Affective disturbances in individuals with methylphenidate use disorder at abstinence

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Research article

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Abstract

Background

Methylphenidate, mainly sold under the trade name Ritalin, is used to clinically treat attention-deficit/hyperactivity disorder (ADHD). There has been an increase in the prevalence of the nonmedical use of methylphenidate among adolescents in the past 30 years.

Methods

Here, we retrospectively analyzed a clinical dataset of 61 individuals with methylphenidate use disorder who were admitted to a drug rehabilitation program at Beijing Gaoxin Hospital from January 2017 to March 2019.

Results

The results showed that the majority of individuals with methylphenidate use disorder were adolescents, and the onset of drug use was mainly driven by academic purposes. The abstinence period was accompanied by severe anxiety and depression symptoms in these subjects, and these symptoms were significantly alleviated following four weeks of treatment. In addition, high levels of social support is associated with better affective states.

Conclusion

To sum up, methylphenidate use disorder individuals are associated with mood disturbances at abstinence, which might be implicated in clinical management strategies.

1. Introduction

Methylphenidate, mainly sold under the trade name Ritalin, is a prescription psychostimulant that increases the dopamine concentration by targeting the dopamine transporter. Methylphenidate is approved as a pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD), and narcolepsy (1). In addition, previous studies have reported the efficacy of methylphenidate as a replacement therapy for individuals with methamphetamine use disorder (2, 3).

Oral intake of methylphenidate at a normal dosage does not elicit reinforcing effects. On the other hand, intravenous infusion of methylphenidate is considered potentially addictive (4), which can be explained by the sharp increase in dopamine in the striatum detected by (positron emission tomography) PET imaging (5). In the United States, there has been an increase in the prevalence of the nonmedical use of methylphenidate among high school students in the past 30 years (from 0.1%-0.7% to 2.2–2.8%) (6). In

Switzerland, 4.0% of secondary school students reported using methylphenidate for nonmedical purposes (7). Moreover, 23% of adolescents reported using methylphenidate when they were referred for substance abuse assessment, 6% of whom were diagnosed with methylphenidate use disorder (8). Most users report intaking methylphenidate via injections or sniffing, while few users report oral intake of pills.

In China, methylphenidate has been listed as a first-class psychotropic drug by the National Medical Products Administration (NMPA) since 2007. However, there has been a rapid increase in the nonmedical use of prescribed medicine in China (estimated prevalence of 6%), including methylphenidate (9). Multiple reasons can contribute to the prescription medicine misuse, such as internal personality characteristics like self-efficacy and external environment influence like social support (10–12). Therefore, the present study retrospectively analyzed the clinical characteristics of 61 subjects with methylphenidate use disorder who used oral administration. Putative factors that may affect drug use and withdrawal symptoms were explored.

2. Method

2.1 Clinical data

We retrospectively analyzed the clinical characteristics of 61 subjects with methylphenidate use disorder (aged 16–27 years, according to the criteria of stimulant use disorder of DSM-5 diagnosis) who were admitted to the Beijing Gaoxin Hospital drug rehabilitation program from Jan 2017 to Mar 2019. The drugs that patients administrated was “NOVARTIS” Ritalin. Patients medication history were obtained through self-report or from their parents. There was no concurrent use of other medications. All the participants were screened for Magnetic resonance imaging (MRI) and a range of psychiatric symptoms on admission, such as Brief Psychiatric Rating Scale (BPRS), Scale for Assessment of Positive Symptoms (SAPS), Scale for Assessment of Negative Symptoms (SANS), Bech-Rafaelsen Mania Rating Scale (BRMS), and DSM-5 diagnostic criteria for Attention-Deficit/Hyperactivity Disorder (ADHD), to rule out other psychiatric disorders. No subject had attention-deficit/hyperactivity disorder (ADHD) or any other major psychiatric disease. All subjects reported a long history of methylphenidate oral administration at high doses and exhibited withdrawal symptoms after cessation. All patients continuously took methylphenidate before or on the day of admission, according to the self-report and parents report. The patients were hospitalized with psychotherapy and medication. In the medication treatment, patients with sleep disorders were prescribed benzodiazepines (estazolam; Apazolam; chloritazepam), Imidazole pyridine (Zonpyrenite) and The third generation of the hypnotic drug of the cyclopyrrosterone. Patients with anxiety symptoms took benzodiazepines (Laura zipani) and non-benzodiazepines antianxiety drug (buspirone). Patients with depression symptoms were prescribed Serotonin reuptake inhibitors, Citalopram, paroxetine and Atypical antidepressants, such as trazodone. The medication was given according to patients individualized conditions. In the psychotherapy, mindfulness therapy and cognitive behaviour therapy were applied. Four participants were discharged after two weeks of treatment, 11 were discharged after three weeks of treatment, and the remaining 46

