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ORIGINAL INVESTIGATION

Cilostazol as an adjunctive treatment in major depressive disorder: a pilot randomized, double-blind, and placebo-controlled clinical trial

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Abstract

Background Cilostazol, a phosphodiesterase-3 inhibitor, has been reported to improve depressive-like behavior in experimental studies of depression. We investigated the safety and efficacy of cilostazol combination therapy with sertraline in treating patients with major depressive disorder (MDD) in a 6-week, parallel, randomized controlled trial.

Method Among patients referred to the outpatient clinic of a tertiary hospital, those with a diagnosis of MDD with moderate to severe severity (a score of >19 on the Hamilton depression rating scale (HAM-D)) were enrolled. A total of 54 MDD patients aged 18–65 years were randomly assigned to either the cilostazol (100 mg daily) or the placebo group. Both groups received sertraline 100 mg per day similarly. Changes in HAM-D at weeks 2, 4, and 6 were the primary outcome. Participants and outcome assessors were blinded.

Results At week 6, patients in the cilostazol group had significantly lower HAM-D score (p value= 0.015). General linear model repeated-measure analysis showed significant effect for treatment in improving MDD severity (p value <0.001). The remission rate at the study endpoint and number of responders at week 4 were significantly higher in the cilostazol group (p value= 0.047, p value= 0.032, respectively). The cilostazol group demonstrated a significantly shorter time to response. No significant difference was observed in treatment response at the study endpoint, and there were no serious adverse effects.

Conclusion Our study supports safety and efficacy of cilostazol in treating MDD patients.

Trial registration This trial was registered at the Iranian registry of clinical trials (IRCT: www.irct.ir; registration number: IRCT20090117001556N130)

Keywords Antidepressive agents · Cilostazol · Major depressive disorder · Hamilton rating scale for depression · Neuroprotective agents · Phosphodiesterase inhibitor

Abbreviations

AD	Alzheimer's disease
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic adenosine monophosphate
cGMP	Cyclic guanosine monophosphate
CREB	CAMP-response element-binding protein
CVD	Cardiovascular disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECT	Electroconvulsive therapy
GLM	General linear model
HAM-D	Hamilton rating scale for depression
IGF-1	Insulin-like growth factor-I
MD	Mean difference
MDD	Major depressive disorder
Nrf2	Nuclear factor-erythroid 2-related factor-2
PDE	Phosphodiesterase
TrkB	Tropomyosin receptor kinase B

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Introduction

Major depressive disorder (MDD), a major cause of disability, is one of the most common psychiatric disorders with a global prevalence of approximately 5% (Ferrari et al. 2013; Haapakoski et al. 2015). The expanding therapeutic armamentarium for MDD includes pharmacological and non-pharmacological options. However, the majority of the non-pharmacological approaches, except for cognitive behavioral therapy, are not evidence-based (Gartlehner et al. 2017). Tricyclic antidepressants, monoamine oxidase inhibitors, and serotonin reuptake inhibitors, such as sertraline, are the most commonly prescribed medications (Smit et al. 2016). Despite substantial advances in the treatment of MDD, major challenges are still unsolved. A significant proportion of the patients (30–40%) do not respond to initial treatment (Sackeim 2001), and almost one-fifth show poor adherence to treatment due to adverse effects (Brunoni et al. 2009). The burden of MDD and the remaining challenges in achieving optimal outcomes highlight the need for investigation of other alternative therapies.

Phosphodiesterase (PDE) inhibitors have shown positive effects in treating a wide range of psychiatric and neurodevelopmental disorders. PDE enzymes play an essential role in cell function adjustments via regulating intracellular levels of second messenger cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) by hydrolyzing cyclic nucleotides (Bobon et al.; Delhaye and Bardoni 2021). Therefore, PDEs can play a critical role in synaptic plasticity and regulation of neuronal pathways, a potential role in learning, mood adjustment, and memory functions (Hebb and Robertson 2007; Houslay et al. 2007; Houslay et al. 2005; O'Donnell and Zhang 2004). Several PDEs, such as PDE3, are expressed in the brain with altered expression in MDD (Nandhakumar et al. 2010). The potential therapeutic applications of PDE inhibitors have been extensively explored in various neurodevelopmental disorders, and they have shown promising results in the management of mood disorders, including MDD (Itoh et al. 2004; Zhang et al. 2002), dementia (Campbell and Edwards 2006), psychosis (Akhondzadeh et al. 2011; Maxwell et al. 2004; Menniti et al. 2007), and autism spectrum disorder.

