Metformin is Protective Against the Development of Mood Disorders

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ABSTRACT

Introduction Mood disorders are a major cause of disability, and current treatment options are inadequate for reducing the burden on a global scale. The aim of this project was to identify drugs suitable for repurposing to treat mood disorders.

Methods This mixed-method study utilized gene expression signature technology and pharmacoepidemiology to investigate drugs that may be suitable for repurposing to treat mood disorders.

Results The transcriptional effects of a combination of drugs commonly used to treat mood disorders included regulation of the steroid and terpenoid backbone biosynthesis pathways, suggesting a mechanism involving cholesterol biosynthesis, and effects on the thyroid hormone signaling pathway. Connectivity Map analysis highlighted metformin, an FDA-approved treatment for type 2 diabetes, as a drug having global transcriptional effects similar to the mood disorder drug combination investigated. In a retrospective cohort study, we found evidence that metformin is protective against the onset of mood disorders.

Discussion These results provide proof-of-principle of combining gene expression signature technology with pharmacoepidemiology to identify potential novel drugs for treating mood disorders. Importantly, metformin may have utility in the treatment of mood disorders, warranting future randomized controlled trials to test its efficacy.

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Introduction

Mood disorders are characterized by concurrent emotional and motivational disturbances, contributing to an incalculable toll on the quality of life [1, 2]. Mood disorders have affected approximately 309 million people worldwide [3]. Despite such substantial burden, existing medications leave much to be desired, with notable tolerability concerns and inadequacy in alleviating symptoms across all patients [1]. As a result, medication non-compliance and episode recurrence are exceedingly apparent in this patient population [4, 5].

While there is a clear need for more effective and tolerable medications, the development of novel psychopharmaceuticals to treat mood disorders is not being prioritized [4, 6]. Therefore, it is imperative to identify new medications with improved capacity to alleviate the symptomatic and functional repercussions of mood disorders. One approach to identifying such medications is by screening already-approved drugs used to treat non-psychiatric illnesses and selecting those that target the common transcriptional pathways altered by widely used mood stabilizers [7]. This repurposing process can then be further confirmed via pharmacoepidemiology to test for existing evidence of the potential efficacy of the identified medication.

Using such approaches, this mixed-method study aimed to identify existing off-patent medications suitable for repurposing to treat mood disorders.

Methods

Part A: Repurposable Drug Identification

Gene expression

Data from a previous study in our laboratory was utilized for gene expression analysis [7]. Briefly, human neuronal-like cells (Ntera2/clone D1 (NT2) cells [ATTC CRL-1973]) were treated with a combination of commonly prescribed drugs (2.5 mM lithium chloride, 0.5 mM valproate, 50 µM lamotrigine, and 50 µM quetiapine) used in the treatment of mood disorders, or vehicle control (0.2 % DMSO), for a period of 24 h. A group of drugs thought to have heterogeneous mechanisms of action was selected to cover as broadly as possible biological pathways that may be involved in the beneficial effects of drugs that successfully treat mood disorders in at least some patients. Following treatment, next-generation sequencing was performed on the total RNA. The differential expression of genes was assessed using EdgeR [8].

To ensure that only genes with the best evidence of differential expression were assessed, genes with an adjusted p-value > 10^{-100} were excluded from further analysis. The remaining genes were separated into "up"- or "down"-regulated genes following drug treatment.

Gene set enrichment analysis

Gene set enrichment analysis of the differentially expressed genes was performed using the Database for Annotation, Visualization and Integrated Discovery (DAVID) software (NIH) [9]. The "up" and "down" gene lists were individually interrogated using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database for gene ontology. Following the correction for multiple testing, enriched KEGG pathways with a Benjamini-adjusted $p < 0.05$ were considered statistically significant.

Connectivity map analysis

To perform the Connectivity Map (CMap; BROAD Institute) [10] analysis, corresponding gene identifications were determined for the differentially expressed genes, using NetAffx Analysis Center (Thermo Fisher Scientific). The set of "up" and "down" genes were evaluated using the publicly available CMap database for relatedness in comparison to a reference dataset comprising expression profiles derived from bioactive compounds. Relatedness was reported in terms of connectivity scores ranging from + 1 to −1. A positive connectivity score denoted functional similarity between the gene set of interest and the reference compounds in the CMap database. A negative connectivity score denoted an inverse relationship.

