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ORIGINAL ARTICLE

Drug repurposing and personalized treatment strategies for bipolar disorder using transcriptomics: an exploratory study

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Objective: The present study combined transcriptomic data and computational techniques based on gene expression signatures to identify new bioactive compounds or Food and Drug Administration-approved drugs for the treatment of bipolar disorder (BD).
Methods: Five transcriptomic datasets containing 165 blood samples from individuals with BD were selected from the Gene Expression Omnibus (GEO). The number of participants varied from six to 60, with a mean age between 35 and 48 years and a gender difference between them. Most of these patients were receiving pharmacological treatment. Master regulator analysis (MRA) and gene set enrichment analysis (GSEA) were performed to identify genes that were significantly different between patients with BD and healthy controls and their associations with mood states in patients with BD. In addition, molecules that could reverse the transcriptomic profiles of BD-altered regulons were identified from the Library of Network-Based Cellular Signatures Consortium (LINCS) and the Broad Institute Connectivity Map Drug Repurposing Database (cMap) databases.
Results: MRA identified 59 candidate master regulators (MRs) that modulate regulatory units enriched with BD-altered genes. In contrast, GSEA identified 134 enriched genes and 982 regulons whose activation state was determined. Both analyses revealed genes exclusively associated with mania, depression, or euthymia, and some genes were shared among these three mood states. We identified bioactive compounds and licensed drug candidates, including antihypertensives and antineoplastic agents, as promising candidates for the treatment of BD. However, experimental validation is essential to confirm these findings in further studies.
Conclusion: Although our data are still preliminary, they provide some insights into the biological patterns of different mood states in patients with BD and their potential therapeutic targets. The strategy of transcriptomics plus bioinformatics offers a way to advance drug discovery and personalized medicine by using gene expression information.

Keywords: Computational biology; personalized medicine; drug repurposing; psychiatry pharmacology

Introduction

Bipolar disorder (BD) is a chronic mental illness that affects more than 40 million people worldwide.[1] It is a highly disabling illness that is associated with high rates of premature mortality due to suicide and medical comorbidities.[2] The complexity and heterogeneity of BD pose a challenge to understanding its underlying causes and implementing treatment strategies that address these causes.[3] Patients often show insufficient improvement even after undergoing a series of drug protocols, which demonstrates the low efficacy of conventional treatments.[4] Using high-throughput omics is a potential approach to accelerate the discovery of pathological mechanisms and new therapeutic targets.

Omics data combined with sophisticated computational analysis can provide a comprehensive understanding of the systemic changes that occur in BD, allowing the study

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of multifaceted molecular changes rather than being limited to individual genes or proteins.[5] This methodology has streamlined the identification of novel molecular mechanisms and potential therapeutic targets. In psychiatry, this would lead to a paradigm shift in understanding the biological basis of BD, allowing the identification of more homogeneous biological subtypes, specific biomarkers, and personalized treatments. This innovative approach is in line with the goals of the Research Domain Criteria (RDoC).

In this context, transcriptomics, which comprehensively assesses all transcripts and their abundance in a given sample, plays a fundamental role in understanding the functional components of the genome. Transcriptomic data allow the identification of putative functional mechanisms by which variations in genetic sequence and changes in gene expression can lead to a specific state or disease.[6] An additional advantage of transcriptome analysis is the ability to dissect the intricate interplay between transcription factors (TFs) and DNA. TFs modulate global gene expression and thus play a critical role in transcriptional regulatory networks.[7]

The Broad Institute Connectivity Map Drug Repurposing Database (cMap), a database of whole-genome transcriptomic profiles of bioactive compounds, allows the establishment of relationships between diseases, physiological processes, and the mechanism of action (MOA) of therapeutic compounds.[8] The use of cMap is advantageous because it does not require a detailed MOA or prior knowledge of the molecule's targets to function, thus more effectively achieving the goal of predicting therapeutic compounds for a specific disease.[5] In contrast to classical pharmacology, the transcriptomic profiles provided by cMap use systems biology approaches at the pathway and network levels rather than focusing on a single target. Thus, by combining high-throughput transcriptomics and network analysis, we aimed to identify potential drug candidates for the treatment of BD on the strength of gene expression signatures (GESs). Through this approach, we aim to advance our understanding of BD mechanisms and facilitate the development of personalized therapeutic strategies for this complex disease.