Cilostazol, primarily used in secondary prevention of ischemic stroke, is a reversible, selective PDE3 inhibitor that targets platelets and vascular smooth muscle cells (Uchiyama et al. 2009). Monotherapy with cilostazol has alleviated disease severity in chronic schizophrenia (Rezaei et al. 2017) and improved cognitive abilities (Taguchi et al. 2013). Cilostazol has shown positive results in ameliorating depressive-like behavior in animal models when administered orally (Abuelezz and Hendawy 2018; Kim et al. 2016b) or intraperitoneally (Patel et al. 2012b; Yoneyama et al. 2015). Recently, a study conducted by Abdallah et al. investigated to efficacy and safety profile of cilostazol administered in MDD patients (Abdallah et al. 2021). Cilostazol also improved geriatric depression scale scores in patients with Alzheimer's disease (Hishikawa et al. 2017) in addition to mitigating cognitive deficits. However, to the best of our knowledge, no clinical trial has been conducted so far to assess the effects of cilostazol in the management of MDD.

Given the corroborative evidence, we hypothesized that cilostazol adjuvant therapy might improve severity of MDD. In this 6-week, randomized, double-blind, placebo-controlled clinical trial, we investigated the effects of cilostazol as adjuvant therapy with sertraline in the treatment of MDD.

Materials and methods

Trial design and setting

A 6-week, two-center, randomized, double-blind, placebo-controlled, parallel-group clinical trial was performed on the efficacy of cilostazol compared to placebo as adjuvant therapy in improving symptoms of MDD at the outpatient clinic of Roozbeh Psychiatric Hospital (Tehran University of Medical Sciences) and Tehran Psychiatric Institute (Iran University of Medical Sciences) between July 2020 and July 2021. The trial was registered at the Iranian registry of clinical trials (IRCT: www.irct.ir; registration No.: IRCT20090117001556N130). The protocol was in concordance with the Declaration of Helsinki (Association 2013) and its subsequent revisions. The Tehran University of Medical Sciences institutional review board approved the protocol (approval No. IR.TUMS.VCR.REC.1398.1005). All participants in the present trial were informed that they were free to leave the trial at any time without any consequences on their therapy process. Written informed consent was obtained from all enrolled patients.

Participants

Enrolled participants were male and female outpatients aged between 18 and 65 years. Patients were included if (1) they were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association 1980) and had a minimum score of 19 on the 17-item Hamilton rating scale for depression (HAM-D). Exclusion criteria were as follows: receiving any antidepressant drug during the previous month, receiving electroconvulsive therapy (ECT)

during the past 2 months, presence of psychosis or diagnosis of other prominent mental disorders (e.g., bipolar I or II disorders, anxiety disorder, personality disorder, eating disorder), suicidal ideation (score > 2 on the suicide item of the HAM-D), depression due to other diseases, alcohol or substance (except nicotine) abuse, any uncontrolled medical condition such as a history of thyroid disease, renal disease, cardiovascular problems, and liver disorders, pregnancy, or lactation. A board-certified psychiatrist assessed patients to ensure the presence of the inclusion criteria and absence of the items on the exclusion criteria.

Intervention

Participants were randomly assigned (1:1) either to the placebo or the experimental group. Both groups received 100-mg sertraline (Sobhan Co.) daily in a similar manner. For the intervention group, 100-mg cilostazol (Otsuka Co.) per day was administered while the placebo group received placebo tablets. During this trial, no other psychiatric medications were allowed.

Outcomes

The severity of depression and cilostazol effect on the improvement of depressive symptoms were examined using the HAM-D, a highly used 17-item rating scale for depressive symptoms severity assessment. Each item was scored on a 3- to 5-point scale. Participants were assessed at baseline, week 2, week 4, and week 6. Outcome measures were developed based on the HAM-D score changes between baseline and study time points. These are as follows: change scores from baseline to each time point as the primary outcome measure and (1) early improvement (≥20% reduction in HAM-D score in the first two weeks), (2) rate of response to treatment (≥50% reduction in the HAM-D score), (3) rate of remission (HAM-D score≤7), and (4) time needed to respond to treatment as the secondary outcome measures (Zeinoddini et al. 2015). Two experienced psychiatrists carried out all assessments with an inter-reliability > 90% on the HAM-D score.