Part B: Pharmacoepidemiological Study

To test whether the drug(s) identified by the CMap analysis are associated with the incidence of mood disorders, a pharmacoepidemiology approach was utilized. This approach utilized longitudinal, population-based data collected from women participating in the Geelong Osteoporosis Study (GOS).

Participants

Between 1994–1996, 1,494 women were randomly recruited from the Australian Commonwealth electoral rolls for the Barwon Statistical Division [11]. An additional sample of 246 women aged 20–29 years was recruited between 2004–2008, allowing for continuing investigation of the full adult age range [11, 12]. Longitudinal data were available for 896 of the 1,133 participants who underwent psychiatric assessment. Based on retrospective data, exposure to the drug of interest was acknowledged if use preceded mood disorder onset; otherwise, they were removed from the cohort (n = 18). Furthermore, 159 participants whose mood disorder onset preceded baseline assessment, were not included in the analysis. Lastly, 15 participants with less than two years of observation between commencing the study period and mood disorder onset were additionally excluded. Thus, a cohort of 704 women was eligible for analysis in the retrospective cohort study. The Human Research Ethics Committees at Barwon Health (92/01) provided approval for this study. Informed, written consent was provided by all study participants.

Data

The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, the Non-patient edition (SCID-IV/NP) [13] was administered at the GOS 10 and 15-year follow-up appointments by trained personnel with post-graduate qualifications in psychology. Participants were classified as having a mood disorder if past or current symptoms met the diagnostic criteria for bipolar disorder, major depressive disorder, minor depression, dysthymia, substance-induced mood disorder, or mood disorder due to a general medical condition. Age of onset was also determined.

Comprehensive questionnaires were used to document demographic and lifestyle information, and anthropometry was measured at baseline and subsequent follow-up visits. Current medication use was self-reported. A list of medications or containers was requested to be brought to the study visit to assist with the accurate recording of details. The Index of Relative Socioeconomic Dis-

advantage was utilized to determine the socioeconomic status of participants based on Australian Bureau of Statistics census data. The participants were categorized into five groups, with quintile one being the most disadvantaged. Mobility was self-reported, with participants who regularly engaged in vigorous or light exercise classified as active. Sedentary, limited, inactive, or bed-ridden participants were otherwise classified as inactive. Current cigarette smoking (yes/no) and alcohol consumption (yes/no) were self-reported. Weight (± 0.1 kg) and height (± 0.1 cm) were measured.

Statistical analyses

Statistical analyses were performed using R commander (version 2.7–0). Independent samples t-tests were used for continuous parametric variables, Kruskal-Wallis test was used for non-parametric variables, and Chi-squared tests were utilised for discrete variables. Fisher's exact tests were applied where expected cell counts were less than five.

Cox proportional hazards regression modeling was used to calculate hazard ratios (HR) with 95 % confidence intervals (CIs) to determine the effect of exposure to the drug of interest on *de novo* mood disorder onset. Participants were followed from the point where drug exposure was documented until *de novo* mood disorder onset or until the end of the study period. Exposure to the drug of interest was determined by data documented throughout the allotted study period. Baseline data were utilized for participants not exposed to the drug of interest. Models were adjusted for participant's age at drug exposure or age at baseline for those not exposed. Socioeconomic status, weight, height, mobility, alcohol consumption, and smoking were assessed for effect modification and retained in the model if estimated to be significant ($p < 0.05$). Proportional hazard assumptions were checked using Schoenfeld residuals before and after confounders were added.

Results

Part A: Repurposable Drug Identification

Differential gene expression analyses of NT2-N cells (drug combination treated or vehicle control; n = 20/group) resulted in a total of 232 genes of interest (**Supplementary Tables 1, 2**) that met adjusted $p < 10^{-100}$ cut-off, referred to as the gene expression signature (GES) for this study. GES comprised 132 genes with increased expression following drug treatment ("up" genes) and 100 genes with decreased expression ("down" genes; **Supplementary Table 1 & 2**). These 232 genes were analyzed using DAVID to identify enriched biological pathways. Five pathways were upregulated following treatment with the mood disorder drugs (▶ **Table 1**), while six pathways were downregulated (▶ **Table 1**).