Methods

Data acquisition and differential expression analysis

Datasets were searched in the Gene Expression Omnibus (GEO) repository in July 2023 using the following search strategy: (''bipolar disorder''[MeSH Terms] OR bipolar disorder[All Fields]) AND (''blood''[Subheading] OR ''blood''[MeSH Terms] OR blood[All Fields]). In addition, ''*Homo sapiens*,'' ''expression profiling by array,'' and ''expression profiling by high throughput sequencing'' filters were applied, resulting in 32 databases. The inclusion criteria were i) case-control studies in which the mood state of individuals with BD was previously characterized, ii) TFs assessed by microarray analysis, and iii) studies conducted on human blood samples. We excluded studies using brain tissue, cell culture, redundant databases, RNA-Seq analysis, or patients without BD state stratification (Table S1, available as supplementary material). Five microarray transcriptomics datasets representing different phases of BD (i.e., euthymia, mania, and depression) were selected from the GEO repository (i.e., GSE121963, GSE46416, GSE45484, GSE39653, and GSE23848) (Figure 1) and downloaded using the GEO query. The dataset was batch-filtered and corrected using the *virtualArrayComBat* function,[9-11] resulting in 165 samples. Differential expression analyses were performed using the *limma* package, applying multiple linear models and moderated t-statistics to identify differentially expressed genes (DEGs) via empirical Bayes moderation.[10] Altered genes with an unadjusted $p < 0.05$ and a fold change greater than 15% were considered DEGs (Table S2, available as supplementary material).

Blood samples from healthy humans were obtained from two large microarray datasets (GSE48348 and GSE99039) from the GEO. The datasets were combined and processed using the GEOquery and *virtualArray* packages, including a batch correction for batch effects.[9-11] The final dataset comprised 967 healthy blood samples used for transcriptional network (TN) inference (Figure 1).

Reverse engineering of the transcriptional network

We used a large cohort of healthy blood samples to infer TF-centered TNs and their predicted target genes. The obtained TF-centered TNs were merged as described in the Data Acquisition section. In the present study, the term ''regulatory unit,'' also known as ''regulon,'' refers to the inferred gene groups and their associated TFs. The RTN package (v2.16.1) was used to reconstruct and analyze TNs via the algorithm for the reconstruction of accurate cellular networks (ARACNe) and mutual information (MI).[12] The regulatory structure of the network was determined by mapping significant associations between known TFs and their potential targets. A selected gene list was used to annotate the suitability of the TF for TN inference entry.[7] To generate a consensus bootstrap network, a permutation step eliminates interactions below a minimum MI threshold, and unstable interactions are additionally removed by bootstrapping. Data processing inequality was applied with zero tolerance to eliminate interactions that might be mediated by a third TF. The reference blood TN was constructed using the package's default settings: 5,000 permutations and 100 bootstraps ($p < 0.001$).

Master regulator analysis and gene set enrichment analysis

We performed master regulator analysis (MRA) following the method proposed by Carro et al.[13] For each regulatory unit in the blood TN, the algorithm calculates the statistical overrepresentation (calculated by a modified Fisher exact test) of genes obtained from differential expression analyses (unadjusted $p < 0.05$ and variation greater than 15%). In addition, one-tailed gene set enrichment analysis (GSEA) was used to assess whether