participants were discharged after four weeks of treatment. The study was approved by the Ethics Committee for Medical Research of Beijing Gaoxin Hospital.

2.2 Neuropsychological evaluations

Upon admission to the hospital, information about drug use was collected, and the Social Support Self-Rating Scale (SSRS)(13), General Self-Efficacy scale (GSE)(14), and drug use motivation scale(15) were administered. The Hamilton Depression Rating Scale, Hamilton Anxiety Rating Scale and the DSM-5 measure were administered by one specialized psychiatrist each week during the 4-week rehabilitation program.

The Social Support Self-Rating Scale (SSRS) is one of the most commonly used instruments for measuring social support in China. The scale has three dimensions: subjective support, objective support and support-seeking behavior. The total SSRS score ranged from 12 to 66. A higher score indicates a higher level of perceived social support.

The drug use motivation scale has six dimensions: social pressure, values to drug use, environmental factors, physical symptoms, negative emotion and high sensation-seeking. The total score ranged from 32 to 224. A higher score indicates a higher level of drug use motivation.

For the Hamilton Depression Rating Scale (HAMD-17), a total score ranging from 0–7 was considered normal, scores ranging from 8–16 indicate mild depression, scores ranging from 17–23 indicate moderate depression, and scores greater than 23 indicate severe depression. The HAMD-17 contains five factors: (1) anxiety/somatic, (2) weight, (3) cognitive dysfunction, (4) stuck, and (5) sleep difficulty.

For the Hamilton Anxiety Rating Scales (HARS), a total score ranging from 0–6 indicates a normal condition, scores ranging from 7–13 indicate mild anxiety, scores ranging from 14–20 indicate moderate anxiety, and scores above 20 indicate severe anxiety.

2.3. Statistical analysis

All data analysis was performed with R Studio 1.0.153.0 (RStudio, Inc) and SPSS v. 21 (IBM Corp., NY, USA). Pearson’s and Spearman’s correlation analyses were used to analyze the relationship between demographic information and clinical outcomes of participants. Kernel density curve estimation was used to explore the distribution of participants' demographic data, such as age, Body Mass Index (BMI), and age at first drug use. Pearson’s correlation analysis was used to examine the correlation between baseline levels and posttreatment levels of anxiety and depression, as well as BMI and daily dosage (gram). Three linear regression models were employed to investigate the potential predictors for daily dosage, depression and anxiety. In model 1, the dependent variable was the daily dosage, and the independent variables were addiction year and total score of drug use motivation, social support self-rating scale and self-efficacy scale. In model 2 and 3, the dependent variables were depression and anxiety score separately. The independent variables were daily dosage, the total score of drug use

motivation, social support and self-efficacy. The overall statistical significance threshold was set as two-tailed, $p < 0.05$.

3. Result

3.1 Demographics of participants

The demographic information is presented in Table 1. Most subjects were males (51 out of 61). The mean age was 19.607 years old (*SD* = 1.891). Thirty-two participants had a high school education, 14 had a junior high school education, and 10 participants were undergraduates. Two-thirds of the participants lived in the city (*n* = 41), and one-third lived in rural areas (*n* = 20). Eighteen out of 61 participants were first introduced to methylphenidate by parents, 19 were introduced by friends and 24 discovered the drug on their own. The most common reason for beginning to use methylphenidate was to improve studying.

