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Pharmaceutical Care and Smartphone Applications in Major Depressive Disorder: Effects on Medication Adherence

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ABSTRACT

Failure to adhere to prescribed medications can result in numerous adverse clinical outcomes, such as elevated chances of relapse and disease recurrence. Through the delivery of personalized, face-to-face pharmaceutical care guidance, pharmacists have a vital role in fostering better medication adherence. In contemporary society, smartphones are among the most prevalent modes of communication. Therefore, incorporating a dedicated smartphone application for managing depression represents a promising approach to optimizing patient results. To determine if targeted counseling for depression paired with a specialized smartphone application can boost medication adherence in individuals recently diagnosed with major depressive disorder (MDD). This was a prospective, randomized pilot trial involving patients with newly identified major depressive disorder. Participants were allocated randomly to the intervention or standard care arms in a 1:1 ratio. The intervention arm received face-to-face pharmaceutical care guidance combined with training on a depression-focused smartphone application, while the standard care arm was provided with conventional pharmaceutical guidance and a basic chatbot. Medication adherence, the main endpoint, was assessed via the Medication Adherence Rating Scale (MARS) and pill count percentage (PC) during the one-month follow-up visit. As a secondary endpoint, the Patient Health Questionnaire-9 (PHQ-9) was employed to evaluate changes in depressive symptomatology. A total of 36 individuals finished the trial (18 in each arm). The mean participant age was 29.81 years, and 65.38% were women. Both arms exhibited comparable baseline features, including initial PHQ-9 values. The intervention arm recorded a mean MARS score of 7.0 (IQR=5), surpassing the standard care arm's mean of 4.5 (IQR=7; p-value=0.04). Pill count percentage was higher in the intervention arm at 81.75 (IQR=33.33) compared to 69.95 (IQR=78.57) in the standard care arm (p-value=0.10). The average change in PHQ-9 scores across visits showed a difference of -1.44 [-2.61 to -0.28] favoring the intervention arm (p-value=0.02). The findings indicate that individuals newly diagnosed with major depression who were given specialized pharmaceutical guidance for depression alongside a smartphone application exhibited enhanced medication adherence. Moreover, there was a notable amelioration in general depressive symptomatology.

Keywords: Medication adherence, Pharmaceutical care, Counseling smartphone, Pharmacist, Depression, Mental health

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Introduction

Depression ranks as one of the most widespread mental health conditions globally. It affects roughly 280 million people worldwide. The prevalence of depression remains substantial and is on an upward trajectory, influencing about 3.8% of the global population—this includes 5.0% of adults and 5.7% of those aged over 60. On a global scale, suicide claims nearly 800,000 lives each year, translating to one death every 40 seconds. Within the World Health Organization (WHO) European region, annual suicides number around 128,000 [1].

At present, the primary treatment modalities for major depressive disorders encompass pharmacotherapy and non-pharmacological interventions. For moderate to severe cases, antidepressants are frequently prescribed to help

modulate brain-derived neurotrophic factor (BDNF) pathways. BDNF serves as a key modulator of diverse neuronal plasticity mechanisms in the brain, and such plasticity is increasingly associated with the therapeutic actions of antidepressants [2]. These medications aid in diminishing symptom intensity, stabilizing manifestations, and lowering relapse risks. Effective pharmacotherapy often demands extended use of antidepressants, underscoring the importance of consistent adherence for successful depression management [3].

Individuals suffering from depression frequently display poor medication adherence, with this issue being particularly pronounced among those newly diagnosed. First-time antidepressant users typically achieve adherence levels of only around 50% in the early months [4]. According to a contemporary meta-analysis, patients with severe psychiatric illnesses (encompassing schizophrenia, major depressive disorder, and bipolar disorder) using psychotropic drugs showed a collective nonadherence rate of 49%, and for MDD in particular, adherence stood at just 50% [5].