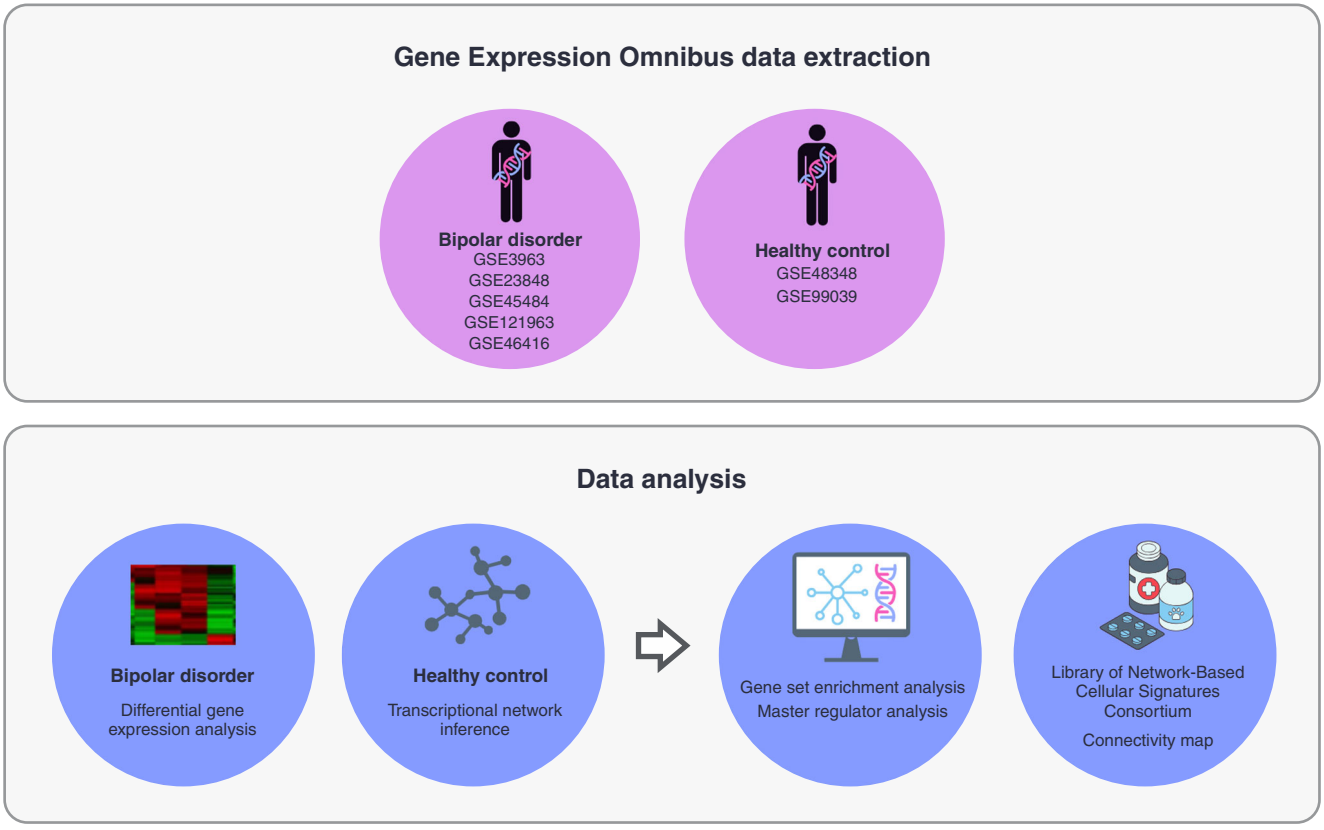

Figure 1 Flowchart of the methodology. Data regarding patients with bipolar disorder (BD) and healthy controls were obtained from the Gene Expression Omnibus (GEO) database. Gene expression data from healthy human blood was used to construct a normal blood regulatory network centered on transcription factors (TFs). Differentially expressed genes were calculated from the data of the control group and each phase of the patients with BD. The convergence of results from master regulator analysis (MRA) and one-tailed and two-tailed gene set enrichment analysis (GSEA) were used as input to reveal bioactive compounds. The Library of Network-Based Cellular Signatures Consortium (LINCS) and the Broad Institute Connectivity Map Drug Repurposing Database (cMap) were used to identify potential candidates for drug repurposing in BD.

members of a gene set were associated with phenotypic class distinctions.[14] Finally, two-tailed gene set enrichment analysis was also performed using the RTN package (v2.16.1) with a p-value threshold of 0.05 and using 1,000 permutations. Pearson correlation was used to separate regulatory units into two subgroups: positively associated targets (A) and negatively associated targets (B). GSEA statistics[14] were then used to test the phenotypic association of each subset, resulting in independent enrichment scores (ESs) for each subset. An additional step was performed to test for differential enrichment (ES_A-ES_B), considering that a maximum variation of 0 near opposite extremes and good separation of the two distributions are desirable for a clear association. Thus, a high negative differential score implies that the regulon is suppressed in the disorder phenotype. In contrast, a high positive differential score indicates that the regulon is induced in the disorder phenotype.