Safety

A psychiatrist carefully monitored adverse events at baseline and each follow-up visit (weeks 2, 4, and 6). Adverse events were recorded using a 25-item checklist of possible side effects of the medications (Amiri et al. 2008; Khajavi et al. 2012; Shahmansouri et al. 2014). Moreover, the research team recorded any adverse effects by a phone call one week after starting the study. In addition, patients were also provided with a 24-h medical helpline phone number for medical advice if they experienced any adverse effects.

Sample size

According to a previously performed pilot study, considering the assumption of a mean difference (MD) of 2.5 on the HDRS score between the cilostazol and the placebo groups, with a standard deviation (SD) of 2.5 on HDRS score and a power of 80%, and a two-tailed significance level of 5%, a sample size of 30 patients in each group was calculated. Moreover, after assuming a 20% attrition rate, 25 patients were needed in each group.

Randomization, blinding, and drug allocation

A permuted blocked randomization method (blocks of four, allocation ratio 1:1) was used, and the randomized codes were generated using computer software. Cilostazol and placebo tablets were indistinguishable in their size, shape, color, texture, and odor. The allocation process was concealed using sequentially numbered, sealed opaque envelopes. The participants, the care providers, the outcome assessors, and the statistician were all blinded to treatment allocation. At week 6, patients were asked to guess whether they were in the experimental or control group. The results confirmed the success of blinding. In addition, two separate groups performed random allocation and clinical assessments.

Statistical analysis

All statistical analyses were performed using the SPSS Version 26 (IBM, Armonk, NY, USA). Continuous variables were presented as mean ± SD, and categorical variables were shown as frequencies with percentages. The primary and secondary outcome measures of the study were compared between patients in the cilostazol arm and the placebo arm.

Independent sample *t* test was performed for comparison of continuous variables (e.g., HAM-D score and changes of HAM-D score from baseline to each study time point) and chi-square (to compare sex ratio), binary logistic regression (to calculate the odds ratio (OR)), and Fisher's exact tests were conducted for making comparisons between categorical variables (early improvement, rate of response to treatment, and rate of remission), when appropriate. We calculated the mean difference (MD) in change score and respective sample *t* test confidence intervals (95%CI) between baseline and week 2, week 4, and week 6. General linear model (GLM) repeated measures analysis was conducted to investigate time, treatment, and time × treatment effects. The between-subject factor was derived from the two treatment groups, and within-subject factors were HAM-D scores. If Mauchly's test of sphericity was significant, a Greenhouse-Geisser adjustment in degrees of freedom was made. Kaplan-Meier

estimation with the log-rank test was used to compare the time needed to respond to treatment between two groups. We used the last observation carried forward analysis to perform intention-to-treat analysis. A p value of < 0.05 was considered statistically significant in all analyses.

Results

Participants

Figure 1 illustrates the flow diagram of the trial. A total of 114 patients were screened, and 58 patients met the inclusion criteria, among whom four patients (two in each arm) dropped out from the study before the first clinical examination (week 2) due to withdrawal of consent or substance abuse. As a result, 50 patients were enrolled in the study and randomized into either the (i) cilostazol+ sertraline group or (ii) placebo+ sertraline group with an equal allocation ratio of 1:1. Nevertheless, we included the two patients who withdrew in each arm using the last observation carried forward analysis, resulting in a total of 27 participants in each arm.

The two groups were matched in gender and age at baseline (Table 1). No statistically significant difference in HAM-D score was observed between the two groups at baseline (25.4 ± 2.5 vs. 25.6 ± 2.2 for cilostazol and placebo groups, respectively, p value=0.775).

Outcomes

Table 2 illustrates patients' scores at each time point and changes from the baseline. At week 6, the HAM-D score was significantly lower in patients in the cilostazol group (mean difference (MD) [95%CI= −2.9 [-5.3, −0.6], p value= 0.015). Reduction in HAM-D scores compared to baseline was comparable between the two groups with a trend for a larger reduction in the cilostazol group at week 6 (p value= 0.063) (Table 2 and Fig. 2).