Lack of adherence to medications triggers a range of negative clinical impacts. Primarily, it markedly increases the likelihood of relapse and recurrence, with evidence indicating these occurrences are 8 times more common than in patients maintaining ongoing treatment. Furthermore, those demonstrating strong antidepressant adherence experience approximately 20% reductions in hospitalization durations and emergency visits relative to poorly adherent counterparts. Additionally, optimal adherence correlates with superior therapeutic responses, including symptom reductions of up to 50%. From an economic perspective, sustained adherence is linked to reduced overall healthcare expenditures owing to abbreviated treatment needs [6].

Pharmacists are instrumental in enhancing adherence by offering tailored guidance that addresses aspects like patient expectations and perspectives, detailed antidepressant information (encompassing advantages, adverse effects, and coping strategies), as well as regular monitoring of treatment effectiveness and safety [7]. Evidence suggests that interventions led by pharmacists can bolster adherence and yield improved outcomes in conditions such as hypercholesterolemia, hypertension, chronic obstructive pulmonary disease, and asthma, although statistical significance for depressive symptoms was not established in that work [8]. An up-to-date meta-analysis of randomized controlled trials (RCTs) has affirmed that pharmacist-led efforts, particularly face-to-face education and counseling, positively impact adherence among those with depression [9, 10].

Presently, smartphones represent one of the most common means of communication, owing to extensive technological penetration, particularly internet access. As such, interventions delivered via smartphones ought to serve as a vital approach for enhancing patient outcomes. For instance, SMS-based interventions, incorporating medication reminders and psychoeducational content, have been shown to boost adherence and achieve better HIV viral suppression in individuals living with HIV [11]. A systematic review has offered support for the efficacy of smartphone applications in managing mental health conditions, with a significant portion of studies focusing on depression [12]. Additionally, a meta-analysis of randomized controlled trials (RCTs) indicated that mental health interventions delivered through smartphones, including cognitive behavioral therapy (CBT) and other psychological approaches, can effectively alleviate depressive symptoms [12-14].

Regarding medication adherence, smartphone-based interventions stand out as an effective method for encouraging patients to follow their regimens. Multiple investigations have highlighted the advantages of such interventions in elevating adherence levels among individuals with chronic illnesses, notably HIV, type 2 diabetes, and cancer [15-17].

One digital-based approach reported elevated levels of self-reported medication compliance. A contemporary systematic review observed that adherence rates were generally high throughout the study period in patients with mood disorders; however, definitive attribution of improvements over baseline to the intervention was challenging due to the reliance on observational designs and absence of control groups [18]. In one RCT, mobile technology was employed to enhance adherence in HIV patients who also had comorbid bipolar disorder [19]. Adherence to both antiretroviral and psychotropic medications was greater in the intervention arm, though the differences did not reach statistical significance. Research specifically examining smartphone-based interventions utilizing a dedicated depression app for improving adherence in patients with major depressive disorder (MDD) is still limited. The researchers undertook this investigation to assess whether pharmaceutical care counseling tailored for depression, combined with a specialized smartphone app, could enhance medication adherence in patients newly diagnosed with MDD.

Materials and Methods

Study design and setting

This prospective, randomized pilot trial was performed at the outpatient clinic of Suan Prung Psychiatric Hospital (a super-tertiary care facility) in Thailand.

Participants and randomization

The study protocol received approval from the Human Research Ethics Committee of Suan Prung Psychiatric Hospital (4/2020). Informed consent was obtained from all participants. Inclusion criteria encompassed outpatients who were receiving a first-time diagnosis of major depressive episode according to the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes F32.0 to F32.2 by psychiatrists, aged 18 years or older, willing to utilize a smartphone application, and undergoing treatment during the data collection timeframe from November 2020 to February 2021. Exclusion criteria included a Clinical Global Impression – Severity scale (CGI-S) score exceeding 6, inability to attend follow-up visits, visual or hearing impairments, communication difficulties, diagnoses of Alzheimer's disease, dementia, neurodegenerative disorders, or any chronic condition necessitating additional medications.