Drug repurposing

We used the Library of Integrated Network-Based Cellular Signatures (LINCS)[15] program and cMap[16] to identify existing molecules that reverse the transcriptomic profiles of disease-altered regulons found in each phase of BD. In this study, we used the qSig function (method = "LINCS") of the R package "signatureSearch" to perform GES genetic searches and then interpreted the results using specialized enrichment methods.[17] In drug discovery, these tools can identify novel MOAs through which bioactive compounds may act.

Results

Sample characterization

Table 1 shows the characteristics of the sample. The number of participants (n) varied from six to 60. Four studies used whole blood, while one specifically used peripheral blood mononuclear cells (PBMCs) for analysis. In addition, two studies investigated manic versus euthymic mood states in detail, while three studies focused on the evaluation of depressive states in individuals with BD. The mean age of the participants in the five studies ranged from 35 to 48.3 years. The sex distribution within the studies varied significantly: one

Table 1 Sample characterization

GEO ID	PMID	Mood state	Age	Gender (%, male)	n	Tissue	Medication
GSE121963	31118907	Mania × euthymia	45.2 ± 9.9	50.0	6	Whole blood	No individual information
GSE46416	25136889	Mania × euthymia	48.3 ± 12.0	100.0	11	Whole blood	Antipsychotics, mood stabilizers, anticonvulsants, antidepressants, benzodiazepines
GSE45484	23670706	Depression	39.45 ± 12.2	31.6	60	Whole blood	Mood stabilizers
GSE39653	23064081	Depression	35 ± 10.0	32.0	29	PBMC	No medication
GSE23848	21176028	Depression	38.4 ± 9.5	30.0	20	Whole blood	Antipsychotic, mood stabilizers, anticonvulsants

GEO = Gene Expression Omnibus repository; PBMCs = peripheral blood mononuclear cells; PMID = PubMed Unique Identifier.

study included predominantly men, three included women, and one study had an even sex distribution of 50%. Concerning pharmacological interventions, one study did not specify the medication used. In contrast, another study described patients who received a combination of antipsychotics, mood stabilizers, anticonvulsants, antidepressants, and benzodiazepines. One study mentioned that subjects from the depression-focused cohorts did not use any medication. Two other studies reported the use of antipsychotics, mood stabilizers, and anticonvulsants.

Master regulator analysis (MRA)

MRA is an approach that aims to identify the TFs that act as master regulators (MRs) responsible for changes in gene expression between different conditions. In our study, MRA identified 59 potential candidate MRs modulating regulatory units enriched with genes altered in BD. We observed specific MRs in patients during the depressive and euthymic phases, but no exclusive MRs were identified during mania. In addition, we found 12 MRs that were common between euthymia and depression and two MRs that were common between depression and mania (Table S3, available as supplementary material).

Gene set enrichment analysis (GSEA)

Unilateral GSEA assesses whether a predefined set of genes, based on biological information, is enriched among a set of DEGs under different conditions. In our dataset, GSEA identified 134 enriched gene sets (regulatory units), of which two were exclusively associated with bipolar depression, three were specific to the euthymic phase, and four were implicated in mania. The intersection between BD phases led to the identification of 31 genes (Table S4, available as supplementary material). Two-tailed GSEA was then performed to infer the activity state (i.e., activated or repressed) of the MRs in each dataset. The activation states of a total of 982 regulons were identified: 167 in mania, 437 in euthymia, and 378 in bipolar depression (Table S5, available as supplementary material).

Drug repurposing

To identify potential drug repurposing candidates for BD treatment, we used the LINCS and cMap databases. These databases relate to pharmacology and use systems biology approaches to study large-scale interactions between drugs and cells. In this study, we used the convergence of MRA, one-tailed GSEA, and two-tailed GSEA results as inputs to reveal bioactive compounds and their MOAs. Thus, we obtained two regulons for mania, 16 for euthymia and 11 for depression. The associations of these regulons with their corresponding MOAs are shown in Figure 2. A comprehensive dataset containing information on drugs, MOAs, and regulons is provided in Table S6 (available as supplementary material). The initial list of drugs was filtered to retain only the top 20 drugs for each regulon in the different disease phases. The analyses were performed for three phases of BD, suggesting a single treatment for mania, euthymia, and depression, as well as showing common drugs for all three phases (Figure 3).

