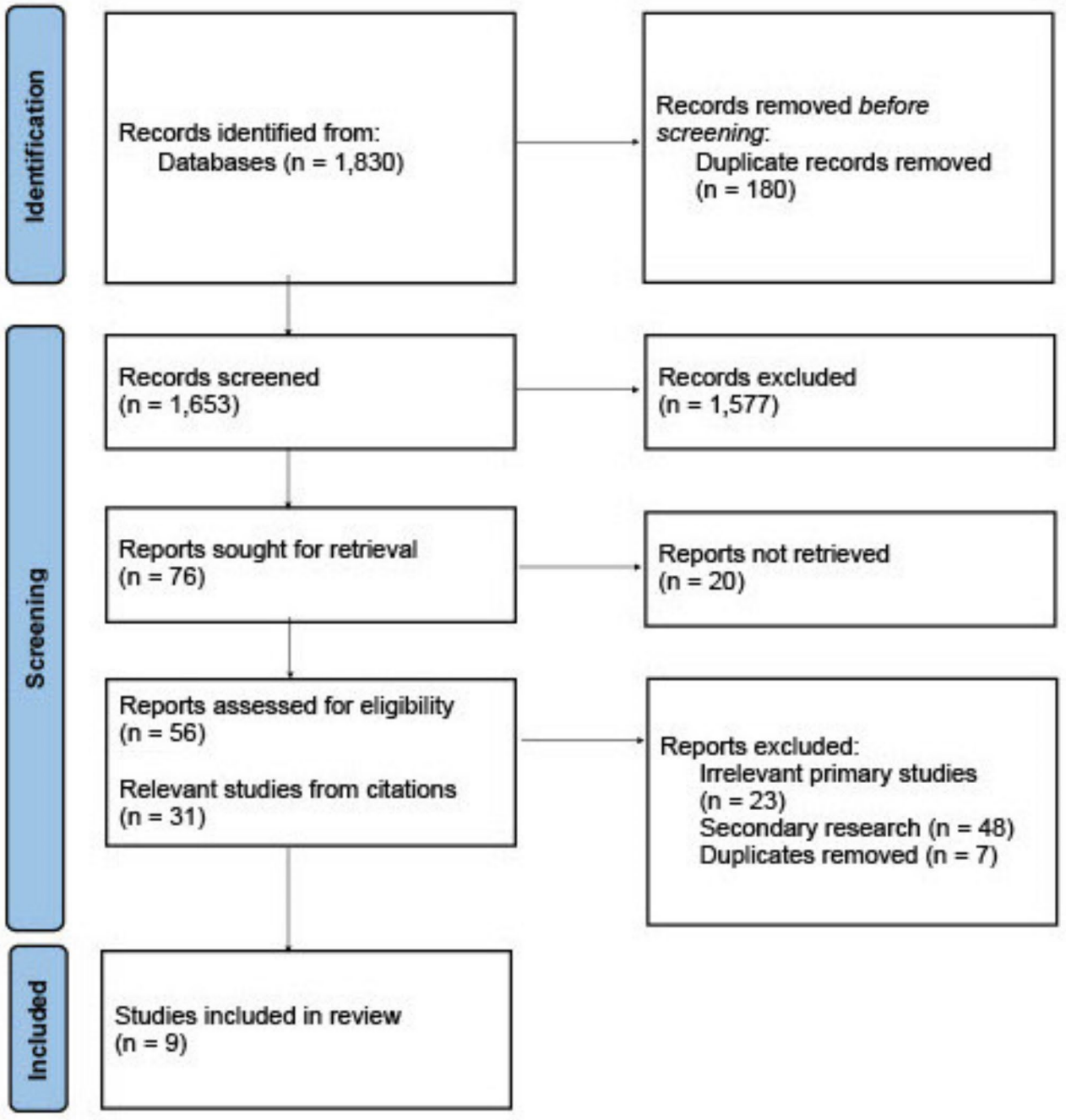

Fig. 1 Prisma flowchart. The PRISMA flow diagram for the scoping review detailing the number of records identified, screened, assessed for eligibility, and included in the review

3 studies did not include healthy controls (HC). Instead, Foland et al. and C. Barth et al. only compared BDP using lithium and BDP not using lithium, and Germaná et al. compared BDP using lithium, BDP not using lithium, and BDP using anticonvulsants [14–16].

