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Original Research

Impact of a Depression-Specific Pharmaceutical Care Counseling and Smartphone App in Medication Adherence among Patients with Major Depressive Disorders: A pilot study

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Abstract

Introduction: Medication nonadherence has a number of clinical consequences, including an increased risk of relapse and recurrence. By offering individualized in-person pharmaceutical care counseling, pharmacists play a significant part in encouraging medication adherence. One of the most popular forms of communication in nowadays is the smartphone. As a result, one of the measures for enhancing patients' outcomes should be a smartphone app specifically designed for depression. **Objectives:** To investigate whether depression-specific counseling and smartphone app could improve medication adherence in newly diagnosed MDD patients. **Methods:** A prospective, randomized, pilot study was conducted in newly diagnosed major depressive disorder patients. They were randomly assigned to either the intervention or usual care groups (1:1). The intervention included in-person pharmaceutical care counseling along with the introduction use of a depression-specific smartphone app, whereas the usual care group received traditional pharmaceutical care counseling and simple chatbot. The primary outcome, medication adherence was measured using the Medication Adherence Rating Scale (MARS) and the percentage of pills counted (PC) at the one-month follow-up. The Patient Health Questionnaire-9 (PHQ-9) was used to assess depressive symptoms as a secondary outcome. **Results:** The study was completed by 36 participants (18 intervention and 18 usual care). The average age was 29.81 years, and 65.38% of the participants were female. The two groups had similar baseline characteristics, including baseline PHQ-9 scores. The intervention group had a mean MARS score of 7.0 (IQR=5) higher than the usual group, which had a mean score of 4.5 (IQR=7; p-value=0.04). The intervention group had a higher PC percentage of 81.75 (IQR=33.33) more than the usual care group, which had a mean percentage of 69.95 (IQR=78.57; p-value=0.10). The mean difference of PHQ-9 scores between two visits for the intervention and usual groups was -1.44 [-2.61 - -0.28]. (p-value=0.02). **Discussion and Conclusions:** This study discovered that new patients with major depression who received depression-specific pharmaceutical care counseling along with smartphone app improved their medication adherence. In addition, improvement in overall depression symptoms was discovered.

Keywords: medication adherence; pharmaceutical care; counseling smartphone; pharmacist; depression; mental health

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INTRODUCTION

Depression is a common mental health disorder. Approximately 280 million people in the world experience depression. Currently, the number of populations with depression is quite high and continuously increasing, with an estimated 3.8% of the population affected, including 5.0% among adults and 5.7% among adults older than 60 years. According to global suicide death rates, close to 800,000 people die by suicide every year; one person dies by suicide every 40 seconds. In the European region of the World Health Organization (WHO), 128,000 people take their own lives every year.[1]

Currently, two main strategies are used to treat major depressive disorders, namely, pharmacotherapy and nonpharmacotherapy. Antidepressants are usually used to treat moderate to severe symptoms and help regulate brain-derived neurotrophic factor (BDNF) signals. BDNF is a critical regulator of several types of neuronal plasticity in the brain, and plasticity has increasingly been related to antidepressant benefits.[2] Antidepressants can reduce severity, control symptoms, and prevent relapse of the disease. Drug therapy requires a substantial period spent on antidepressants. Therefore, medication adherence is crucial to recover from depression.[3]

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Patients with depression tend to present medication nonadherence, especially in new cases. New patients with depression receiving antidepressants for first time have a medication adherence rate of approximately 50% during the first months.[4] A recent meta-analysis revealed that patients with major psychiatric disorder (schizophrenia, major depressive disorder, and bipolar disorder) receiving psychotropic medication had an overall nonadherence of 49%. Of these, medication adherence of MDD was only 50%.[5]

Medication nonadherence causes several clinical effects. First, it creates a higher risk of relapse and recurrence. The study reported that relapses and recurrences were 8 times higher than among those receiving continuous therapy. Secondly, patients presenting good adherence to antidepressants had hospital stay lengths and emergency department admissions 20% fewer than those who presenting low adherence. Lastly, patients with good medication adherence responded well and the symptoms were reduced by as much as 50%. In terms of economic impact, those maintaining good medication adherence had lower total medical costs than those presenting low adherence due to the longer duration of treatment.[6]