Discussion

When applied to pharmacology, systems biology and bioinformatics can assist in discovering novel compounds or even new indications for Food and Drug Administration (FDA)-approved drugs, a method known as drug repurposing. In the present exploratory study, five microarray transcriptomics datasets representing different mood states of patients with BD (i.e., euthymia, mania, depression) were selected from the GEO repository. Differential expression analyses were performed to identify DEGs and generate enriched gene sets. Then, we used the MRA to identify the MRs responsible for changes in gene expression between subjects with BD and controls. Finally, we explored drug-gene interactions using the LINCS and cMap databases to identify key drugs or compounds whose MOAs were related to the GES of BD. Interestingly, some of these compounds were specific to mania, depression, or euthymia, while others were common to all of these states. These drugs are antineoplastic agents (e.g., dasatinib, sorafenib, and sunitinib), antihypertensive agents (e.g., minoxidil and aliskiren), or bioactive compounds tested in animal

Figure 2 Broad Institute Connectivity Map Drug Repurposing Database (cMap) of regulons with their corresponding mechanisms of action (MOAs) in the different phases of bipolar disorder (BD). A) Depression. B) Euthymia. C) Mania.

models (e.g., guggulsterone, betulinic acid, caffeic acid, and others).

The repurposing of antihypertensive agents for the treatment of psychiatric disorders is an underdeveloped

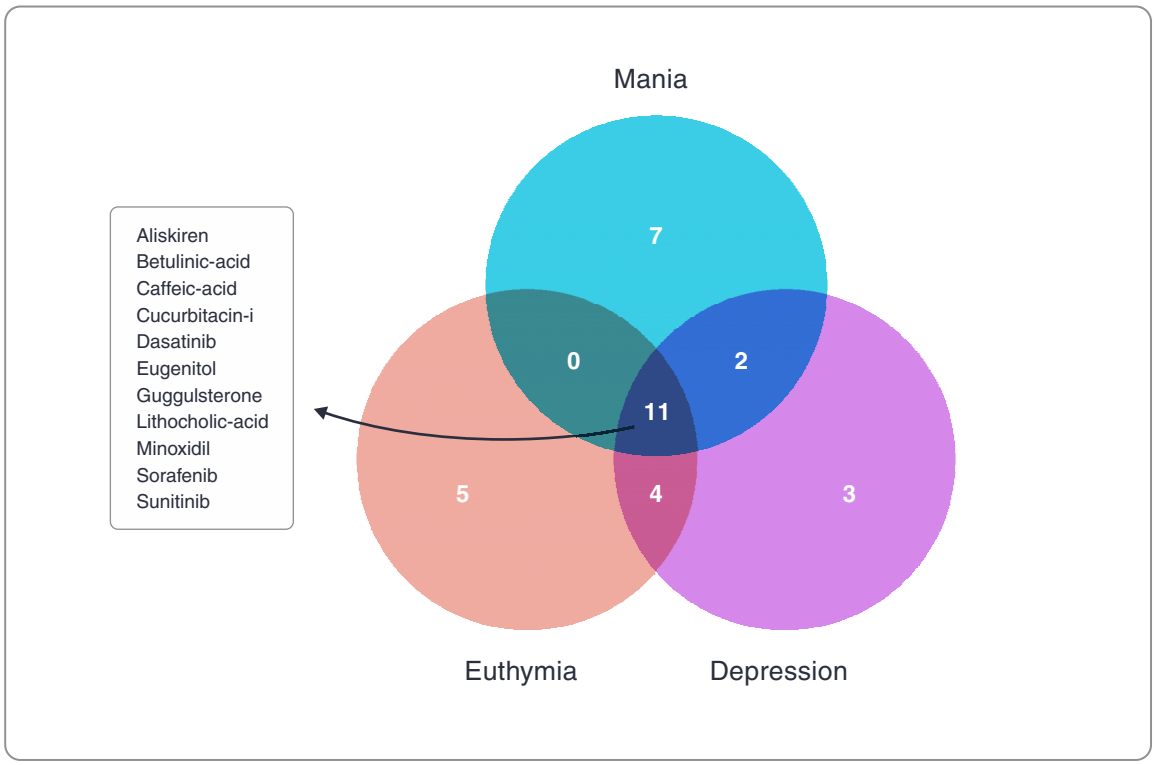

Figure 3 Venn diagram showing the top 20 drugs for each regulon in the different phases of bipolar disorder (BD) (depression, euthymia, and mania). Eleven compounds were common to all of them.