The subjects reported scores greater than six on the measure of substance use disorder (DSM-5), indicating severe substance use disorder (M = 9.426, SD = 0.8388). Subjects were usually between 14 and 16 years old at the first use of methylphenidate (M = 16.803, SD = 2.1257), which is at the high school admission stage. In the present population, we did not detect a positive correlation between BMI and the intake dosage (gram) (r = 0.126, *p* = 0.3347) (Fig. 1D).

3.2 Alterations of mood states during abstinence

The subjects reported high levels of anxiety and depression upon admission, and these factors were significantly correlated with each other (*r* = 0.418, *p* < 0.001) (Fig. 2A). During the abstinence period, the anxiety and depression scores continuously decreased (Fig. 2B). Notably, the change in anxiety scores was not correlated with the change in depression scores (*r* = 0.04032, *p* = 0.758) (Fig. 2C).

3.3 Factors affecting daily dosage and mood status

In the linear regression model, only the negative emotion factor of the drug use motivation scale was positively associated with daily dosage ($F(1,59) = 7.393$, $R^2 = 0.111$, $p = 0.0086$) (Fig. 3A). The social pressure factor of the drug use motivation scale marginally positively associated with daily dosage ($F(1,59) = 3.367$, $p = 0.0716$), but not enter the model. None of the other variables, such as addiction years, self-efficacy score and social support score, were enter in the model. More details can be seen in table 2.

In terms of factors that contributed to the depressive and anxiety symptoms, the total score of SSRS showed a significant negative association with baseline depression and anxiety scores (depression: $F(1,59) = 8.907$, $R^2 = 0.131$, $p = 0.0041$, anxiety: $F(1,59) = 102.4$, $R^2 = 0.635$, $p < 0.0001$) (Fig. 3B, Fig. 3C). The daily dosage was neither associated with depression score nor anxiety score ($F(1,59) = 1.719$, $p = 0.195$ and $F(1,59) = 0.0007677$, $p = 0.978$, respectively).

4. Discussion

The present study revealed that the oral intake of methylphenidate at a high dosage could trigger severe abuse-related mood disturbances. Affective disturbances have been reported among individuals with different substance use disorders (SUDs), including those with additions to methamphetamine, alcohol, nicotine, and heroin (16, 17). The presence of mood disorders at abstinence could indicate the need for targeted management (e.g., the administration of antidepressants) among individuals with methylphenidate use disorder.

The disruption of mesolimbic dopamine transmission, the decrease of the neurotrophic factor, and alterations in opioid receptor signaling have been implicated in the altered affective processing observed during abstinence from substances, including other psychostimulants (e.g., methamphetamine) (18–20). Animal studies have reported that withdrawal from methylphenidate increases midbrain neural activity and alters the stress sensitivity system (21). Clinical studies have reported depression, fatigue, loss of appetite, and even movement disorders (e.g., dystonia) in subjects experiencing abstinence from methylphenidate (22, 23). Future studies are required to further elucidate the clinical characteristics and neural mechanisms underlying methylphenidate abstinence.

The results demonstrated a positive correlation between negative emotion, social pressure and the amount of daily dosage in these subjects. Most subjects likely began to take methylphenidate to increase study/work capacity (24, 25), aiming to relieve school competition (Busardò., Kyriakou. (26) and productivity-related demands (27–29). All these results suggested that academic stress might facilitate the formation of methylphenidate use disorder. Besides, the lack of relevant knowledge leads to the misunderstanding of Ritalin in parents populations. Therefore, they hold the wrong belief that Ritalin can facilitate the academic performance of their children with no harm. It further promotes the abuse of Ritalin.

The dose-dependence effect on anxiety and depression was not observed in this study. Previous study indicated that the dosage and route of Heroin administration had a significant impact on withdrawal scores. Injectors and high dosage participants showed higher withdrawal severity (30). In smokers, smokers with higher cigarettes consumptions have shorter withdrawal latency (31). The lack of the dose-dependent effect may be due to the insufficient measure of withdrawal symptoms. We only measured the anxiety and depression score. Therefore, it may weaken the potential dose-dependent effect.