Sample size was determined using the mean and standard deviation from the Morisky Medication Adherence Scale (MMAS) in a prior study (control group: 0.9 ± 1.4; intervention group: 2.2 ± 1.8), with $\alpha = 0.05$ and power $(1-\beta) = 0.80$ [19]. This yielded a requirement of 25 participants per group, resulting in a total of 50 subjects randomly assigned to either the intervention or usual care group in a 1:1 ratio. Randomization was achieved through computer-generated random numbers.

Intervention

The interveners consisted of pharmacy students operating under the guidance of a pharmacy faculty member and a clinical pharmacist from the Psychiatric Hospital. They provided customized face-to-face pharmaceutical care counseling to newly diagnosed depression patients and introduced the use of a depression-targeted smartphone app via a Line official account called "beside you" (known as "Kiang Kang" in Thai) to those in the intervention group (at Visit 0).

During Visit 0, intervention group participants were given personalized pharmaceutical care counseling covering fundamental aspects of depression, advantages of antidepressant therapy, expected treatment duration, basic lifestyle adjustments, medication details, frequent side effects, and self-management techniques for prevention and handling. After the counseling session, the "beside you" app was installed on participants' smartphones. The application was designed for ease of use and simplicity. It featured content on depressive disorders, antidepressant benefits, side effects and management strategies, self-care techniques, motivational messages, a real-time chat function with the investigators (enabling bidirectional interaction), and access to a mental health hotline. A key feature was automated daily medication reminders, dispatched twice daily at 8:00 a.m. and 8:00 p.m. **Figure 1** illustrates a sample of the app's content. The app's content was reviewed and validated for accuracy by two experts: a pharmacist specializing in psychiatry and a clinical pharmacist.