In terms of between-subject effects, a significant effect of treatment was detected according to GLM repeated measures (F= 4.16, df=1, p value= 0.047) (Table 3).

No significant difference was found between cilostazol and placebo groups regarding early improvement rate (85% versus 82%; respectively, p value= 0.715). At week 4, the number of patients responding to treatment was significantly higher in the cilostazol group than in the placebo group (67% versus 37%, p value=

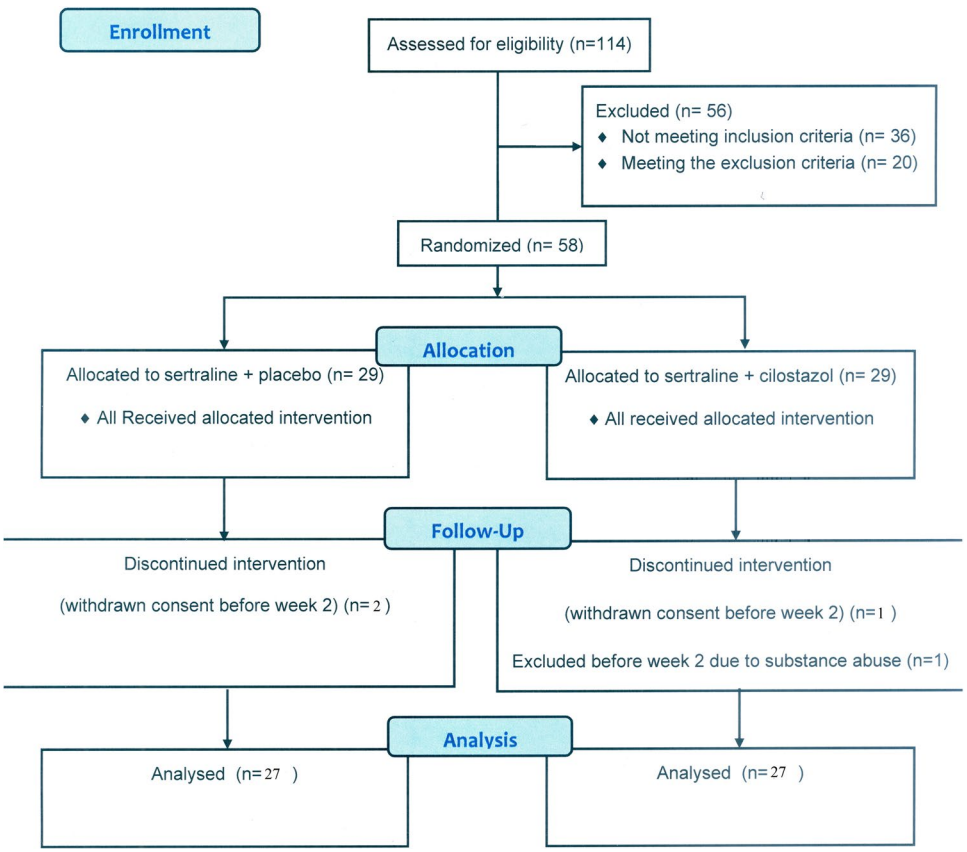

Fig. 1 Flow diagram of the study

Table 1 Baseline demographic and clinical characteristics of the patients in the two study groups

Variable			Cilostazol + sertraline (n=27)	Placebo+ sertraline (n=27)	p value
Age, mean (SD), years			36.0 (7.0)	35.4 (4.8)	0.701
Duration of illness, mean (SD), years			2.9 (1.1)	3.0 (0.8)	0.492
Male (%)			16 (59%)	22 (82%)	0.135
Duration of current episode, mean (SD), months			2.1 (0.8)	1.8 (0.7)	0.163
Number of previous episodes			1.9 (0.9)	2.0 (0.9)	0.637
Medication history		Fluoxetine (%)	8 (30%)	10 (37%)	0.773
		Escitalopram (%)	6 (22%)	5 (19%)	1.000
		Venlafaxine (%)	4 (15%)	6 (22%)	0.728
		Sertraline (%)	11 (41%)	16 (59%)	0.276
Smoking status	Smoker		19 (70%)	21 (78%)	0.757
	Nonsmoker		8 (30%)	6 (22%)	
Marital status	Single (%)		8 (30%)	3 (11%)	
	Married (%)		18 (67%)	21 (78%)	
	Widowed (%)		1 (4%)	3 (11%)	
Education level	Illiterate (%)		1 (4%)	2 (7%)	
	Primary school (%)		12 (44%)	14 (59%)	
	Secondary school (%)		11 (41%)	5 (19%)	
	Diploma (%)		2 (7%)	2 (7%)	
	Higher education (%)		1 (4%)	2 (7%)	

