Evaluation of MAOA Gene Polymorphism on the Efficacy of Antidepressant Treatment and Craving Severity for Betel-Quid Use Disorder

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Article

Evaluation of MAOA Gene Polymorphism on the Efficacy of Antidepressant Treatment and Craving Severity for Betel-Quid Use Disorder

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Abstract: Betel quid (BQ) use disorder (BUD) is prevalent in many Asian countries, impacting approximately 600 million people. We conducted a randomized clinical trial to analyze the impact of MAOA genetic variations on the severity of BQ craving. This was measured using DSM-5 criteria and Yale-Brown Obsessive Compulsive Scale modified for betel-quid (Y-BOCS-BQ). Participants were grouped according to the severity of BUD and MAOA gene single nucleotide polymorphism (SNP) rs5953210 genotypes. Y-BOCS-BQ were assessed at baseline (week 0) and during follow-up at weeks 2, 4, 6, and 8. The AA genotype group showed significantly greater reductions in Y-BOCS-BQ at weeks 2 (p=0.0194), 4 (p=0.0078), 6 (p=0.0277), and 8 (p=0.0376) compared to the GG genotype group. Additionally, within the antidepressant group, the AA genotype showed significant reductions in Y-BOCS-BQ at weeks 2 (p=0.0313), 4 (p=0.0134), 6 (p=0.0061), and 8 (p=0.0241) compared to the GG genotype. Statistical analysis revealed a significant interaction between the treatment and placebo groups based on MAOA genotypes, with the AA genotype in the treatment group exhibiting a more pronounced decrease in Y-BOCS-BQ (p interaction <0.05) at week 6. These findings highlight the importance of considering genetic factors when developing personalized treatment plans for BUD.

Keywords: betel-quid use disorder; craving severity; MAOA gene polymorphism; personalized medicine; randomized clinical trial

1. Introduction

The Betel quid (BQ) use disorder (BUD) is a prevalently addictive disease in many Asian countries [1], affecting approximately 600 million people globally [2]. Betel quid (BQ), the fourth most popular psychoactive substance [3], is a group I human carcinogen that significantly increases the risk of oral potentially malignant disorders (OPMD) [4] and cancers of the oral cavity and pharynx

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[5,6]. This carcinogenic risk related to BQ consumption is particularly higher in regions like Taiwan, where oral and pharyngeal cancers are among the most common etiologies of morbidity and mortality in men [7].

The addictive nature and property of BQ is not entirely understood, but it is known to interact with monoamine oxidase inhibitors (MAOIs), impacting cellular neurotransmitter levels in the brain [8]. One of the key components of BQ, arecoline, exhibits MAO-A inhibitor-like properties, preventing the breakdown of neurotransmitters and increasing concentrations of dopamine and serotonin in the brain. This mechanism is similar to how certain antidepressants, such as MAOIs and SSRIs, function. Antidepressant drugs, including MAOIs and SSRIs, can reduce AN use in mice [9], potentially influencing BQ consumption among the individuals with depression. Studies have shown that antidepressant therapy with MAOIs and SSRIs can decrease daily BQ use in patients with depression [10,11].

The MAO-A genetic variations are associated with heavy BQ use, which positively correlate with MAO-A enzymatic activity levels in the human plasma [12]. Cell and animal models have revealed that AN (areca nut) and arecoline inhibit MAO-A mRNA and protein expression, and have MAO-A inhibitor-like properties. However, multiple gene variants in combination due to the genetic complexity of addiction diseases can explain a larger proportion of genetic contribution to BUD which will allow to improve the treatment strategies of addiction diseases [13].

Previously clinical evidence supports using antidepressants to treat BUD. The retrospective studies suggest that antidepressants can reduce BQ consumption and addiction severity in depressed patients. A clinical trial showed that antidepressants could effectively decreased BQ use within 2-4 weeks [11]. However, individual responses to treatment can vary significantly due to genetic differences, affecting the metabolism and efficacy of antidepressants in reducing BQ use, rendering different outcomes of the patients with BUD.

We conducted a clinical trial to investigate the response to antidepressant treatment for BUD in relation to MAOA gene polymorphism. The primary objective of this study was to enhance BUD therapy by developing reliable biomarkers. Specifically, we examined the impact of MAOA genetic variations on the severity of betel-quid craving. Incorporating genetic biomarkers can improve diagnostic accuracy and enable personalized treatment by considering genetic differences among patients.