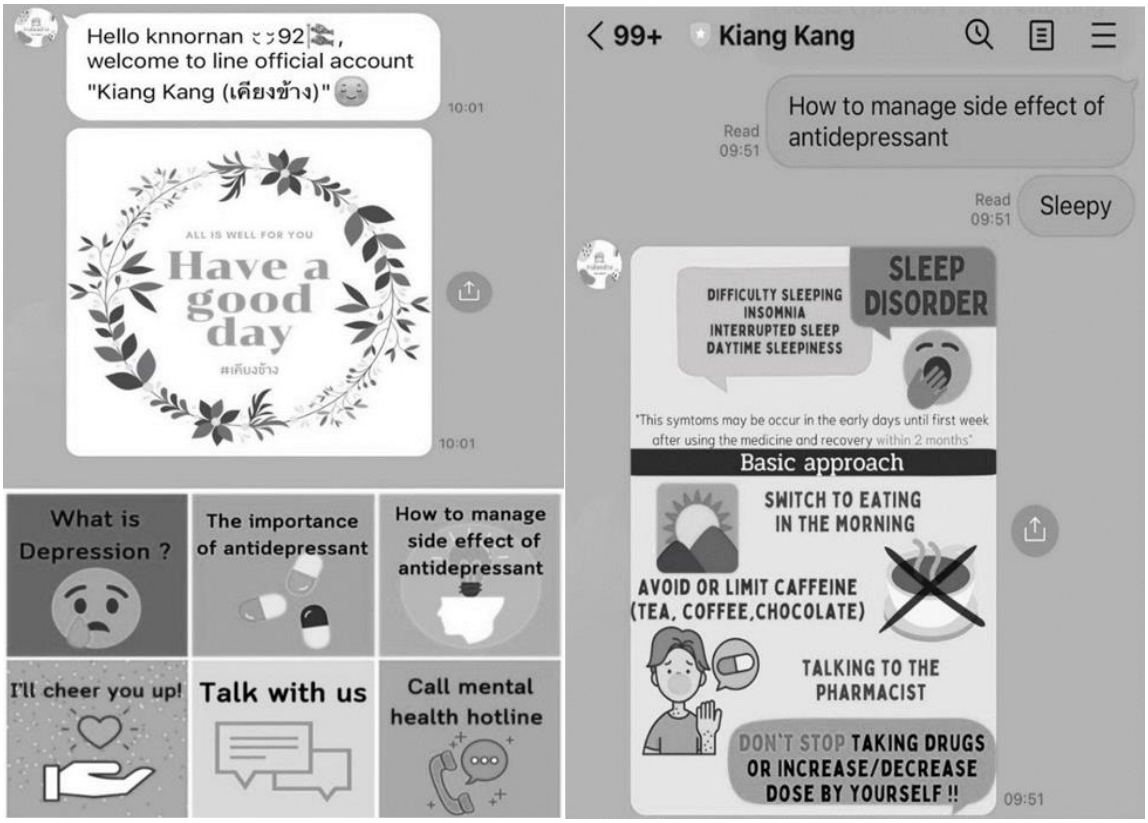

Figure 1. An example of app "Beside you or Kiang Kang in Thai" content

In the control group (usual care), participants were provided with conventional pharmaceutical care counseling that encompassed basic medication details, typical side effects, and self-management techniques for preventing or addressing them. The session primarily emphasized dispensing-related aspects, including the drug's indications and recommended administration times. Additionally, participants received access to a smartphone application, though it was limited to a basic chatbot functionality.

Outcome measures

The primary endpoint focused on medication adherence levels, evaluated through the Medication Adherence Rating Scale (MARS), supplemented by the pill count percentage in comparison to the usual care group at the one-month follow-up (Visit 1). The MARS serves as a validated and dependable instrument for assessing compliance with psychotropic drugs [20]. Participants chose the response that most accurately captured their medication-related behaviors or perspectives over the preceding week. Pill count percentage was derived by dividing the number of doses actually consumed by the expected total and then multiplying by 100. The secondary endpoint involved depressive symptomatology, quantified via the Thai-language Patient Health Questionnaire-9 (PHQ-9) [21]. The investigators recorded all endpoints during the participants' second clinical appointment (Visit 1).

Data and statistical analysis

Data processing and statistical evaluation were performed using STATA software, Version 14.0. The analysis adhered to an intention-to-treat protocol. Summary statistics for continuous variables were expressed as means accompanied by standard deviations. Variable distribution normality was evaluated via the Kolmogorov-Smirnov test. Inter-group comparisons employed the Mann-Whitney U Test (rank-sum approach). A p-value below 0.05 indicated statistical significance.

Results and Discussion

Baseline characteristics

Overall, 36 individuals were randomized into two arms: one receiving personalized initial in-person pharmaceutical care counseling combined with orientation to the "beside you" application, and the other receiving standard pharmaceutical care counseling with orientation to a chatbot application. The study flow is illustrated in **Figure 2**. At follow-up, four individuals from the intervention arm and six from the usual care arm failed to attend their scheduled appointments. The overall mean age stood at 29.81 years, with females comprising 65.38% of the sample. As detailed in **Table 1**, no meaningful differences emerged in baseline features across groups. Depression severity was gauged using the PHQ-9, where the predominant category in both arms was moderate, reflected in mean scores of 15.61 ± 4.3 for the intervention arm and 14.61 ± 3.9 for the usual care arm. Mild suicidality affected 55.6% of individuals in each arm. Selective Serotonin Reuptake Inhibitors (SSRIs) were prescribed to 83.3% of cases across both arms. Typically, the intervention arm involved three prescribed items, compared to two in the usual care arm.