On the other hand, strengthening social support might alleviate mood disturbances. Social support has stress-buffering effects which reduce the probability of prescription medicine non-medical use (11). Besides, previous studies suggested that social support plays important roles in reducing the risk of substance use disorder formation and increasing the rate of successful cessation (32). Therefore, providing social support may contribute to better clinical outcomes in subjects with methylphenidate use disorder.

The study is limited in several aspects. First, the cross-sectional study covered 4 weeks of the in-hospital period. Longer follow-up durations are required to understand the relapse status of these subjects. Second, it will be helpful to perform neuroimaging examinations to elucidate the potential structural and

functional changes in the brain network underlying methylphenidate use disorder. Third, it will be interesting to compare these subjects to individuals with other psychostimulants (e.g., methamphetamine) use disorders in terms of clinical symptom severity and other neuropsychological performances. Moreover, we only measured the mood disturbances of the methylphenidate use disorder individuals at abstinence. Further study should measure the withdrawal symptoms more comprehensively. Last but not least, in the present study, not all the potential factors that may relate to drug use characteristics and mood disturbance were the measure, future studies are required to explore the potential factors more comprehensively.

In conclusion, the present study reported disrupted affective states in individuals with methylphenidate use disorder at abstinence. Negative emotion status acts as an important predictor for clinical severity and is potentially a target for the clinical management of these subjects.

Declarations

Financial Disclosures

The authors reported no conflicts of interest.

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Data availability

The original data are available from the corresponding author upon request.

Code availability

All data analysis was performed with R Studio 1.0.153.0 (RStudio, Inc) and SPSS v. 21 (IBM Corp., NY, USA).

Ethics approval

The study was approved by the Ethics Committee for Medical Research of Beijing Gaoxin Hospital.

Consent to participate

All participants provided written informed consent.

Consent for publication

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

Authors' contributions

Jie Xu: Conceptualization, Validation, Investigation, resources, data curation, supervision, project administration.

Ti-Fei Yuan: Conceptualization, supervision, Methodology, writing-review & Editing, Funding acquisition.

Yi Zhang: Methodology, Software, Formal analysis, writing-Original Draft, Visualization.

Pei Sun: writing-review & Editing.