2. Results and Discussion

2.1. Basic Demographic Information of the Study Subjects

Table 1 presents the characteristics of study subjects across the Treatment (N=35) and Placebo (N=15) groups. The mean age of the treatment group is 44.34 years (SD=8.93), while the placebo group has a mean age of 43.07 years (SD=8.40), with a p-value of 0.64. The average frequency of BQ use is 5.54 days per week (SD=2.33) in the treatment group and 6.13 days per week (SD=1.81) in the placebo group, with a p-value of 0.39. The mean amount of BQ used in the treatment group is 50.97 (SD=55.73), compared to 36.27 (SD=39.64) in the placebo group, with a p-value of 0.36. Regarding DSM 5 criteria for BQ, tobacco, and alcohol, as well as SUSRS scores, there are no significant differences between the treatment and placebo groups. Additionally, the Y-BOCS-BQ scores show no significant difference between the treatment and placebo groups from baseline to week 8 of the clinical trial.

Table 1. Basic Characteristics of Study Subjects and Follow-Up of Y-BOCS-BQ.

Variables	Treatment Group (N=35)	Placebo Group (N=15)	
	Mean (SD)	Mean (SD)	P-Value
Age	44.34 (8.93)	43.07 (8.40)	0.64
Days of BQ Consumption	5.54 (2.33)	6.13 (1.81)	0.39
BQ Amount	50.97 (55.73)	36.27 (39.64)	0.36
DSM-5 BQ	6.57 (2.50)	6.80 (2.54)	0.77

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DSM-5 Tobacoo	7.26 (2.80)	6.00 (3.85)	0.20
DSM-5 Alcohol	2.74 (3.62)	2.47 (3.58)	0.81
SUSRS BQ	13.31 (5.40)	13.47 (4.02)	0.92
SUSRS Tobacoo	13.60 (4.53)	12.67 (5.65)	0.54
SUSRS Alcohol	6.34 (6.83)	6.00 (7.76)	0.88
Y-BOCS-BQ Week 0	28.37 (9.84)	29.73 (8.48)	0.64
Y-BOCS-BQ Week 2	21.74 (15.61)	22.07 (10.91)	0.94
Y-BOCS-BQ Week 4	18.20 (15.70)	15.93 (9.38)	0.61
Y-BOCS-BQ Week 6	18.00 (16.10)	15.87 (15.04)	0.66
Y-BOCS-BQ Week 8	15.97 (17.79)	18.40 (16.60)	0.65

Abbreviation: BQ: betel-quid. DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. SUSRS: Substance Use Severity Rating Scale. Y-BOCS-BQ: Yale-Brown Obsessive Compulsive Scale modified for betel-quid; Scores are presented as Mean (SD: Standard Deviation). P-values indicate the significance of the difference between the treatment and placebo groups for each variable.

2.2. Association between Severity of BUD and Their Follow-Up of Y-BOCS-BQ

Table 2 presents the association between the severity of BUD and follow-up Y-BOCS-BQ scores. At week 0, the severe BUD group has a mean Y-BOCS-BQ score of 31.6 (SD=8.5), compared to 22.7 (SD=8.3) in the non-severe BUD group, with a p-value of 0.0011. At week 2, the severe BUD group scores 24.6 (SD=14.7) versus 16 (SD=11.6) in the non-severe BUD group, with a p-value of 0.0457. At week 4, the severe BUD group scores 20.5 (SD=16.6), while the non-severe BUD group scores 11.2 (SD=10.1), with a p-value of 0.0272. Significant differences in Y-BOCS-BQ scores are observed between severe and non-severe BUD groups at weeks 0, 2, and 4, but not at weeks 6 and 8.

Table 2. Association Between the Severity of BUD and Their Follow-Up of Y-BOCS-BQ.

Varibles	Severe BUD (N=34)	Non-Severe BUD (N=16)	P-value
Y-BOCS-BQ Week 0	31.6 (8.5)	22.7 (8.3)	0.0011**
Y-BOCS-BQ Week 2	24.6 (14.7)	16 (11.6)	0.0457*
Y-BOCS-BQ Week 4	20.5 (16.6)	11.2 (10.1)	0.0272*
Y-BOCS-BQ Week 6	17.7 (16.6)	16.6 (14)	0.8227
Y-BOCS-BQ Week 8	18.7 (18.4)	12.4 (14.4)	0.2292

Abbreviations: BQ: betel-quid. BUD: Betel-Quid Use Disorder. Y-BOCS-BQ: Yale-Brown Obsessive Compulsive Scale modified for betel-quid. Scores are presented as Mean (SD: Standard Deviation). P-values indicate the significance of the difference in scores between severe and non-severe BUD groups at each time point of visit. *$p < 0.05$ and **$p < 0.01$, statistical significance between groups.