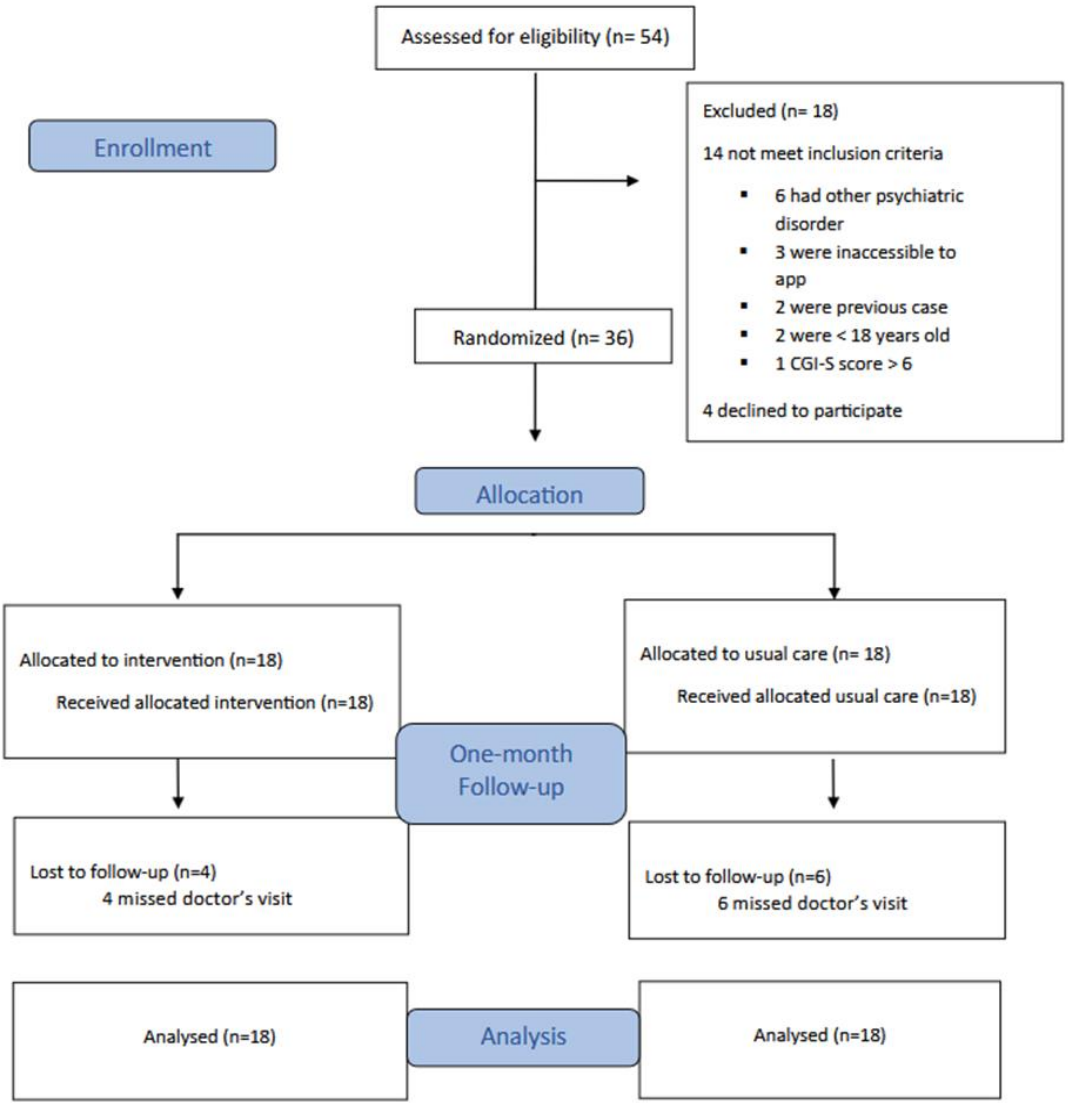

Figure 2. Flow diagram of the study

Table 1. Baseline Characteristics

Characteristic	Usual Care Group (n=18)	Intervention Group (n=18)	P-value
	n (%)	n (%)	
Gender			
Female	10 (55.56)	11 (61.11)	
Age (mean ± SD)	32.61 ± 14.6	29.56 ± 12.0	0.50
Education			0.40