but promising area.[18] An observational study of a cohort of 60,045 Finnish individuals revealed a significant association between the use of calcium channel blockers plus dihydropyridines and a reduction in mood-related hospitalizations in patients with BD.[19] Similarly, eight individuals with drug-resistant BD had a significant reduction in the frequency and severity of manic and depressive episodes after treatment with diltiazem, a calcium channel blocker, compared with the period before treatment with the same drug, which suggests that diltiazem is an effective adjunctive treatment for the management of BD.[20] Calcium channel blockers play an interesting role as mood stabilizers because they share an essential MOA with lithium and carbamazepine, which are the primary treatments for BD.[21,22] Another class of antihypertensive agents with potential applications in psychiatry are the renin-angiotensin system antagonists.[23] For example, telmisartan was tested as an adjunctive treatment for schizophrenia in a randomized clinical trial, which showed a significant reduction in the total score on the Positive and Negative Syndrome Scale (PANSS) in the telmisartan group compared to the placebo group.[24] In addition, a significant association between angiotensin-converting enzyme inhibitors (ACE-Is) and posttraumatic stress disorder (PTSD) was demonstrated in an observational study of more than 800 individuals. These findings were confirmed in subsequent analyses using a large biorepository database (Partners HealthCare Biobank, n=116,389).[25] We also identified a renin-angiotensin system antagonist as a promising compound to test in BD based on previous studies.

Minoxidil was another repurposing drug identified in our findings. Although widely used to treat alopecia, minoxidil was originally developed as a potent peripheral vasodilator for the treatment of severe refractory hypertension. It exerts antihypertensive effects by opening adenosine triphosphate (ATP)-sensitive potassium channels. Reduced expression of the astrocytic ATP-sensitive potassium channel (Kir6.1/ATP) was found in the hippocampus of mice exposed to the chronic stress model, suggesting that the Kir6.1/K-ATP channel may hold promise as a potential target for the treatment of depression.[26] On the other hand, a randomized clinical trial investigating the antidepressant effects of a potassium channel activator (e.g., diazoxide) was discontinued due to severe adverse effects of diazoxide.[27] Taken together, our results suggest that some of the targets involved in the MOAs of certain antihypertensive agents are promising candidates for psychiatric treatment, although these preliminary data require further experimental validation studies. Our study also demonstrated the potential applicability of ATP-competitive protein tyrosine kinase (PTK) inhibitors (e.g., antineoplastic drugs) in psychopharmacology.[28] The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway comprises a family of nonreceptor PTKs that modulate various cytokines, growth factors, and PTKs. Once activated, JAKs phosphorylate downstream targets; the primary effector in this category is the STAT

family. Upon phosphorylation by JAK, STATs dimerize and translocate to the nucleus, where they regulate the expression of various genes.[29] The JAK/STAT pathway has also emerged as a key mechanism in regulating synaptic plasticity and plays a role in neuronal and glial responses to injury in the central nervous system (CNS). Specifically, the JAK2/STAT3 pathway is involved in long-term depression, a process by which synapses become less effective at transmitting signals over time. JAK3 is also part of the MOA of tricyclic antidepressants (such as amitriptyline), as demonstrated in a preclinical study of depression.[30] In addition, the procognitive effects of ceramide are mediated by the JAK/STAT pathway. Several lines of evidence support the role of JAK/STAT signaling in the pathogenesis of psychiatric disorders and psychopharmacology.