2.3. Association between MAOA Gene Polymorphism (rs5953210) and Follow-Up of Y-BOCS-BQ Scores in Betel-Quid Use Disorder Patients

Table 3 presents the association between the MAOA gene SNP rs5953210 and follow-up Y-BOCS-BQ scores. The data compares the mean Y-BOCS-BQ scores between two genotype groups: AA (n=22) and GG (n=28). No significant difference between the two genotype groups was observed at week 0. However, the AA genotype is associated with significantly greater reductions in Y-BOCS-BQ scores at weeks 2 (p = 0.0194), 4 (p = 0.0078), 6 (p = 0.0277), and 8 (p = 0.0376) compared to the GG genotype. Specifically, the craving score in the AA genotype group decreased from 27.0 at week 0 to 11.0 at week 8. In contrast, the craving score in the GG genotype group decreased from 30.2 at week 0 to 21.2 at week 8.

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Table 3. Association Between MAOA Gene Polymorphism (rs5953210) and Follow-Up of Y-BOCS-BQ Scores in Betel-Quid Use Disorder Patients.

	rs5953210		
Varibles	AA (n=22)	GG (n=28)	
	Mean (SD)	Mean (SD)	P-value
Y-BOCS-BQ Week 0	27.0 (9.8)	30.2 (8.9)	0.2266
Y-BOCS-BQ Week 2	16.6 (13.1)	26.0 (13.9)	0.0194*
Y-BOCS-BQ Week 4	11.7 (12.1)	22.1 (13.9)	0.0078**
Y-BOCS-BQ Week 6	11.9 (13.7)	21.6 (15.9)	0.0277*
Y-BOCS-BQ Week 8	11.0 (15)	21.2 (17.7)	0.0376*

Abbreviations: BQ: betel-quid. MAOA: Monoamine Oxidase A. SNP: Single Nucleotide Polymorphism. Y-BOCS-BQ: Yale-Brown Obsessive Compulsive Scale modified for betel-quid. Scores are presented as Mean (SD: Standard Deviation). P-values indicate the significance of the difference in scores between AA and GG genotypes at each time point of visit. *p < 0.05 and **p < 0.01, statistical significance between groups.

2.4. Differential Treatment Response Based on Y-BOCS-BQ Scores and Severity of BUD in Antidepressant and Placebo Groups

Table 4 presents the different treatment responses for follow-up YBOCS-BQ scores and the severity of BUD in the antidepressant and placebo groups. In the antidepressant group, there is a significant difference in YBOCS-BQ scores at baseline (week 0) between the Severe and Non-Severe groups (p=0.0006). However, after the initiation of antidepressant treatment, YBOCS-BQ scores do not show significant differences during the follow-up period. In the placebo group, no significant differences are observed in YBOCS-BQ scores between the Severe and Non-Severe groups at any follow-up week.

Table 4. Differential Treatment Response Based on Y-BOCS-BQ Scores and Severity of BUD in Antidepressant and Placebo Groups: A Randomized Clinical Trial.

	Treatment Group			Placebo Group		
	Severe (n=23)	Non-Severe (n=12)		Severe (n=11)	Non-Severe (n=4)	
	Mean (SD)	Mean (SD)	P-value	Mean (SD)	Mean (SD)	P-value
Y-BOCS-BQ Week 0	32.2 (9.3)	21 (6.1)	0.0006**	30.5 (7.0)	27.8 (12.9)	0.6037
Y-BOCS-BQ Week 2	24.7 (16.5)	16.1 (12.5)	0.1229	24.4 (10.7)	15.8 (9.9)	0.1857
Y-BOCS-BQ Week 4	21.5 (16.8)	11.8 (11.4)	0.0829	18.4 (9.4)	9.3 (5.7)	0.0969
Y-BOCS-BQ Week 6	20.1 (17.9)	14.0 (11.5)	0.2952	12.7 (12.9)	24.5 (19.2)	0.1898
Y-BOCS-BQ Week 8	18.4 (19.4)	11.3 (13.8)	0.2629	19.4 (17.0)	15.8 (17.6)	0.7238

Abbreviations: BQ: betel-quid. BUD: Betel-quid Use Disorder. Y-BOCS-BQ: Yale-Brown Obsessive Compulsive Scale modified for betel-quid. Scores are presented as Mean (SD: Standard Deviation). P-values indicate the significance of the difference between severe and non-severe BUD groups within each treatment group (antidepressant and placebo) at each time point. **p < 0.01, statistical significance between groups.