Several studies differentiated between the right and left hemispheres of the amygdala and found differences in the two. In 2 studies, changes were identified only in either the right hemisphere [11] or the left hemisphere [15]; in the remaining 7 studies, the same results were found for both hemispheres [12–14, 16–19]. All the studies either observed a positive increase in the volume of the amygdala of BDP treated with lithium [11–15] or observed no significant change after correction [16–19].

Of the 9 studies included, 5 noticed an increase in the amygdalar volume in BDP who received lithium in

Table 1 Summary of included studies studying the effects of lithium on BDP

#	Study Name	Authors	Study Design	Cohort Size	Technique	Study Focus/Limitations	Results/ Conclusions
11	Increased right amygdala volume in lithium-treated patients with bipolar I disorder	Usher et al.	Cross-sectional Study	15 BDP with lithium 24 BDP without lithium 41 HC	MRI	Focus: This study focused on determining if lithium influenced the volume of the amygdala. Limitations: (i) Small sample size (ii) Cross-sectional study design	In comparison with HC, BDP on lithium showed a larger right absolute (+17.9%, $P=.015$, $d=0.831$) and relative (+18%, $P=.017$, $d=0.8$) amygdala volume.
12	Increased hippocampal, thalamus and amygdala volume in long-term lithium-treated bipolar I disorder patients compared with unmedicated patients and healthy subjects	López- Jaramillo et al.	Cross-sectional Study	16 BDP with lithium 16 BDP without lithium 20 HC	MRI	Focus: This study focused on volume changes in cortico-limbic structures (including the amygdala) using multivariable analysis. All BDP had a relatively long duration of illness (mean = 17 yrs), and the BDP on lithium were long-term lithium users (mean = 0.8 yrs). Limitations: (i) Small sample size (ii) Unable to determine a cause–effect relationship between lithium treatment and brain volume increase (iii) Neuroprotection and neurotropism may also have been the cause for changes	In comparison with BDP without lithium, BDP on lithium showed a larger right (+10.2332%, $P=.04$, $d=0.557$) and left (+32.4281%, $P=.002$, $d=1.328$) amygdala volume.
13	Association between duration of lithium exposure and hippocampus/ amygdala volumes in type I bipolar disorder	Sani et al.	Cross-sectional Study	30 BDP with lithium (15 long exposure, 15 short exposure) 15 BDP without lithium 15 HC	MRI	Focus: This study focused on volume changes in limbic and subcortical GMV. BDP using lithium were included in the study, but this study uniquely included duration of treatment as an important variable regarding changes in volume. The BDP using lithium group was divided into a short exposure (SE; exposed to lithium for < 24 months) and long exposure (LE; exposed to lithium for > 24 months) to assess if the length of treatment resulted in different changes in volume. Limitations: (i) Retrospective, cross-sectional design (ii) Other medications used along with lithium (anticonvulsants, antipsychotics) which may have normalizing effects on the brain structure of BDP	In comparison with BDP without lithium, BDP on lithium with SE showed a larger right (+16.1386%, $P=.002$, $d=1.182$) and left (+20.352%, $P=.002$, $d=1.482$) amygdala volume, and BDP on lithium with LE showed a larger right (+11.7822%, $P=.021$, $d=1.196$) and left (+20.352%, $P=.018$, $d=1.186$) amygdala volume.

Table 1 (continued)