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Not applicable

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Tables

Tables 1 and 2 are not available with this version

Figures

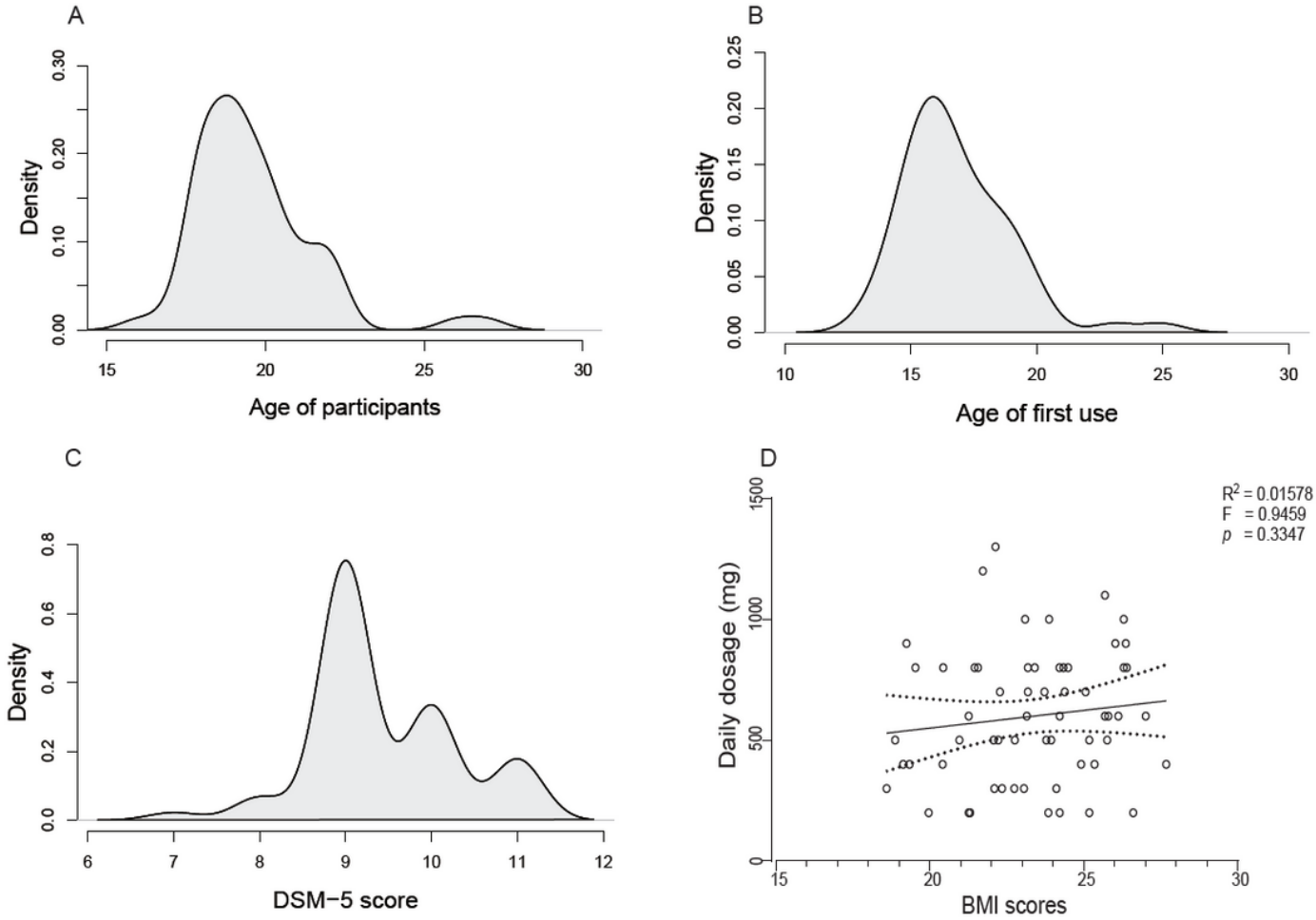

Figure 1

Density plot for participants' age. (A), age of first use (B), DSM-5 score (C) and correlation between BMI and daily dosage (D).

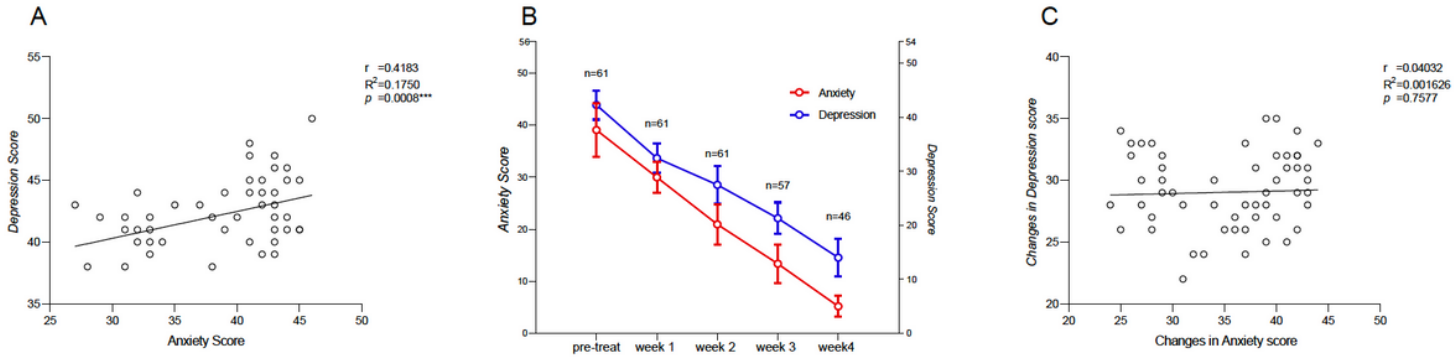

Figure 2

Correlation between depression and anxiety score in subjects with methylphenidate use disorder (A); trend of anxiety scores and depression scores during the treatment, the left Y axis represents the anxiety

score, the right Y axis represents the depression score (B); correlation between the change in depression scores and the change in anxiety scores during the 4 weeks of treatment (C).