Of the GES genes, 191 had corresponding gene IDs recognized by CMap, with the analysis detecting 100 significantly associated drugs/compounds ($p < 0.05$), 70 of which had a positive connectivity score (▶ **Table 2**). These 70 compounds that affect gene expression in a manner most similar to the combination of mood disorder drugs (▶ **Table 2**) were investigated for suitability for drug repurposing to treat mood disorders. Drugs were excluded if they were not orally bioavailable, not marketed in Australia, already used to treat mood disorders (i. e., not novel), or had known toxicity (withdrawn from the market or given a black box warning). Finally, nine compounds had the evidence to support the potential repurposing to treat mood disorders (▶ **Table 3**). Of these agents, metformin was selected to undergo further investigation using a pharmacoepidemiology approach because it was the most commonly used in the GOS participants.

▶ **Table 1** Pathways enriched for genes with A) increased and B) decreased expression in NT2-N cells following treatment with mood disorder drug combination (n = number of genes, adj.*p* = Benjamini adjustment for multiple testing).

A: Increased expression			
KEGG pathway	n	p	adj. p
Steroid biosynthesis	9	6.10E-12	7.40E-10
Biosynthesis of antibiotics	15	1.10E-09	6.70E-08
Terpenoid backbone biosynthesis	7	4.50E-08	1.80E-06
Metabolic pathways	25	3.00E-04	9.00E-03
Fatty acid metabolism	5	1.20E-03	2.80E-02
B: Decreased expression			
KEGG Pathway	n	p	adj. p
Proteoglycans in cancer	10	5.90E-07	5.10E-05
Focal adhesion	9	8.30E-06	3.60E-04
Viral myocarditis	5	2.00E-04	5.90E-03
Thyroid hormone signaling pathway	6	3.00E-04	6.50E-03
Hippo signaling pathway	6	1.00E-03	1.80E-02
MicroRNAs in cancer	7	3.30E-03	4.70E-02

Part B: Pharmacoepidemiological Study

Among 704 participants with no history of mood disorder, 4 of 27 metformin users and 102 of 677 non-metformin users developed *de novo* mood disorder over 16 years of follow-up. There was no difference in socioeconomic status between the groups; however, participants exposed to metformin were older, heavier, shorter, less active, and less likely to smoke and consume alcohol compared to the unexposed participants (▶ **Table 4**).

Following adjustment for age, exposure to metformin led to a 69 % decrease in the probability of developing a *de novo* mood disorder (HR = 0.31, 95 %CI = 0.11–0.88, $p = 0.028$). Socioeconomic status, weight, height, mobility, alcohol consumption, and smoking did not explain the finding. ▶ **Fig. 1** presents a Kaplan-Meier survival plot demonstrating the probability of remaining free of *de novo* mood disorder over a period of 16.6 years for women exposed and not exposed to metformin.

Discussion

Treatment of human neuronal-like cells with a combination of mood disorder drugs enriched genes for 11 biological pathways. Of particular interest, the steroid biosynthesis and terpenoid backbone biosynthesis pathways had increased expression. These pathways are closely linked with cholesterol homeostasis [14], which affects the structural integrity and functioning of neuronal cells, contributing to synapse formation and axonal regeneration

▶ **Table 2** Compounds that act most similarly to the mood disorder drug combination used to treat the NT2-N cells (CMap output; n = number of genes).