#	Study Name	Authors	Study Design	Cohort Size	Technique	Study Focus/Limitations	Results/ Conclusions
14	Increased volume of the amygdala and hippocampus in bipolar patients treated with lithium	Foland et al.	Cross-sectional Study	12 BDP with lithium 37 BDP without lithium N/A HC	MRI and TBM	Focus: This study tested if lithium treatment led to an increase in amygdalar volumes in BDP using lithium in comparison to euthymic BDP who were lithium-free but taking other medications. Foland et al. employed tensor-based morphometry (TBM) in addition to MRI to analyze the effect of lithium treatment of the amygdala. As part of the TBM technique, the study used MRI to create a template scan based on the average of 27 T-1 weighted MRI acquisitions, compared the MRI scans of each individual to this template scan, and noted the warping. Limitations: (i) Small sample size (ii) Higher proportion of males in BD group (iii) Younger lithium-free group compared to lithium-treated group (iv) Other medications used along with lithium (v) Unknown if lithium-free group had taken lithium in the past (vi) No HC group	In comparison with BDP without lithium, BDP on lithium showed larger right (+ 1.53846%, $P = 1.63$, $d = 1.9$), left (+ 3.82775%, $P = .035$, $d = 3.138$), and bilateral (+ 2.9703%, $P = .023$, $d = 3.795$) amygdala volumes.
15	The effects of lithium and anticonvulsants on brain structure in bipolar disorder	Germaná et al.	Cross-sectional Study	28 BDP with lithium 28 BDP without lithium 18 BDP on antipsychotics N/A HC	MRI and VBM	Focus: This study focused on the effect of not only lithium but also other anticonvulsants and antipsychotics on the brain structure of BDP. BDP using lithium were not compared to a control group as there were no HC or BDP not using medication. Voxel-based morphometry (VBM) was used to analyze 74 MRI scans to identify changes in GMV as a result of lithium treatment. Limitations: (i) Unable to determine if changes in volume were from a neurotropic/neuroprotective effect or osmotic effect (ii) No HC group or unmedicated BDP group (iii) No random assignment, possibility of bias	In comparison with BDP without lithium, BDP on lithium showed a larger left hippocampus/amygdala complex (***P* < .001**).
16	In Vivo Amygdala Nuclei Volumes in Schizophrenia and Bipolar Disorders (supplementary material)	C. Barth et al.	Cross-sectional Study	54 BDP on lithium 247 BDP without lithium N/A HC	MRI	Focus: This study focused on amygdalar volume changes in people with both schizophrenia and BD. While this study did not focus on the effect of lithium, supplementary material was provided that covered the effect of lithium on the amygdalae of BDP. Limitations: (i) Cross-sectional design study (ii) MRI has limited ability in imaging technology so volumes of smaller regions within the amygdala should be treated with caution	No association was found between psychotropic drugs or mood stabilizers (lithium) and volume in schizophrenia and bipolar patients.

Table 1 (continued)

#	Study Name	Authors	Study Design	Cohort Size	Technique	Study Focus/Limitations	Results/ Conclusions
17	Lithium treatment and hippocampal subfields and amygdala volumes in bipolar disorder	Hartberg et al.	Cross-sectional Study	34 BDP with lithium 147 BDP without lithium 300 HC	MRI	Focus: This study focused on comparing amygdalar, and hippocampal, volumes between BDP using lithium, BDP not using lithium, and HC, and on the statistical effects of the illness' course. Limitations: (i) No randomization in treatment groups, may have selection bias (ii) Small BDP on lithium group compared to HC and nonlithium BDP (iii) No system to check for previous compliance with lithium treatment (iv) Use of neuroleptic medications other than lithium (however, was corrected for) (v) Drug or alcohol use may have affected results (vi) Results may have been a result of statistical power issues	In comparison with BDP without lithium, BDP on lithium showed a larger right (+3.4891%, $d=2.236$) and left (+1.98718%, $d=1.2$) amygdala volumes. However, these values were not significant.
18	Volume and shape analysis of subcortical brain structures and ventricles in euthymic bipolar I disorder	Quigley et al.	Cross-sectional Study	46 BDP with lithium 14 BDP without lithium 60 HC	MRI	Focus: This study aimed to establish trait-related subcortical structural and volumetric changes or abnormalities, by comparing euthymic BDP using lithium to HC. Such a large cohort size was purposefully used to attempt to combat the heterogeneity of previous studies. Limitations: (i) Varied individual clinical histories of BDP (ii) Other medications used along with lithium (iii) Unable to determine causation effect of lithium due to not being a longitudinal study (iv) Only euthymic BDP in study; inclusion of manic or depressed may have an effect	In comparison with HC, BDP on lithium showed a larger right (+3.34262%, $P=.397$, $d=0.174$) and left (+3.46608%, $P=.419$, $d=0.171$) amygdalar volume.
19	A 7 Tesla Amygdalar-Hippocampal Shape Analysis of Lithium Response in Bipolar Disorder	Athey et al.	Cross-sectional Study	14 BDP on lithium 21 HC	MRI	Focus: This study aimed to investigate structural surface anatomy–volume and shape metrics–in the amygdala and hippocampus as a result of treatment for BDP. Participants in this study went through a 16-week stabilization phase and a 4-week observation phase. Afterwards, those who were considered mildly ill according to the Clinical Global Impression Severity Test advanced to a maintenance phase that lasted between 4 weeks to 24 months. Every 2 months participants were assessed and those who relapsed or had failed to remit during the stabilization/observation phase were deemed nonresponders, referencing their lithium response. Scans using 7 Tesla structural MRI were taken of the BDP using lithium and compared to those of nonresponders and HC. Limitations: (i) Small sample size (ii) No males in nonresponder group, may impact generalization-ability of results (iii) Confounding variables such as duration of treatment, depressive predominant polarity, or stressful life events may have affected results (iv) Used a manual segmentation process (v) Changes within structures would not have been detected because subregions were split on the surface	There were no significant differences in volumes of amygdalae or hippocampi between the lithium responders, nonresponders, and HC groups.