2.5. Differential Response of MAOA Gene Polymorphism on Antidepressant Treatment Efficacy and Craving Severity in BUD

Table 5. presents the different treatment responses for follow-up YBOCS-BQ scores based on MAOA gene genotypes in the antidepressant and placebo groups. the AA genotype in the treatment group showed significant reductions in YBOCS-BQ scores at weeks 2 (p = 0.0313), 4 (p = 0.0134), 6 (p

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= 0.0061), and 8 (p = 0.0241) compared to the GG genotype. However, no significant differences were observed in the placebo group at any time point of visit.

Table 5. Differential Response of MAOA Gene Polymorphism on Antidepressant Treatment Efficacy and Craving Severity in BUD: A Randomized Clinical Trial.

	Treatment Group			Placebo Group		
	AA (n=15)	GG (n=20)		AA (n=7)	GG (n=8)	
	Mean (SD)	Mean (SD)	P-value	Mean (SD)	Mean (SD)	P-value
Y-BOCS-BQ Week 0	26.2 (10.7)	30 (9.1)	0.2644	28.6 (8.0)	30.8 (9.3)	0.6374
Y-BOCS-BQ Week 2	15.3 (14.7)	26.6 (14.7)	0.0313*	19.4 (8.9)	24.4 (12.5)	0.4011
Y-BOCS-BQ Week 4	10.8 (13.7)	23.8 (15.0)	0.0134*	13.6 (8.0)	18 (10.5)	0.3814
Y-BOCS-BQ Week 6	9.7 (11.4)	24.3 (16.5)	0.0061**	16.7 (17.7)	15.1 (13.5)	0.8469
Y-BOCS-BQ Week 8	8.3 (13.5)	21.8 (18.7)	0.0241*	16.9 (18.3)	19.8 (16.0)	0.7498

Abbreviations: BQ: betel-quid. BUD: Betel-quid Use Disorder. MAOA: Monoamine Oxidase A. Y-BOCS-BQ: Yale-Brown Obsessive Compulsive Scale modified for betel-quid. Scores are presented as Mean (SD: Standard Deviation). P-values indicate the significance of the difference in scores between AA and GG genotypes within each treatment group (antidepressant and placebo) at each time point of visits. *p < 0.05 and **p < 0.01, statistical significance between groups.

Additionally, the Figures S1–S5 (Supplementary Figures) illustrate the interaction between MAOA genotypes and follow-up YBOCS-BQ scores. In comparisons of the treatment and placebo groups in week 6 (Figure S4), the data points are plotted for two genotypes: AA (blue) and GG (red). And statistical analysis reveals a significant interaction between the treatment and placebo groups based on MAOA genotypes. The treatment group exhibits a more pronounced decrease in YBOCS-BQ scores for the AA genotype compared to the GG genotype (p interaction <0.05). In contrast, the placebo group does not show significant changes.

2.6. Discussion

Our study investigates the effects of the MAOA gene SNP rs5953210 on BUD treatment outcomes using the YBOCS-BQ scores. The results reveal significant gene and treatment interactions. Subjects with the AA genotype of rs5953210 exhibit greater reductions in YBOCS-BQ scores over time compared to those with the GG genotype, particularly in the treatment group. No significant differences are observed between the AA and GG genotypes in the placebo group. Statistical analysis confirms significant differences in YBOCS-BQ scores between severe and non-severe BUD groups at weeks 0, 2, and 4, but not at weeks 6 and 8. The treatment group, especially those with the AA genotype, shows significant reductions in YBOCS-BQ scores at weeks 2, 4, 6, and 8 compared to the GG genotype, indicating a more pronounced decrease in craving symptoms.