Pharmacists play an important role in promoting medication adherence by providing individualized counseling with a wide range of content, such as understanding patients' expectations and attitudes, providing patients with necessary information about antidepressants, including their benefits, side effects, and management, and monitoring efficacy and safety outcomes.[7] The study found that pharmacist interventions could improve patient adherence and lead to better clinical outcomes such as cholesterol control, blood pressure control, chronic obstructive pulmonary disease control, and asthma control. However, this study did not prove statistically significant effects of interventions on depressive symtoms.[8] A recent meta-analysis of randomized controlled trials (RCTs) found that pharmacist activities such as in-person counseling and education influenced medication adherence in patients suffering from depression.[9, 10]

Presently, smartphones are one of the most widespread communication channels due to the coverage of technology, especially the internet. Therefore, smartphone-delivered interventions should be one channel of strategies for promoting patient's outcomes. SMS messages include medication reminders, and psychoeducation enhancing adherence and improving HIV viral load suppression among patients with HIV.[11] Systematic review has provided evidence of the effectiveness of smartphone apps to treat mental disorders and most research targets depressive disorder.[12] A meta-analysis of RCTs found that smartphone-based mental health interventions, specifically cognitive behavioral therapy (CBT) and psychological interventions, could reduce depressive symptoms.[12, 13, 14]

In terms of medication adherence, one of the strategies for promoting patient medication adherence is smartphone-delivered intervention. Numerous studies have demonstrated the benefits of smartphone-delivered interventions for improving medication adherence in chronic disease patients, particularly those with HIV, type 2 diabetes, and cancer.[15-17] A digital intervention discovered a high rate of self-report medication use. A recent systematic review found that while medication adherence was high during the study in patients with mood disorders, improvements from baseline could not be definitively attributed to the intervention due to observational study designs and a lack of comparison groups.[18] One RCT used mobile technology to improve medication adherence in HIV patients with co-occurring bipolar disorder.[19] Medication adherence was higher in the intervention group for antiretroviral treatment and psychotropic treatment, but not statistically significant. Studies of smartphone-delivered intervention especially using a depression-specific smartphone app on medication adherence among patients with MDD remain a minority. The investigators conducted a study to see if a depression-specific pharmaceutical care counseling and smartphone app could improve medication adherence in newly diagnosed MDD patients.

METHODS

Study design and setting

This prospective, randomized, pilot study was conducted at the outpatient department of Suan Prung Psychiatric Hospital (Super-tertiary Care) in Thailand.

Participants and randomization

The study's protocols were approved by the Human Research Ethics Committee of Suan Prung Psychiatric Hospital (4/2020). All participants signed the informed consent. Patient were included if they were outpatient and firstly received a diagnosis of the International Classification of Diseases and Related Health Problem 10th Revision (ICD 10) with disease codes F32.0 to F32.2 by psychiatrists, aged 18 years, were willing to use smartphone app and received treatment during the data collection period, that is, from November, 2020 to February, 2021. They were excluded if they presented a Clinical Global Impression – Severity scale (CGI-S) score greater than 6, were unable to follow up during the study, were visually impaired, hearing impaired or unable to communicate, received a diagnosis with Alzheimer's disease, dementia, neurodegenerative disorder, or a chronic disease requiring other medications.

This study used the mean and standard deviation of mean Morisky Medication Adherence Scale (MMAS) a from a previous study to calculate sample size (control group 0.9±1.4 and intervention group 2.2±1.8) where $\alpha = 0.05$ and a power $(1-\beta) = 0.80$ were determined.[19] The calculation showed a sample size of 25 subjects per group. A total sample size of 50 participants divided into either an intervention or usual care group (1:1). Simple randomization was performed by computer-generated random numbers.

INTERVENTION

The investigators were pharmacy students working under the supervision of a pharmacy faculty instructor and a clinical pharmacist from Psychiatric Hospital. They tailored in-

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person pharmaceutical care counseling to new patients with depression, along with the introduction use of a depression-specific smartphone app called Line official account named "beside you" (or Kiang Kang in Thai) in the intervention group (Visit 0).