Significant P values are in **bold**, *d*=Cohen's *d*

comparison to the other groups. These 5 studies differed in focus and technique. Of the 5 studies, 3 focused on volume changes at a broader scope, either looking at the whole brain or at a larger section that encompassed the amygdala [12, 13, 15]. In contrast, 2 studies focused on changes in amygdalar volume [11, 14]. Although all the studies primarily utilized MRI, Foland et al. and Germaná et al. also used TBM and VBM, respectively.

Study results at a more detail-oriented level also greatly varied. In Usher et al.'s study, a significant increase in the size of only the right hemisphere of the amygdala was found. Additionally, correlations between amygdalar volume and other factors associated with BD, including age of onset, duration of disease, and number of manic and depressive episodes, were not found to be significant. Instead, the study assumed that there was a connection between lithium and an increase in gray matter volume (GMV), which manifests as an increase in amygdalar volume in BDP. Conversely, in Foland et al.'s study, BDP treated with lithium had significantly greater left amygdalar volumes than did BDP not treated with lithium. However, similar to Usher et al., Foland et al. highlighted the connection between lithium and increases in cortical GMV and suggested that this connection may be the cause of discrepancies in the effect of lithium on corticolimbic structures. Similarly, attempting to explain the current inconsistency in the related literature, Sani et al. considered the length of treatment as a possible source of this heterogeneity. Sani et al. concluded that the duration of treatment did have an impact on volume changes. In their study, the bilateral amygdalar volume was smaller in the no-exposure (NE) group than in the HC group, but the amygdalar volume was not significantly different between the long-exposure (LE) group and the NE group or HC group. However, compared with those in the NE group, the amygdalar volume in the short-exposure (SE) group was significantly greater, suggesting that there is a difference in amygdalar volume based on the duration of lithium treatment that may be responsible for the heterogeneous results among related studies. Similar to Sani et al., Germaná et al. also reported a significant correlation between the duration of lithium treatment and overall gray matter density. Additionally, similar to Foland et al., Germaná et al. reported significant increases in the GMV of the left amygdala in BDP treated with lithium compared to other treatment groups. In this study, the amygdala was noted to be in a complex with the hippocampus, which may have accounted for the increase in volume, but this increase was still considered significant. On the other hand, a separate study by López-Jaramillo et al. revealed a significant increase in the volumes of both the right and left amygdalae of BDP treated with lithium. Interestingly, they found that serum levels of lithium were not directly correlated with an increase in the volume of the amygdala, although the strength of correlation in the right hemisphere was greater than in the left hemisphere.

Conversely, 4 of the 9 studies found no significant change in the amygdalar volume of BDP treated with lithium compared to the other groups. However, these conclusions were not definite. C. Barth et al. reported significant positive associations between the bilateral accessory basal nucleus volume of the amygdala and lithium use, but these associations did not survive correction. In the main study, however, C. Barth et al. acknowledged that their findings were in opposition to the general trend shown in previous studies. Hartberg et al. deduced that although the BDP in the lithium-use group had larger amygdalar volumes than did BDP not using lithium, ultimately, no significant differences were found between the volumes of BDP treated with lithium and that of HC or BDP not receiving lithium. Hartberg et al. conceded that this may be a statistical power issue. By analyzing the statistical effects of the illness course, Hartberg et al. utilized regression analyses of the BDP treated with lithium and showed positive associations between the length of lithium treatment and both hemispheres of the amygdala. After correction, however, these associations were once again no longer significant. The last two studies by Quigley et al. and Athey et al. found no significant differences in amygdalar volume between their cohorts. As a result, no relationship was identified between lithium use or duration of treatment and changes in the volume of the amygdala of BDP in either study.