In addition, our study identified bioactive compounds with promising therapeutic properties for treating psychiatric disorders. Guggulsterone is a bioactive compound from *Commiphora mukul* that shows fluoxetine-like antidepressant effects in an animal model of chronic, unpredictable stress. These effects appear to be mediated by activation of the brain-derived neurotrophic factor (BDNF) signaling pathway.[31] BDNF is a protein critical for promoting neuronal growth, survival, and maintenance in the brain and is involved in various processes such as neurogenesis, synaptic plasticity, and overall brain health. Previous studies have shown that alterations in plasma BDNF levels in BD patients[32] and the effects of lithium may be mediated by BDNF,[33] which supports guggulsterone as a promising candidate for the treatment of BD. Betulinic acid is a triterpene tetracyclic compound found in various plants and has a wide range of pharmacological properties.[34,35] It has shown potent anticancer activity in several cancers, mainly by regulating the JAK/STAT, VEGF, EGF/EGFR, TRAIL/TRAIL-R, AKT/mTOR, and ubiquitination pathways.[34] An important effect of this compound is its anti-inflammatory activity, most likely related to the inhibition of the NF-kB and MAPK pathways.[36] Despite the lack of evidence in psychiatry, the effects of betulinic acid have been associated with improved cerebral blood flow and memory in a vascular dementia model.[37]

In addition to these compounds, caffeic acid has some benefits for treating central nervous system disorders. For example, caffeic acid showed antidepressant-like effects in chronic stress models via epigenetic mechanisms. Mechanistically, the mRNA levels of hydroxymethylation (ten-eleven translocation [TET]1-3) (associated with global DNA hydroxymethylation) decreased in the stress group, an effect that was restored to normal levels following treatment with caffeic acid in combination with paroxetine compared to those in the control group.[38] In addition, caffeic acid attenuated the decreased cortical BDNF mRNA expression induced by swim stress in wild-type mice.[39] Animal models of amyloid-beta-induced neurodegeneration also demonstrated that caffeic acid reduced reactive oxygen species, lipid peroxidation, and the expression of astrocyte-activated and microglia-activated markers. These effects were also correlated with cognitive improvement.[40]

In conclusion, our preliminary data identified novel drug candidates via computational drug repurposing based on the transcriptome signature of individuals with BD via subsequent analysis of drug-induced expression profiles. In the era of bioinformatics and precision medicine, the use of innovative advances, including systems biology models and multiomics approaches, is welcomed to address important challenges in psychiatric disorders due to i) a limited understanding of neurobiology, ii) disease heterogeneity, and iii) a lack of validated animal models. Although most of the drug candidates identified here are supported by the literature, our analysis was based on hypothesis generation. Experimental validation is required before clinical translation.

The limitations of our study should be acknowledged. Our dataset lacks certain essential metadata, which may limit the depth and precision of our analyses. This fact may potentially affect the generalizability and robustness of our findings. Second, data were obtained exclusively from blood transcriptomics, which may limit the representativeness of the sample. In addition, we cannot rule out the influence of variables such as age, sex, race, and medications on the findings. Third, gene expression data were obtained only from blood samples, which may not fully capture the complex molecular changes associated with BD throughout the brain. Fourth, while our methodology provides a robust approach to gene expression analysis, it relies on computational models influenced by data quality and underlying assumptions. The choice of parameters can affect how the network is constructed, potentially leading to different interpretations. Fifth, drug discovery is a multifaceted process that goes beyond gene expression and includes critical aspects such as pharmacokinetics and toxicology, which are also essential for the development of new drugs. Finally, this exploratory study provides preliminary data on the mechanisms involved in the etiology of BD. We aimed to provide insights into the molecular signature associated with BD rather than to confirm or test specific hypotheses. Therefore, our findings need to be validated by molecular biological methods in further studies.

In conclusion, our study underscores the promise of using advanced gene expression analysis methods to identify new drugs or repurpose existing drugs to treat psychiatric disorders. This strategy offers a way to advance drug discovery and personalized medicine by harnessing genetic information. While our exploratory study provides preliminary data on the molecular signature of BD and interesting compounds for its treatment, experimental validation of such findings in further studies is essential before clinical translation.

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Disclosure

The authors report no conflicts of interest.

Author contributions

PRZ: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.
MAB: Conceptualization, Data curation, Formal analysis.
ES: Writing – original draft.
PHR: Writing – original draft, Writing – review & editing.
TS: Writing – original draft, Writing – review & editing.
GM: Writing – original draft, Writing – review & editing.
QC: Writing – original draft, Writing – review & editing.
FK: Supervision.
ARR: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.
All authors have read and approved of the final version to be published.

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