For the visit 0, participants in the intervention group received tailored pharmaceutical care counseling including basic knowledge of depression, benefits of antidepressants, treatment course, basic lifestyle modification, drug information, common adverse effects, and how to prevent and manage them on their own. Following in-person pharmaceutical care counseling, the participants' smartphones were installed with the "beside you" app. The app was created to be user-friendly and simple. The app provided information on depressive disorder, benefits of antidepressants, adverse effects and how to manage them, self-management skills, encouragement messages, a real-time chat channel with the investigators (two-way communication), and a link to the mental health hotline. The important component was automatic daily reminders to participants to take their medications. The alerts were sent twice per day, at 8:00 a.m. and 8:00 p.m. Figure 1 shows an example of app content. Two experts, a psychiatry specialized pharmacist and a clinical pharmacist, reviewed and validated the app's content validity.

In the usual care group, participants received traditional pharmaceutical care counseling including general drug information, common adverse effects, and how to prevent and manage them on their own. The counseling mainly covered drug dispensing information such as indications for the drug, and the time of taking the drug. Participants were also given a smartphone app; however, it was a simple chatbot.

Outcome measures

The primary outcome was the medication adherence rate as measured by the Medication Adherence Rating Scale (MARS), as well as the percentage of pills counted compared to the usual care group at visit 1 (one month period). MARS was a valid and reliable measure of medication adherence to psychotropic medications.[20] The best option was selected by the patients to reflect their recent behaviors or attitudes about their medication during the past week. A percentage of pills counted was calculated by dividing the actual amount of drug taken by the total amount of drugs that should be taken and multiplying by 100. The secondary outcome was depressive symptoms as measured by the Patient Health Questionnaire-9 (PHQ-9) Thai version.[21] On the second doctor's visit, the investigators tracked all the outcomes (Visit 1).

Figure 1. An example of app "Beside you or Kiang Kang in Thai" content

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Data and statistical analysis

The collected data were then analyzed for statistical correlation using STATA, Version 14.0. The analysis performed an intention-to-treat method. Descriptive statistics were demonstrated using the mean and the standard deviation. To determine the normality of variables, the Kolmogorov-Smirnov was used. The comparative data between groups was analyzed using a Mann-Whitney U Test (rank-sum). A p-value less than 0.05 was used to test the statistical significance.

RESULTS

Baseline characteristics

A total of 36 participants were randomly assigned to one of two groups: those who received tailored in-person pharmaceutical care counseling for the first time and were introduced to the "beside you" app, and those who received traditional pharmaceutical care counseling and were introduced to a chatbot app. Figure 2 depicts a flow diagram. During the visit, four intervention group participants and six usual care group participants missed their doctor's visits. The average age was 29.81 years, and women made up 65.38% of the participants. Table 1 shows that there was no significant difference in baseline characteristics between the two groups. The PHQ-9 was used to assess depression severity; most people in both groups were classified as moderate, with a mean score of 15.61 ± 4.3 in the intervention group and 14.61 ± 3.9 in the usual care group. The majority were mildly suicidal, with 55.6% in both groups. Selective Serotonin Reuptake Inhibitors (SSRIs) were given to 83.3% of participants in both groups. For the most part, the intervention group received three items of medication, while the usual care group received two.