Compound	n	Connectivity score	p
MG-262	3	0.707	0.00016
Vorinostat	12	0.696	<0.00001
5182598	2	0.660	0.020
Metergoline	4	0.658	0.000020
Semustine	4	0.654	0.00010
Tonzonium bromide	4	0.639	0.011
Noretynodrel	4	0.636	0.0013
Prenylamine	4	0.629	0.0025
Thiostrepton	4	0.628	0.0091
Lomustine	4	0.603	0.000040
Scriptaid	3	0.600	0.011
Syrosingopine	4	0.597	0.012
5155877	4	0.594	0.0010
Phenazopyridine	4	0.593	0.0099
Bepridil	4	0.590	0.00040
Withaferin A	4	0.588	0.00010
Rifabutin	3	0.581	0.0019
Arachidonic acid	3	0.578	0.0018
Bufexamac	4	0.574	0.00018
Phenoxybenzamine	4	0.573	0.00014
Trichostatin	182	0.568	<0.00001
Parthenolide	4	0.567	0.00054
F0447–0125	4	0.554	0.00056
Epitiostanol	4	0.533	0.0075
Norcyclobenzaprine	4	0.516	0.013
Nortriptyline	4	0.504	0.018
Resveratrol	9	0.492	0.000060
Oxetacaine	5	0.490	0.00060
Enilconazole	4	0.486	0.0040
Diperodon	3	0.486	0.013
15-delta prostaglandin J2	15	0.477	0.000060
Isotretinoin	4	0.471	0.017
Fluphenazine	18	0.469	<0.00001
Prochlorperazine	16	0.467	<0.00001
Fenbendazole	4	0.465	0.0029
0225151–0000	3	0.455	0.023
Loperamide	6	0.451	0.0072
Mometasone	4	0.448	0.021
Miconazole	5	0.422	0.026
Ciclosporin	6	0.420	0.0034
Butoconazole	4	0.420	0.025
Esculetin	3	0.419	0.022
Astemizole	5	0.418	0.0072
Perphenazine	5	0.416	0.016
Trifluoperazine	16	0.415	<0.00001
Protriptyline	4	0.409	0.023
Clozapine	17	0.408	<0.00001
Thioridazine	20	0.399	<0.00001
Gossypol	6	0.387	0.0052
Zuclopenthixol	4	0.381	0.020
Prestwick-685	5	0.373	0.010
Chlorcyclizine	6	0.372	0.0055
Alexidine	4	0.370	0.020
Chlorprothixene	4	0.367	0.020
Copper sulfate	4	0.354	0.029
Niclosamide	5	0.338	0.0078
0175029–0000	6	0.334	0.0055
Tetrandrine	4	0.332	0.029
Nicergoline	5	0.325	0.028
Isoconazole	5	0.313	0.0085
Flecainide	6	0.303	0.015
GW-8510	4	0.294	0.025
Terconazole	4	0.290	0.026
Valproic acid	57	0.276	0.0011
Troglitazone	16	0.264	0.0037
Metixene	4	0.261	0.020
Metformin	10	0.260	0.018
Maprotiline	4	0.253	0.019
Geldanamycin	15	0.242	0.017
Econazole	4	0.223	0.023

[15, 16]. Aberrations in these processes have been linked to mood disorder pathophysiology [17, 18].

Conversely, the thyroid hormone signaling pathway displayed evidence of decreased expression following treatment with mood stabilizers. Dysfunctional thyroid signaling compromises the modulation of growth, development, and metabolic processes [19]. There are reports of patients with mood disorders presenting evidence of altered or abnormal levels of thyroid hormones [20]. Indeed, thyroid dysfunction is common and affects treatment response in patients with bipolar disorder [21, 22]. Thyroid dysfunction is also associated with mood disorders [22], with both hypothyroidism and hyperthyroidism reportedly increasing the risk for mood disorders [23, 24].

Taken together, the GES appears to provide a biologically valid representation of the effects of the mood stabilizers, supporting its use for repurposing drugs to treat mood disorders using CMap. Drug repurposing, in which new indications are found for existing drugs, is an attractive alternative to conventional drug discovery paradigms. The drugs for repurposing already have clinical safety profiles, bioavailability data, and established manufacturing processes, which reduces the time and cost required to bring the drug to the (new) market [25].

Using the GES and CMap, 70 drugs were identified to alter gene expression most similar to the combination of mood stabilizers. It is promising that a number of drugs identified by the CMap analysis reflect known and proposed pathophysiological mechanisms of mood disorders. For example, while clozapine is indicated for use in treatment-resistant schizophrenia, there is evidence noting clozapine as an effective monotherapy for both severe bipolar disor-

▶ **Table 3** Drugs that can be potentially repurposed to treat mood disorders (MIMS = Monthly Index of Medical Specialties).