P value of <0.05 was considered statistically significant

Table 2 Comparison of HAM-D scores and score changes between the two study group

	Cilostazol+ sertraline Mean (SD)	Placebo+ sertraline Mean (SD)	MD [95%CI]	Cohen's d	t	p-value
Baseline	25.4 (2.5)	25.6 (2.2)	−0.2 [−1.5; 1.1]	−0.09	0.288	0.775
Week 2	16.1 (2.4)	17.2 (3.7)	−1.1 [−2.8; 0.6]	−0.36	−1.312	0.195
Week 4	13.0 (3.0)	14.6 (4.3)	−1.6 [−3.6; 0.4]	−0.44	−1.582	0.120
Week 6	9.9 (3.7)	12.8 (4.8)	−2.9 [−5.3; −0.6]	−0.69	−2.510	**0.015**
Reduction from Baseline to week 2	9.3 (4.1)	8.4 (4.3)	0.9 [−1.4; 3.2]	0.22	0.809	0.422
Reduction from baseline to week 4	12.4 (4.9)	11.0 (4.7)	1.4 [−1.2; 4.0]	0.30	1.083	0.284
Reduction from Baseline to week 6	15.6 (5.5)	12.9 (5.1)	2.7 [−0.15; 5.6]	0.52	1.902	0.063

P value of <0.05 was considered statistically significant (shown in bold)

0.032). However, the difference did not remain significant at week 6 (89% in the cilostazol group versus 85% in the placebo group, p value= 0.686) (Table 4). The remission rate was significantly higher in the cilostazol group (26%) compared with the placebo group (4%) at the study endpoint (p value= 0.047). Number needed to treat (NNT) analysis revealed that in order for one extra patient to experience remission after 6 weeks, 4.5 patients would have to get experimental therapy (rather than control treatment). According to the Kaplan-Meier estimation, the time needed for patient response to treatment in the cilostazol group was significantly shorter compared with the placebo group (4.24 ± 0.267 versus 5.04 ± 0.262 weeks; respectively, log-rank p value= 0.041).

Adverse effects

Muscle pain, abdominal pain, and nausea were the most common adverse effects in both groups (15% in cilostazol and 7% in placebo) (Table 5). No serious or unforeseen side effect was recorded. There was no statistically significant difference in the frequency of adverse effects between the two groups (p value>0.05 for all items).

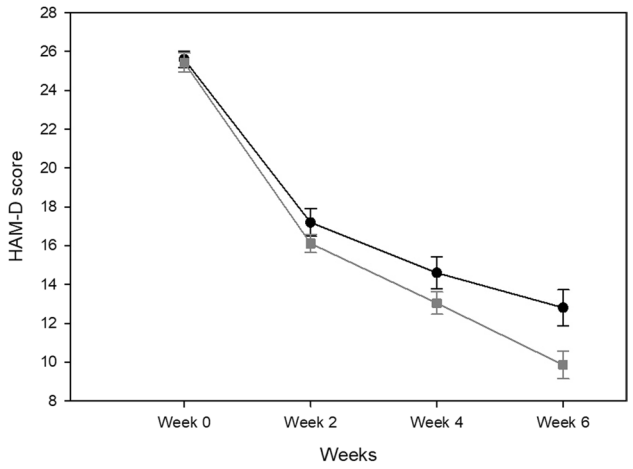

Fig. 2 Comparison of the Hamilton depression rating scale (HAM-D) score (mean [standard error]) between the (▬●▬) cilostazol group and the (▬■▬) placebo group

Table 3 Results of the general linear model repeated-measures analysis (between-subjects)

	Type III sum of squares	df	Mean square	*F*	*p* value
Intercept	61239.67	1	61239.67	2230.07	**<0.001**
Treatment	114.12	1	114.12	4.16	**0.047**
Error	1427.96	52	27.46		

P value of <0.05 was considered statistically significant (shown in bold)

Discussion

Our results demonstrate that patients receiving 100-mg cilostazol daily as adjuvant therapy had more remarkable improvements in their depressive symptoms after 6 weeks. Moreover, the remission rate at the study endpoint and the response rate at week 4 were significantly higher in the cilostazol group compared to the placebo group.