The polymorphisms of MAOA gene are associated with different types of addictive substances and illicit drugs, with varying results across different populations and substances. The MAOA variable-number tandem repeat (VNTR) polymorphism has been studied in relation to alcohol use disorder [24–27], as well as various types of substance and drug addiction [28–30]. Fite et al. (2019) found that MAOA VNTR variants influence polysubstance use, with this relationship being moderated by childhood emotional or physical abuse in a sex-specific manner [31]. Sun et al. (2017) identified an association between the MAOA rs1137070 C allele and heroin addiction in Chinese individuals [32]. Conversely, Chien et al. (2010) found no link between the MAOA promoter VNTR polymorphism and heroin addiction in Chinese men [30]. Hung et al. (2024) identified an association between the MAOA rs5953210 variant and patients with severe BUD [13]. The underlying mechanisms by which the MAOA gene is associated with substance use disorders and illicit drug use are not yet fully understood but are likely due to overlapping neurobiological pathways.

Monoamine oxidases (MAOs) A and B are mitochondrial-bound isoenzymes that catalyze the oxidative deamination of dietary amines and neurotransmitters such as serotonin, norepinephrine, dopamine, beta-phenylethylamine, and other trace amines [33]. This rapid degradation is crucial for

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maintaining proper synaptic neurotransmission and regulating emotional behaviors and brain functions [34]. MAOA, primarily found in dopaminergic neurons, and MAOB, mainly expressed in serotonergic neurons, both contribute to the etiology of addiction disorders [35]. The dopamine system plays a central role in the biology of BUD. Cell and animal models have shown that AN and arecoline inhibit MAOA mRNA and protein expression, exhibiting monoamine oxidase inhibitor (MAOI)-like properties [12]. Arecoline (AN) primarily increases serotonin levels, likely through MAO-A inhibition, preventing neurotransmitter breakdown and thereby increasing dopamine and serotonin concentrations in the brain [36]. AN has potential antidepressant effects by elevating serotonin and noradrenaline levels. Thus, the use of MAOIs may have clinical benefits for BQ cessation among heavy BQ users. Antidepressant therapy has been observed to reduce daily BQ use in patients with depression [11]. Currently, no pharmacologically-based cessation therapies are available to alleviate symptoms in patients with BUD who intend to reduce or quit BQ use. Our study found that different MAOA genotypes exhibit varying responses to antidepressant treatment. This finding enables the identification of individuals who respond well to antidepressant therapy. Since not all patients seem to benefit from antidepressants, the use of genetic testing might be important in improving the effectiveness of treatment with MAOA inhibitors.

2.7. Study Limitations

There are several limitations in this study that warrant consideration. Firstly, our study included only limited phenotypic and genotypic information, indicating the necessity for genotyping additional novel susceptibility genes identified by genome-wide association studies. Secondly, this study is the first randomized clinical trial to evaluate the efficacy of MAOA and SSRI antidepressants for betel-quid cessation treatment. However, as a pioneering study with a relatively small sample size, it provides only preliminary evidence, necessitating replication in larger trials to validate these findings.

3. Materials and Methods

3.1. Study Participants

The study recruited participants from the cancer centers of the Department of Dentistry and the Department of General Physicians at China Medical University Hospital in Taichung, Taiwan, between January 2016 and April 2019. A total of 50 patients with betel quid (BQ) chewing habits were enrolled. Data on their basic demographic characteristics were collected, and the clinical features related to their BQ addiction were assessed. All participants provided informed consent and underwent clinical interviews conducted by a psychiatrist. BQ use disorder (BUD) was diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. The diagnosis of BUD was determined by the presence of at least two of the following 11 symptoms within the past year: (1) extensive or prolonged BQ consumption, (2) unsuccessful attempts to reduce BQ use, (3) significant time spent chewing, (4) cravings, (5) neglect of major responsibilities, (6) social or interpersonal issues, (7) abandoning activities, (8) hazardous use, (9) continued use despite awareness of problems, (10) tolerance, and (11) withdrawal. BUD severity was classified as mild (2–3 symptoms), moderate (4–5 symptoms), or severe (≥6 symptoms). Severe BUD subjects were classified as symptoms more than 6 of DSM-5 for BUD while Non-Severe BUD less than 6.