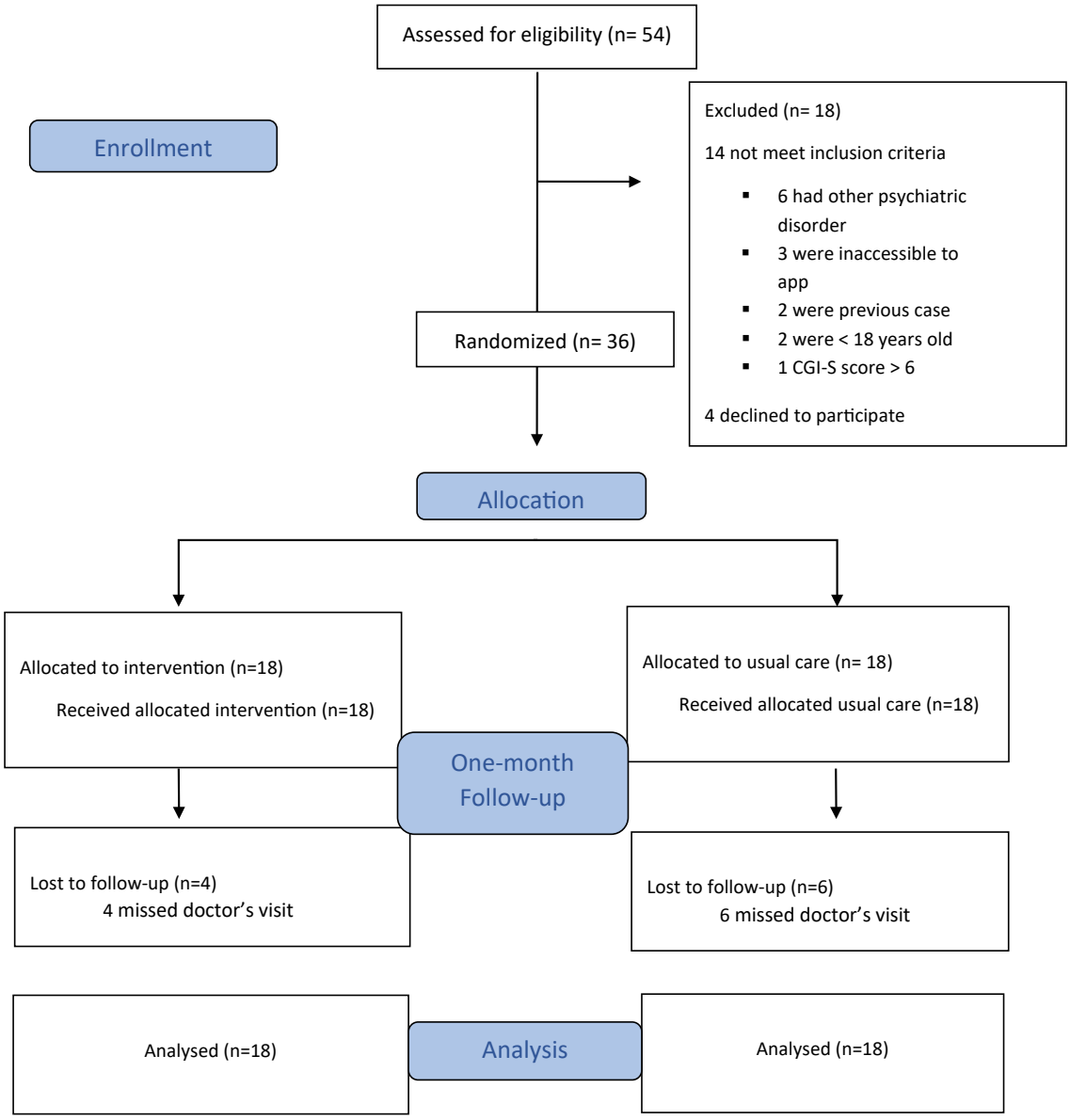

Figure 2. Flow diagram of the study

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Table 1. Baseline Characteristics

Characteristic	Intervention group (n=18)	Usual care group (n=18)	P-value
	n (%)	n (%)	
Gender			
Female	11 (61.11)	10 (55.56)	
Age (mean ± SD)	29.56 ± 12.0	32.61 ± 14.6	0.50
Education			
Unschooled	1 (5.56)	0 (0.00)	0.40
Primary	2 (11.11)	4 (22.22)	
High school	4 (22.23)	3 (16.67)	
University	11 (61.11)	11 (61.11)	
Marital status			
Single	15 (83.33)	14 (77.78)	0.69
Married	1 (5.56)	3 (16.67)	
Divorced	2 (11.11)	1 (5.56)	
Occupation			
Occupation	1 (5.56)	2 (11.11)	0.81
Unemployed	6 (33.33)	5 (27.78)	
Student	11 (61.11)	11 (61.11)	
Comorbidity			
at least 1 comorbid	5 (27.78)	4 (22.22)	0.70
Depression severity (PHQ-9 score)			
Mild	4 (22.22)	7 (38.89)	0.50
Moderate	9 (50.00)	8 (44.44)	
Severe	5 (27.78)	3 (16.67)	
Mean (±SD)	15.61 ± 4.3	14.61 ± 3.9	0.47
Number of psychiatric medications			
1 item **2 items** **3 items**	0 (0·00) 8 (44·44) 10 (55·56)	0 (0·00) 13 (72·22) 5 (27·78)	0.09
Psychotropic agents **SSRIs**	 15 (83·33)	 15 (83·33)	 1·00
TCAs	5 (27·78)	1 (5·56)	0·07
BZDs	17 (94·44)	18 (100·00)	0·31
SNRIs	1 (5·56)	0 (0·00)	0.31
NDRIs	1 (5·56)	1 (5·56)	1·00
Mirtazapine	0 (0·00)	1 (5·56)	0·31
Antipsychotics	5 (27·78)	1 (5·56)	0·07