To date, only a recently published RCT has investigated the antidepressant effects of cilostazol in the management of MDD. Abdallah et al. found that adjuvant therapy with cilostazol in addition to escitalopram resulted in increased early improvement, remission, and response rates compared to placebo (Abdallah et al. 2021). The high response rate of the cilostazol group in our study is comparable with the response rate reported by studies assessing the antidepressant effects of adjuvant cilostazol and pentoxifylline (El-Haggar et al. 2018).

Cilostazol plays its antidepressant and anxiolytic role by increasing cAMP in the hippocampus through PDE3 inhibition. Besides, cilostazol has antiplatelet functions, which, altogether, makes it a promising therapeutic agent in treating patients suffering from MDD and concomitant cerebrovascular disease (CVD). Moreover, it has been established that cilostazol increases insulin-like growth factor-I (IGF-I) in the hippocampus, resulting in improvements in cognitive functions in mice (Zhao et al. 2010). As peripheral and central production of IGF-1 induces antidepressant-like behavior, it can be considered as one of the mechanisms of action of cilostazol as an antidepressant (Duman et al. 2009; Zhao et al. 2010). Notably, cilostazol is suggested as a potential prophylactic antidepressant, which prevents oxidative stress via mediating nuclear factor-erythroid 2-related factor-2 (Nrf2) pathway (Abuelezz and Hendawy 2018).

Several animal studies investigated cilostazol's effect on depressive behavior. The study by Kim et al. (Kim et al. 2016a) on the poststroke depression animal model showed that cilostazol improved all studied depressive behaviors, especially the Morris water maze test performance. Cilostazol treatment reduced noticeable atrophic changes in the ipsilateral striatum and hippocampus of ischemic chronic

Table 4 Comparison of two groups in terms of response to treatment and remission rates at different stages of study

	Cilostazol + sertraline (*n*=27)	Placebo + sertraline (*n*=27)	OR (95%CI)	*p* value
Number (%) of early improvers	23 (85%)	22 (82%)	1.31 (0.31, 5.51)	0.715
Number (%) of remitters at week 6	7 (26%)	1 (4%)	9.10 (1.03, 80.9)	**0.047**
Number (%) of responders at week 4	18 (67%)	10 (37%)	3.40 (1.11, 10.40)	**0.032**
Number (%) of responders at week 6	24 (89%)	23 (85%)	1.39 (0.28, 6.91)	0.686

P value of <0.05 was considered statistically significant (shown in bold)

Table 5 The frequency of adverse events in the study populations

Side effect	Cilostazol + sertraline (*n*=27)	Placebo + sertraline (*n*=27)	*p* value
Muscle pain, No (%)	4 (15%)	2 (7%)	0.669
Diarrhea, No (%)	3 (11%)	1 (4%)	0.610
Abdominal pain, No (%)	4 (15%)	2 (7%)	0.669
Dizziness, No (%)	2 (7%)	1 (4%)	0.99
Nausea, No (%)	3 (11%)	2 (7%)	0.99

p value of < 0.05 was considered statistically significant

*Fisher's exact test was used for comparison of all adverse events

mild stress treated mice by inhibiting neuronal cell death and activating microglia. In addition, treating ischemic chronic mild stress-mice with cilostazol resulted in increased cAMP-response element-binding protein (CREB), brain-derived neurotrophic factor (BDNF), and tropomyosin receptor kinase B (TrkB) expression in the ipsilateral striatum and hippocampus. CREB phosphorylation was also shown in dopaminergic neurons of the midbrain. As a result, the number of newly formed cells and differentiation into neurons in the striatum and hippocampus were increased. These results suggest that cilostazol may have antidepressant effects on poststroke depression by inducing neurogenesis in the primary lesion and secondary foci through activating CREB/BDNF signaling. In another in vivo animal study (Patel et al. 2012a), mice treated with cilostazol had significantly lower mobility time in the forced swim test compared to the control group and those treated with fluoxetine, indicating improvement of depressive-like behavior. Agrawal et al. (Agrawal et al. 2014) showed that intraperitoneal injection of cilostazol has antidepressant activity in the animal model, as it reduces sedentary time in forced tail suspension, reduces motility, and increases wheel rotation during forced swim tests. However, the activity of cilostazol (20 mg/kg) was lower than that of fluoxetine (20 mg/kg).