Discussion

This scoping review included 9 cross-sectional studies, all of which used MRI, and determined whether there was a significant change in the amygdalar volume of BDP treated with lithium. Of these 9 studies, 5 found an increase in the amygdalar volume of the BDP receiving lithium in comparison to the amygdalae of other treatment and control groups, whereas 4 found no significant changes in volume [11–19]. Using these studies, our team aimed to identify either an increase or decrease in amygdalar volume in adults with BD using lithium as a physical substrate for the treatment of BD. We determined that there was a general increase; however, these findings are not explicitly corroborated by all the studies. Both within this review and in the current general literature that discusses volumetric changes in the amygdala in BDP treated with lithium, heterogeneity pervades, making the identification of a simple conclusion is difficult.

Amygdalar hemispheres

Even within this review, studies that shared conclusive results, either finding an increase or no change in amygdalar volume, still had discrepancies in which

hemispheres showed these results and the treatment and control groups that they compared.

Among the studies that found an increase, 1 study found an increase in the right amygdala only [11], 2 studies found an increase in the left amygdala only [14, 15], and 2 found an increase bilaterally [12, 13]. On the other hand, for the studies that found no change, all 4 studies found no significant changes bilaterally. Within this group, however, it is important to note that Athey et al. focused only on surface area changes in the amygdalar hemispheres without noting volumetric changes that may have occurred within these subregions. These discrepancies within each group only serve to emphasize the heterogeneity that exists regarding the amygdala despite its obvious importance within BD as an area of emotional regulation [3].

Cohort types

Cohorts varied across all studies. Among the studies that have shown an increase in amygdala size, most often BDP receiving lithium were compared to BDP not receiving lithium and HC [11–13, 17, 18]; sometimes, BDP treated with lithium were compared to either BDP not treated with lithium [14–16] or solely HC [19]. Some studies included a comparison between BDP using lithium and BDP using other medications [15], and in 2 cases, BDP using lithium were compared to study-specific groups, such as grouping by exposure length [13] or responsivity to treatment [19]. However, in these last 2 studies, BDP treated with lithium were also compared to HC to provide a metric for comparison, in addition to Sani et al.'s comparisons between SE, NE, and LE groups to test the impact of the length of treatment and Athey et al.'s responsive and nonresponsive groups to highlight remittance. Additionally, C. Barth et al. compared patients diagnosed with BDI and BDII in 1 additional study [16].

Techniques

While each study used MRI to take scans of the brain, additional techniques were used in conjunction with MRI [14, 15]. Foland et al. used TBM, and Germaná et al. used VBM. However, others have noted that VBM may not be a good technique for detecting changes in subcortical structure due to its difficulty in detecting more subtle changes in volume [18]. Changes in imaging technique may influence study findings, as the small volume of the amygdala may make it more challenging to detect subtle changes in volume depending on the imaging modality [18].

Duration of treatment

The length of lithium treatment may influence amygdalar volume changes. In Sani et al.'s cross-sectional study, lithium treatment duration was an important factor: exposure groups were created to test the short-term duration of treatment in comparison to the long-term duration. From this study, it was concluded that length of treatment did have an impact on amygdalar volume, as the difference in amygdalar volume was not significant in the LE group, but the SE group had greater amygdalar volume than the NE group. Sani et al. suggested that the difference in the duration of lithium treatment, which is often not uniform across cohorts or studies, leads to heterogeneity among the literature because of the lesser-known effect of the duration of treatment on amygdalar volume changes in BDP treated with lithium. Additionally, a second cross-sectional study by López Amarillo et al. suggested a relationship between the length of treatment and greater volumetric increases in the amygdala of BDP. While both studies suggest different relationships, they both identify the duration of lithium treatment as a cause of heterogeneity. However, Quigley et al. found no significant associations between length of treatment and changes in amygdalar volume, directly contradicting the findings of Sani et al. and López Amarillo et al. and once again exemplifying the continued discourse.

Cohort sizes and mood states

The heterogeneity of volumetric changes may also be explained by varying cohort sizes and mood states. Most of the studies included in this review had relatively small BDP using lithium cohort sizes. The smaller cohort sizes decreased the generalizability of each study and make it difficult to apply to a larger population because there is not an even distribution of different biological categories, such as sex or BD-specific categories, including mood state or BD type [18].