SSRIs Selective Serotonin Reuptake Inhibitors, TCAs Tricyclic Antidepressants, BZDs Benzodiazepines, SNRIs Serotonin Noradrenaline Reuptake Inhibitors, NDRIs Noradrenaline and Dopamine Reuptake Inhibitors.

Medication adherence

Table 2 shows the MARS scores and the percentage of pills counted differences between the intervention and usual care groups at visit 1. Medication adherence showed significant differences between the two groups. The intervention group had a median MARs score of 7.0 (IQR=5) higher than the usual care group, which had a mean score of 4.5 (IQR=7; p-value=0.03). The percentage of pills counted revealed that the intervention group had a median percentage of 81.75 (IQR=33.33) more than the usual care group, which had a mean percentage of 69.95 (IQR=78.57; p-value=0.10).

Depressive symptoms

At visit 1, the results of depressive symptoms assessed using the PHQ-9 showed that both groups had lower mean PHQ-9 item scores when compared to Visit 0 shown in Table 3. As shown in Table 4, the intervention group had a mean difference PHQ-9 score of 2.17±2.09, while the usual care group had a mean difference PHQ-9 score of 0.72±1.22 (p-value= 0.02).

DISCUSSION

According to this study, new patients with depression who received tailored in-person pharmaceutical care counseling, as well as a depression-specific smartphone app, improved their medication adherence as measured by MARS after one month. In addition, the intervention group's total depression symptoms were less severe than those of the usual care group.

The study was conducted on new patients with MDD because they have a high rate of medication nonadherence. According to the study, 42% of patients with depression used medication intermittently during the first 30 days of treatment and discontinued antidepressants within 90 days.[22] Furthermore, up to 70% of patients who received their first antidepressant showed nonadherence within six months.[23] False beliefs about medication addiction, high rates of side effects, lack of therapeutic response, miscommunication about treatment duration, discontinuation, and switching antidepressants were factors influencing medication adherence, particularly with regard to psychotropic medication.[24] Furthermore, according to one survey of clozapine prescription patients, they felt excluded from patient-centered care.[25] To achieve optimal levels of adherence, the investigators developed well-planned interventions in pharmaceutical care counseling for new patients with MDD. We attempted to improve skills such as active listening, open-ended questioning, and deep reflecting during the first time to foster a positive relationship between pharmacists and patients and patient-centered care. The investigators provided information about antidepressants and depressive disorder to participants in the intervention group until they were satisfied. This was consistent with one study that held discussions about the expected duration of therapy and medication side effects to reduce antidepressant medication discontinuation.[22] Furthermore, having access to antidepressant and depression information on the app at all times is critical, especially for participants who want to reassure that they can manage adverse effects rather than discontinue medications. Daily reminders to take medication appear to improve medication adherence. The findings agreed with those of one study, which concluded that sending short messages over the phone could improve medication adherence in people suffering from type-2 diabetes.[26]

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Table 2. Medication adherence score at Visit 1

	Intervention group (n=18) Median [p25-p75, IQR]	**Usual care group (n=18)** Median [p25-p75, IQR]	**P-value***
MARS	7.0 [4-9, 5]	4.5 [0-7, 7]	0.04
Percentage of pills counted	81.75 [66.67-100, 33.33]	69.65 [0-78.57,78.57]	0.10

P-value from Mann-Whitney U Test (Rank-sum) for independent group

Table 3. PHQ-9 item score compared between intervention and usual care groups (V0-V1)