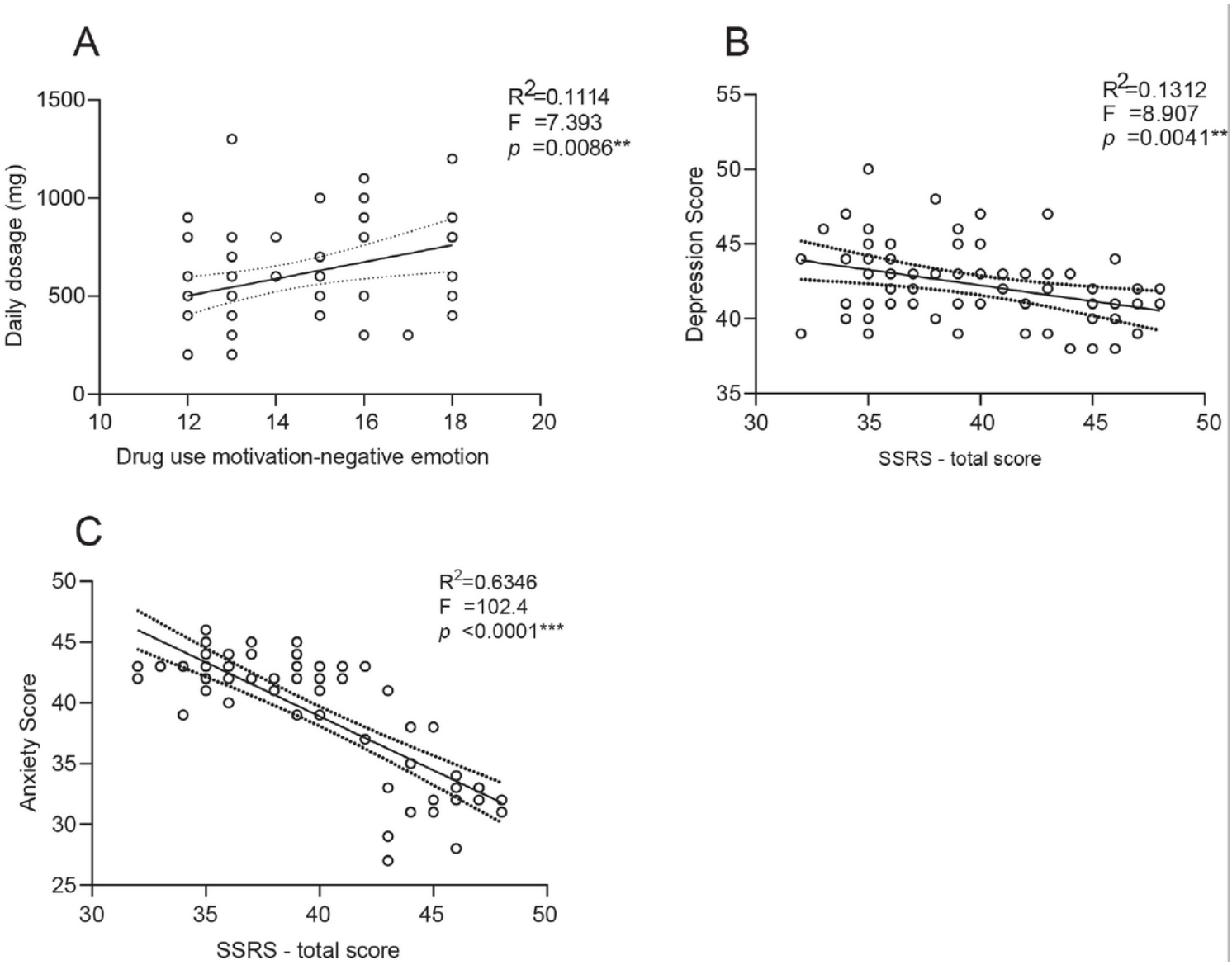

Figure 3

Linear regression analysis for daily dosage, depression score and anxiety score. (A) linear regression analysis for daily dosage and drug use motivation-negative emotion factor; (B) Linear regression analysis for depression and Social Support Rating Scale (SSRS) total score; (C) Linear regression analysis for anxiety and Social Support Rating Scale (SSRS) total score.