Regarding biological discrepancies, Hartberg et al. reported a greater proportion of men in their HC group than in their medicated and unmedicated BDP groups. Quigley et al. had no males in their nonresponsive group. These discrepancies make it difficult to apply these studies to larger populations because they are not representative of certain groups.

Additionally, in the studies by Usher et al. and Quigley et al., only euthymic BDP were included. Conversely, some of the studies that included manic and depressed patients had discrepancies in the number of manic and depressive episodes between the medicated and unmedicated groups [12]. Hartberg et al. established a relationship between mood states and cortico-limbic structure volumes, stating that mood states can affect the latter, which emphasizes how the exclusion of or discrepancies regarding certain mood states can possibly have an unknown effect on changes in amygdalar volume. Referencing BD type, C. Barth et al. was the only study to differentiate between the two and highlight their relationship with respect to volumetric changes in the amygdala

in BDP treated with lithium; however, they found no significant relationship between BDI and BDII.

Despite this heterogeneity, even within this review, our findings overall suggest an increase in the amygdalar volume of BDP receiving lithium as a physical indicator of the effect of lithium on BDP. Of the 4 studies that found no significant change in amygdalar volume, C. Barth et al. and Hartberg et al. both acknowledged that there were respective increases in amygdalae volumes before corrections deemed them mathematically insignificant ($P>.05$). C. Barth et al. reported significant positive associations between lithium usage and the bilateral accessory basal nucleus of the amygdala, and a majority of Hartberg et al.'s BDP using lithium group showed larger amygdalar volumes than did BDP not using lithium. Hartberg et al. conceded the possibility of a statistical power issue that may have impacted the significance of the difference in volume. Quigley et al. also reported that amygdalar volume increases, although the difference was not significant. Athey et al. examined surface-level changes in volume rather than volumetric changes inside both hemispheres, which may have impacted the results. Additionally, despite the discourse over the changes in the amygdalae of BDP after lithium treatment, it is generally agreed that the amygdalae of unmedicated BDP are smaller than those of HC [13]. Therefore, an increase in amygdalar volume would normalize or return BDP amygdalar volumes to a relatively normal volume in comparison to HC, as observed in Sani et al.'s LE group.

Limitations

The findings of this review are limited as the majority of the studies have small, less generalizable cohort sizes which may cause heterogeneity between studies. Additionally, 2 studies used techniques other than MRI, which may have skewed the results of the comparisons [14, 15]. Most of the studies included did not focus solely on volumetric changes in the amygdala; instead, they focused on corticolimbic volume changes or hippocampal and amygdalar volume changes [12–19]. Likewise, other studies not only focused on BD but also evaluated volume changes in patients with other disorders, such as schizophrenia [16].

This review is limited by the use of only three key databases and the omission of gray literature. While no language barriers were placed during the initial search process, papers not written or translated into English were removed. Studies were required to have at least 10 BDP using lithium to ensure that the study results were relevant and could be applied to larger populations; however, this did lead to the removal of multiple studies that may have resulted in different conclusions.

Conclusion

The lack of evidence to sufficiently support the claim that lithium increases the volume of the amygdala in adult bipolar patients indicates a significant gap in the current literature and research on this topic. Most of the studies included in this review stated that longitudinal research studies need to be performed [11–13, 16–19], and additional replication of this evidence needs to occur [14, 17] to confirm this claim. Longitudinal studies should be conducted to expand the current evidence within the related literature and establish clear relationships before conducting further reviews.

Abbreviations

BD	Bipolar disorder
BDP	Bipolar disorder patients
QOL	Quality of life
MRI	Magnetic resonance imaging
HC	Healthy controls
NE	No exposure
SE	Short exposure
LE	Long exposure
TBM	Tensor-based morphometry
VBM	Voxel-based morphometry

Acknowledgements

Not applicable.

Author contributions

Both authors conducted literature search, scanned abstracts, drafted manuscripts and tables, and reviewed the manuscript. A.S. prepared Fig. 1. A.N. submitted the manuscript.

Funding

Not applicable.

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Received: 24 January 2024 / Accepted: 13 October 2024
Published online: 24 October 2024

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