Items	**PHQ-9 content**	**Intervention (n=18)**			**Usual care (n=18)**		
		Visit 0	Visit 1	Mean difference	Visit 0	Visit 1	Mean difference
1	Little interest or pleasure in doing things	1.50±1.10	1.39±1.14	-0.11±0.68	1.22±1.11	1.11±0.96	-0.11±0.58
2	Feeling down, depressed, or hopeless	1.78±1.17	1.78±1.17	-0±0.48	1.39±1.20	1.22±1.06	-0.17±0.62
3	Trouble falling or staying asleep, or sleeping too much	1.78±1.17	1.11±0.83	-0.67±0.84*	1.61±1.29	1.28±1.13	-0.33±0.48*
4	Feeling tired or having little energy	1.50±1.20	1.22±1.06	-0.28± 0.96*	1.11±0.96	1.06±0.94	-0.06±0.24
5	Poor appetite or overeating	1.44±1.10	1.11±0.90	-0.33±1.03*	1.17±1.04	1.00±0.97	-0.17±0.86
6	Feeling bad about yourself or that you are a failure or have let yourself or your family down	1.11±1.02	1.0±0.97	-0.11±0.32	0.94±0.87	0.94±0.87	-0.00±0.00
7	Trouble concentrating on things, such as reading the newspaper or watching television	1.17±1.10	1.11±1.13	-0.66±0.24	0.83±1.04	0.78±0.94	-0.06±0.42
8	Moving or speaking so slowly that other people could have noticed. Or the opposite being so figety or restless that you have been moving around a lot more than usual	0.72±0.83	0.72±0.83	-0.00±0.00	0.39±0.78	0.39±0.78	-0.00±0.00
9	Thoughts that you would be better off dead, or of hurting yourself	0.88±0.90	0.28±0.46	-0.61±0.70*	0.67±0.84	0.83±0.92	-0.17±0.38*
Mean Score		11.89±7.71	9.72±5.94	-2.17±2.09*	9.33±7.65	8.61±7.35	-0.72±1.22*

* **P-value < 0.05 by Wilcoxon signed-rank test**

Table 4. Difference of PHQ-9 score between two group

	Intervention group (n=18) (Mean ± SD)	**Usual care group (n=18)** (Mean ± SD)	**Difference between two group** [95% CI]	P-value*
Mean difference Score	2.17±2.09	0.72±1.22	-1.44 [-2.61 - -0.28]	0.02

P-value from Mann-Whitney U Test (Rank-sum) for independent group

Four participants (22.22%) in the intervention group and six (33.33%) in the usual care group were lost to follow-up at the end of the study. The study's findings were consistent with the attrition and adherence rates in smartphone-delivery interventions for mental health problems, which were both 24.1%.[27] The intervention group, on the other hand, had a lower rate of attrition than related studies, which could have been due to the tailored intervention and the relationship between the investigators and participants.

Several studies found that receiving pharmaceutical care intervention improved medication adherence. Recent systematic reviews and meta-analyses of RCTs discovered that pharmacist intervention with in-person counseling could improve antidepressant adherence. This review, however, found neither evidence of a positive effect on clinical symptoms, which was inconsistent with the findings of this study.[9] The intervention group that received tailored in-person pharmaceutical care counseling as well as the use of a specific-depression app experienced a reduction in mean difference in depression scores with statistical significance.

To the best of our knowledge, this is the first study to investigate tailored in-person pharmaceutical care counseling along with a depression-specific smartphone app to improve medication adherence in new patients with depression. This study, however, had limitations. First, the study enrolled 36 participants based on the sample size, but only 26 participants participated in the results analysis. The COVID-19 outbreak caused the government to lock down all activities at the time. The investigators used the ITT analysis to reduce biases. Second, due to the COVID-19 pandemic, the data collection and follow-up period was reduced from two visits to one. This is still very concerning that one month is usually not enough time to evaluate the full effects of antidepressant therapy. However, some clinical symptoms could respond to antidepressant rapidly such as sleep problems. Third, there could have been other confounding factors that were not controlled for, such as some participants receiving psychotherapy prior to visiting the investigators, which could have influenced the results.

Further research should be carried out with a larger sample size and over a longer period of time. Other patient outcomes

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should be prioritized, particularly hospitalization and costs. Consider developing a tele-pharmacy program for patients suffering from all mental illnesses, particularly schizophrenia.

CONCLUSION

This study found that new patients with major depressive disorders who received tailored in-person pharmaceutical care counseling along with the introduction use of a depression-specific smartphone app improved their medication adherence. In addition, improvement in overall depression symptoms was discovered.

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CONFLICTS OF INTEREST:

The authors declare that there are no conflicts of interest.

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DATA AVAILABILITY:

Data will be available on request from the authors.

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