Takahashi et al. (Takahashi et al. 2008) prescribed cilostazol added to usual antidepressants for a patient with geriatric depressive disorder with white matter T2-hyperintensities to search for a new booster therapy for elderly patients with refractory depression. Cerebral blood flow was assessed before and after cilostazol administration by 99mTc-ethyl-cysteine dimer single-photon emission computed tomography. The patient showed improvement in depressive symptoms as well as increased cerebral blood flow. These findings demonstrated the potential efficacy of cilostazol as a new drug for use in amplification therapy for depressed patients with white matter blood pressure; however, it was only reported in one patient.

Other than depression, several studies evaluated cilostazol's effect on other psychiatric disorders. Sakurai et al. (Sakurai et al. 2013) reported possible preventive effects of cilostazol on cognitive decline in 20 patients with Alzheimer's disease (AD) and CVD. More on its impact on cognition, an open-label pilot trial performed by Shirayama et al. (Shirayama et al. 2011) stated that cilostazol had shown potential therapeutic effects for cognitive deficits in patients with schizophrenia (Rezaei et al. 2017).

In addition to cilostazol, other PDE inhibitors have shown promising outcomes in psychiatric disorders, including MDD. Recently, Farajollahi-Moghadam et al. (Farajollahi-Moghadam et al. 2021) provided supporting evidence for the efficacy of pentoxifylline combination therapy in patients with MDD. Earlier in 2018, El-Haggar et al. (El-Haggar et al. 2018) performed a randomized, double-blind, placebo-controlled trial and suggested pentoxifylline as an adjunct to regularly prescribed antidepressants in treating MDD patients. Correspondingly, Yesrebi et al. (Yasrebi et al. 2021) confirmed the safety and efficacy of short-term monotherapy with pentoxifylline in the treatment of patients with coronary artery disease. Pieces of evidence provided by Wang et al. (Wang et al. 2015) stated that PDE-4 (especially PDE4D4 and PDE4D5) had shown a high therapeutic index in mice and might be targeted to discover new antidepressants. Additionally, in an experimental model study, it has been reported that PDE2 inhibition resulted in increased antioxidant activity, leading to the development of novel drugs for stress-related disorders (Ding et al. 2014).

While this study is one of the first RCTs investigating and supporting the efficacy and safety of cilostazol as an adjuvant treatment for MDD, it faces several limitations. First, the follow-up time was for 6 weeks, limiting our study to assess the long-term effects of cilostazol in treating patients with MDD. Second, the sample size was also relatively small, although sufficient for statistical power. Further investigations with larger sample sizes and longer follow-up periods are required to assess the potential antidepressant effects of cilostazol both as adjuvant and monotherapy. Third, patient-based questionnaires, such as Beck's depression inventory (BDI) or the quick inventory of depressive symptomatology (QIDS-SR), were not utilized as a supplemental tool to HAM-D. Nevertheless, the HAM-D is widely used in the assessment of MDD, and we controlled for the potential bias caused by observer rating with the inter-reliability rate of > 90% between the psychiatrists rating the patients. Fourth, since this study was pilot, serum levels of CREB1, BDNF, NF-κB, IGF-1, and cytokine profile of included patients were not measured. The alterations in the profiles of these biomarkers after treatment with cilostazol should be assessed in the following RCTs. Lastly, future studies with larger sample sizes can investigate the effect of potential confounders, i.e., diseases severity, duration, and the number of previous episodes, on the treatment response.

Conclusion

To conclude, cilostazol, a phosphodiesterase-3 inhibitor, has shown promising antidepressant effects along with its antiplatelet and cardioprotective roles. In our 6-week double-blinded, placebo-controlled clinical trial, we assessed the potential therapeutic effects of cilostazol combination therapy (as an adjunct to sertraline) for patients with MDD. The current RCT reported the safety and efficacy of cilostazol, resulting in improvements in depressive symptoms. Preferably, additional RCTs are

required to further assess the antidepressant effects of cilostazol.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-021-06041-0.

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Declarations

Conflict of interest The authors declare no competing interests.

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