Compound	MIMS Category	Approved Indications
Prochlorperazine	Central nervous system – antiemetics, antinauseants	Nausea and vomiting. Vertigo.
Resveratrol[1]	Herbal and other complementary medicines – general well-being, multipurpose preparations, others	Reduce/decrease free radical damage to cells. Maintain/support cardiovascular system health. Enhance/improve/promote immune system function.
Phenoxybenzamine	Cardiovascular system – peripheral vasodilators	Phaeochromocytoma. Neurogenic urinary retention.
Rifabutin	Infections and infestations – antituberculotic and antileprotics	Prophylaxis of *Mycobacterium avium* complex infections. Treatment of Tuberculosis.
Ciclosporin	Immunology – immunomodifiers	Management of transplant rejection. Severe atopic dermatitis. Severe psoriasis. Nephrotic syndrome. Severe active rheumatoid arthritis.
Loperamide	Alimentary system – antidiarrheals	Diarrhea. Intestinal stoma.
Flecainide	Cardiovascular system – antiarrhythmic agents	Serious ventricular cardiac arrhythmias. Serious supra-ventricular cardiac arrhythmias.
Isotretinoin	Skin – acne, keratolytic, and cleansers	Severe cystic acne.
Metformin	Endocrine and metabolic disorders – hypoglycemic agents	Type 2 diabetes.

[1]Resveratrol is a complementary medicine with permitted indications rather than specific indications, granted by the Therapeutic Goods Administration.

der and depressive disorders [26–28]. Available literature supports the efficacy of clozapine in treating mood disorders, thus, the identification of clozapine by CMap provides confirmation of CMap's utility.

The non-steroidal anti-inflammatory drug (NSAID), bufexamac, detected by the CMap analysis, is also noteworthy. Inflammation likely plays a role in the pathophysiology of mood disorders, both disease progression and onset [29–31]. The potential of NSAIDs as adjunctive therapies for bipolar disorder and depressive disorders has been previously recognized [32–35].

Importantly, the CMap analysis identified metformin with its mechanism of action on the proposed features of mood disorder pathophysiology, demonstrating the theoretical potential for repurposing. Our pharmacoepidemiological study (Part B) provided longitudinal evidence suggesting that the probability of *de novo* mood disorder is likely to be lower in the presence of metformin, with exposure to metformin decreasing the likelihood of developing *de novo* mood disorders by 69 % over the 16.6 year study period.

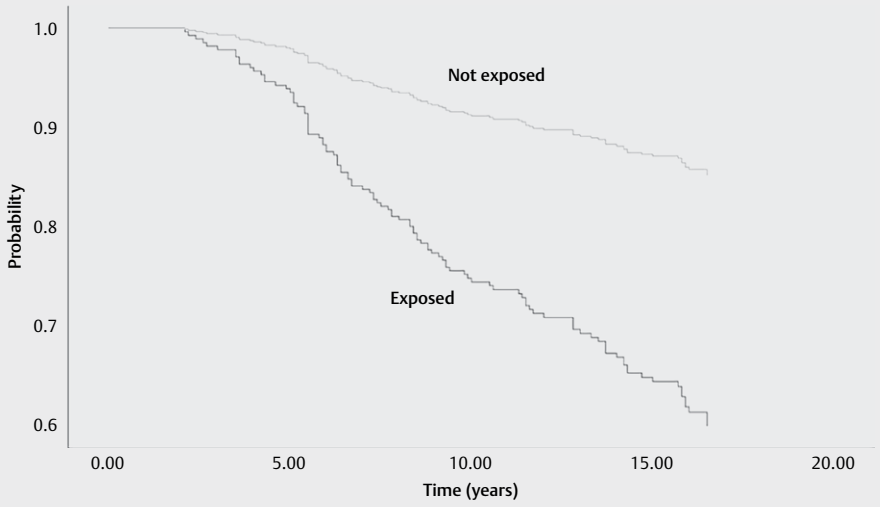
▶ **Table 4** Characteristics of participants according to exposure to metformin. Data are provided as mean (± standard deviation), median (interquartile range) or n (%).