Unschooled	0 (0.00)	1 (5.56)	
Primary	4 (22.22)	2 (11.11)	
High school	3 (16.67)	4 (22.23)	
University	11 (61.11)	11 (61.11)	
Marital status			0.69
Single	14 (77.78)	15 (83.33)	
Married	3 (16.67)	1 (5.56)	
Divorced	1 (5.56)	2 (11.11)	
Occupation			0.81
Employed	2 (11.11)	1 (5.56)	
Unemployed	5 (27.78)	6 (33.33)	
Student	11 (61.11)	11 (61.11)	
Comorbidity			0.70
At least 1 comorbid condition	4 (22.22)	5 (27.78)	
Depression severity (PHQ-9 score)			0.50
Mild	7 (38.89)	4 (22.22)	
Moderate	8 (44.44)	9 (50.00)	
Severe	3 (16.67)	5 (27.78)	
Mean (± SD)	14.61 ± 3.9	15.61 ± 4.3	0.47
Number of psychiatric medications			0.09
1 medication	0 (0.00)	0 (0.00)	
2 medications	13 (72.22)	8 (44.44)	
3 medications	5 (27.78)	10 (55.56)	
Psychotropic agents			
SSRIs	15 (83.33)	15 (83.33)	1.00
TCAs	1 (5.56)	5 (27.78)	0.07
BZDs	18 (100.00)	17 (94.44)	0.31
SNRIs	0 (0.00)	1 (5.56)	0.31
NDRIs	1 (5.56)	1 (5.56)	1.00
Mirtazapine	1 (5.56)	0 (0.00)	0.31
Antipsychotics	1 (5.56)	5 (27.78)	0.07

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

Depressive symptoms

By Visit 1, PHQ-9 evaluations indicated reduced average item scores in both arms relative to baseline (Visit 0), as outlined in **Table 2**. **Table 3** reveals that the intervention arm exhibited a mean PHQ-9 reduction of 2.17 ± 2.09, versus 0.72 ± 1.22 in the usual care arm (p-value = 0.02).

Table 2. PHQ-9 item score compared between intervention and usual care groups (V0-V1)

PHQ-9 Items	Description	Usual Care Group (n=18)			Intervention Group (n=18)		
		Visit 0	Visit 1	Mean Difference	Visit 0	Visit 1	Mean Difference
1	Little interest or pleasure in doing things	1.22±1.11	1.11±0.96	-0.11±0.58	1.50±1.10	1.39±1.14	-0.11±0.68
2	Feeling down, depressed, or hopeless	1.39±1.20	1.22±1.06	-0.17±0.62	1.78±1.17	1.78±1.17	-0±0.48
3	Trouble falling or staying asleep, or sleeping too much	1.61±1.29	1.28±1.13	-0.33±0.48*	1.78±1.17	1.11±0.83	-0.67±0.84*
4	Feeling tired or having little energy	1.11±0.96	1.06±0.94	-0.06±0.24	1.50±1.20	1.22±1.06	-0.28±0.96*
5	Poor appetite or overeating	1.17±1.04	1.00±0.97	-0.17±0.86	1.44±1.10	1.11±0.90	-0.33±1.03*

6	Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0.94±0.87	0.94±0.87	-0.00±0.00	1.11±1.02	1.0±0.97	-0.11±0.32
7	Trouble concentrating on things, such as reading the newspaper or watching television	0.83±1.04	0.78±0.94	-0.06±0.42	1.17±1.10	1.11±1.13	-0.66±0.24
8	Moving or speaking so slowly that other people could have noticed. Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0.39±0.78	0.39±0.78	-0.00±0.00	0.72±0.83	0.72±0.83	-0.00±0.00
9	Thoughts that you would be better off dead, or of hurting yourself	0.67±0.84	0.83±0.92	-0.17±0.38*	0.88±0.90	0.28±0.46	-0.61±0.70*
Total	**Mean Score**	**9.33±7.65**	**8.61±7.35**	**-0.72±1.22***	**11.89±7.71**	**9.72±5.94**	**-2.17±2.09***

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

Table 3. Difference of PHQ-9 score between two group

Outcome	Between-Group Difference [95% CI]	Intervention Group (n=18) (Mean ± SD)	Usual Care Group (n=18) (Mean ± SD)	P-value*
Mean change in PHQ-9 score	-1.44 [-2.61 to -0.28]	2.17 ± 2.09	0.72 ± 1.22	0.02

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

Medication adherence

Differences in MARS scores and pill count percentages between the intervention and usual care arms at Visit 1 are presented in **Table 4**. Notable disparities in adherence emerged between arms. The intervention arm recorded a median MARS score of 7.0 (IQR = 5), surpassing the usual care arm's median of 4.5 (IQR = 7; p-value = 0.03). For pill count percentage, the intervention arm showed a median of 81.75 (IQR = 33.33), compared to 69.95 (IQR = 78.57) in the usual care arm (p-value = 0.10).