Participants were excluded if they: (1) abused illegal substances (e.g., heroin, amphetamines), (2) had major psychiatric disorders (e.g., schizophrenia, bipolar disorder, major depressive disorder, antisocial personality disorder), (3) had organic brain conditions (e.g., cerebrovascular disease, brain tumor, head injury), (4) had any form of cancer or cancer-related disease, or (5) were unable to understand or speak Chinese. The study psychiatrist conducted semi-structured diagnostic interviews and systemic reviews for psychiatric and addictive disorders [14–16]. Cancer diagnoses were confirmed at the study hospital's cancer center, while neurological or other brain disorders were identified based on patient self-reports of their medical histories.Patients diagnosed with anxiety disorders or sleep disturbances and those with habits of consuming alcohol, cigarettes, caffeine, or

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hypnotics were not excluded if their hypnotic dosage had been consistent over the past year and they did not meet more than six criteria for other substance use disorders in the past year.

Information regarding the initial age of BQ consumption, daily BQ consumption amount, and weekly consumption frequency was collected for all BUD patients. Oral hygiene was assessed using the visual analog scale (VAS), and data on the number of broken teeth and daily tooth brushing frequency were obtained through self-reports. The study was approved by the China Medical University and Hospital, Chung Shan Medical University Hospital Research Ethics Committee (CMUH103-REC1-059, CMUH106-REC1-016, CSMUH No: CS1-23163).

3.2. Psychometric Measures of Addiction Severity

To establish a definitive diagnosis and assess the severity of BQ use disorder (BUD), we applied and employed previously validated DSM-5 criteria [1]. The Substance Use Severity Rating Scale (SUSRS) was utilized to evaluate BQ and alcohol consumption, as well as cigarette smoking habits. The SUSRS, developed based on the DSM-IV and the International Classification of Diseases, Eleventh Revision (ICD-11) [15], comprises 21 items that measure the severity of substance use addiction. It has been widely applied in assessing alcohol consumption, cigarette smoking, and drug use[17,18]. In this study, a rater assessed participants' substance use with yes-or-no questions, assigning a score of 1 for "yes" and 0 for "no". Additionally, the Yale–Brown Obsessive Compulsive Disorder Rating Scale for betel quid (Y-BOCS-BQ) was used to determine the severity of BQ craving [19,20]. The Y-BOCS-BQ is specifically designed to measure the behavioral problems associated with BQ use [21,22] and is commonly employed to analyze the severity of cravings in substance abuse [23].

3.3. DNA Extraction and Genotyping

The genomic DNA was extracted from peripheral blood samples using the Puregene DNA Isolation Kit (Gentra Systems, Minneapolis, MN, USA) following the manufacturer's instructions. Genotyping of the MAOA SNPs was performed using the Sequenom MassARRAY System at the Academia Sinica National Genotyping Center (Taipei, Taiwan).

3.4. Methods of Statistical Analysis

The statistical analysis was performed using SAS 9.4 software (Cary, NC, USA). Genotype frequencies in the control population were tested for Hardy–Weinberg equilibrium, with differences between observed and expected genotype numbers compared using the chi-square test. Hardy–Weinberg equilibrium was assumed for p values > 0.05. T-tests were applied to compare the demographic information of BUD patients and the conditions of antidepressant treatment. Since no healthy controls were included in the study, we combined the mild and moderate BUD groups into a non-severe BUD group, which served as the statistical control. A logistic regression analysis model was used to investigate the association between SNPs and the severity of BUD. Mixed models and General Linear Models were used to compare the means and interactions of quantitative variables between the genotypes.

4. Conclusions

These findings highlight the critical role of genetic factors in developing medical therapies for BUD, emphasizing the interaction between MAOA genotypes and antidepressant treatment in mitigating craving scores.Customizing treatment strategies based on individual genetic profiles can significantly enhance the efficacy of interventions for BUD. Identifying genetic biomarkers would improve the accuracy of BUD diagnosis and facilitate personalized treatment approaches by accounting for genetic differences among patients.

Significance Statement: To our knowledge, this manuscript is the first investigation to study the roles of the MAOA genotypes in the treatment effects of antidepressant in BUD patients. Meanwhile, this study also worked out the core symptom of addiction as craving defined by Y-BOCS-BQ scores significant association during the antidepressant treatment of BUD patients.

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Institutional Review Board Statement: This clinical trial was approved by the China Medical University and Hospital, Chung Shan Medical University Hospital Research Ethics Committee. This clinical trial is registered in a public database for clinical studies (ClinicalTrials.gov, ID: NCT 03010761).

Informed Consent Statement: All participants provided written informed consent.

Conflicts of interest: The authors declare that there are no conflicts of interest.

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