	Exposed	Not exposed	p
	n = 27	n = 677	
Age (years)	64.2 (57.5–69.0)	47.4 (34.2–61.7)	< 0.001
Socioeconomic status			0.814
Quintile 1	4 (14.8 %)	122 (18.0 %)	
Quintile 2	6 (22.2 %)	129 (19.1 %)	
Quintile 3	4 (14.8 %)	149 (22.0 %)	
Quintile 4	7 (25.9 %)	128 (18.9 %)	
Quintile 5	6 (22.2 %)	149 (22.0 %)	
Weight (kg)	79.9 (65.9–94.9)	65.9 (59.2–74.7)	< 0.001
Height (cm)	158.5 (± 6.6)	161.5 (± 6.2)	0.027
Mobility (active)	15 (55.6 %)	531 (78.4 %)	0.005
Alcohol use (current)	17 (63.0 %)	587 (86.7 %)	0.002
Smoking (current)	5 (18.5 %)	255 (37.7 %)	0.043
Mood disorder (*de novo*)	4 (14.8 %)	102 (15.1 %)	0.971

Although not directly comparable to the current study, previous findings have shown metformin use to be associated with mood symptom reduction among patients with diabetes mellitus. A placebo-controlled trial of 58 men and women diagnosed with type 2 diabetes mellitus and comorbid depression treated with metformin for 24 weeks showed reduced depressive symptoms at 12 weeks compared to placebo [36]. In a clinical cohort study in the USA, 41,204 male veterans who were ≥ 65 years old with type 2 diabetes mellitus showed a reduction in depression in those treated with metformin over a period of 10 years [37]. Similarly, a Taiwanese population-based cohort study demonstrated that metformin use, in combination with sulfonylureas, reduced the risk of affective disorder incidence by 60 % [38]. However, in this study, they did not observe any association between metformin as a monotherapy and mood disorder incidence.

Evidence for metformin to treat mood disorders is also present in non-diabetic samples. In a recent placebo-controlled study of patients with treatment-resistant bipolar depression, those treated with metformin showed a significant improvement in depressive symptoms and global functioning [39]. A double-blind placebo-controlled study in patients with major depressive disorder demonstrated that 12 weeks of metformin treatment improved the antidepressant effects of fluoxetine compared with placebo [40]. A Swedish population-based study also observed an 80 % reduction in psychiatric hospitalizations, and a 73 % reduction in self-harm in bipolar disorder patients with exposed to metformin compared to those not exposed to metformin [41].

Surprisingly, for such an old drug that is commonly prescribed, little is known about the molecular mechanisms of the action of metformin. It reduces hepatic gluconeogenesis and insulin resistance in tissues such as skeletal muscle and adipose tissue. Given that insulin resistance and type 2 diabetes are more prevalent in people with bipolar disorder [42] and are associated with more severe symptoms and treatment resistance [43], it is hypothesized



▶ **Fig. 1** Survival curve (Kaplan-Meier) demonstrating the probability of remaining free of *de novo* mood disorders over a period of 16.6 years for women exposed and not exposed to metformin.

that the beneficial effects of metformin in bipolar disorder are mediated via a reduction in insulin resistance. Reversal of insulin resistance also improves endothelial function, which reduces blood-brain barrier permeability and may reduce the transfer of circulating pro-inflammatory cytokines from direct contact with the central nervous system [44]. Metformin also activates peroxisome proliferator-activated receptors (PPARs) [45], and animal studies have shown that PPAR agonists reduce neuro-inflammation, oxidative stress, and neuronal injury [46]. We suggest that the positive effects of metformin in mood disorders are mediated through a range of molecular mechanisms that collectively improve insulin resistance.

The present study had certain limitations. The GES was generated using human neuronal-like cells that were not reflective of a mood disorder disease state. Gene expression was measured after a single dose of the drugs and at a single time point. Limitations of the pharmacoepidemiological study include the small number of metformin users, the inability to investigate other agents identified via the CMap analysis and specific mood disorders, the inclusion of women only, and the potential of unrecognized confounding or confounding by indication. There is surprisingly little data comparing the effects of metformin in women versus men. A recent trial showed greater benefits of metformin in women with T2D compared with men, which was accompanied by an increase in insulin secretion not seen in the male study participants [47]. Replication studies will be required before definitive conclusions can be made in this regard. Considering the effects of sex hormones, a number of different models and populations have shown that estrogen contributes to and protects from insulin resistance.

In conclusion, this study provided preliminary, population-based evidence suggesting that metformin use may have therapeutic potential as an adjunctive or monotherapy for mood disorders. Future randomized controlled trials are warranted to test the efficacy of metformin in treating mood disorders. In times when the development of novel psychopharmaceuticals is no longer being prioritized and the understanding of mood disorder pathophysiology is lacking, the methods utilized by this study provide an attractive alternative to traditional drug discovery methods.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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