Table 4. Medication adherence score at Visit 1

Measure	Usual Care Group (n=18) Median [25th-75th percentile, IQR]	Intervention Group (n=18) Median [25th-75th percentile, IQR]	P-value*
MARS	4.5 [0-7, 7]	7.0 [4-9, 5]	0.04
Percentage of pills counted	69.65 [0-78.57, 78.57]	81.75 [66.67-100, 33.33]	0.10

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

Based on the findings of this study, newly diagnosed patients with depression who underwent personalized in-person pharmaceutical care counseling combined with access to a depression-focused smartphone application demonstrated enhanced medication adherence, as assessed by the MARS, following a one-month period. Moreover, the intervention group exhibited a greater reduction in overall depressive symptoms compared to the usual care group.

The research targeted newly diagnosed patients with MDD due to their elevated risk of medication nonadherence. Evidence indicates that 42% of individuals with depression take antidepressants sporadically within the initial 30 days of treatment and cease them within 90 days [22]. Additionally, as many as 70% of patients prescribed their first antidepressant exhibit nonadherence within six months [23]. Key factors affecting adherence to psychotropic medications include misconceptions regarding addiction potential, frequent adverse effects, inadequate therapeutic response, poor communication about treatment duration, discontinuation protocols, and medication switches [24]. One survey of patients prescribed clozapine further revealed feelings of exclusion from patient-centered care [25]. To promote optimal adherence, the researchers designed structured pharmaceutical care interventions tailored for newly diagnosed MDD patients. Efforts were made to enhance skills like active listening,

open-ended inquiries, and empathetic reflection during initial encounters to build trusting pharmacist-patient relationships and support patient-centered approaches. Comprehensive information on antidepressants and depressive disorders was delivered to intervention group participants until full understanding was achieved. This approach aligns with prior research emphasizing discussions on therapy duration and side effects to minimize antidepressant discontinuation [22]. Constant access to reliable information on antidepressants and depression via the app proved valuable, particularly for patients seeking reassurance in managing side effects independently rather than stopping treatment. Automated daily medication reminders also contributed to better adherence. These results parallel those from a study showing that mobile text messages enhanced compliance in individuals with type-2 diabetes [26].

Loss to follow-up occurred in four participants (22.22%) from the intervention group and six (33.33%) from the usual care group by study completion. The observed rates align with attrition and adherence figures in smartphone-based interventions for mental health conditions, reported at 24.1% [27]. Notably, the intervention group displayed lower attrition than comparable studies, potentially attributable to the customized intervention and strengthened investigator-participant rapport.

Multiple investigations have shown that pharmaceutical care interventions boost medication adherence. Recent systematic reviews and meta-analyses of RCTs indicate that pharmacist-led in-person counseling enhances antidepressant compliance. However, these reviews identified no clear benefit on clinical symptoms, contrasting with the current study's outcomes [9]. The group receiving personalized in-person counseling alongside a depression-specific app achieved a statistically significant reduction in mean depression score differences.

To our knowledge, this represents the inaugural investigation examining combined tailored in-person pharmaceutical care counseling and a depression-targeted smartphone application to enhance medication adherence among newly diagnosed depression patients. Nevertheless, limitations exist. Firstly, although recruitment targeted 36 participants per the sample size calculation, only 26 contributed to final analyses. The COVID-19 pandemic prompted governmental lockdowns during this period. Intention-to-treat analysis was applied to mitigate potential biases. Secondly, pandemic restrictions shortened data collection and follow-up from two visits to one. One month remains insufficient for fully assessing antidepressant efficacy, though certain symptoms, such as sleep disturbances, may improve rapidly. Thirdly, uncontrolled confounders may have influenced results, including prior psychotherapy received by some participants before study involvement.

Future studies should involve larger cohorts and extended durations. Additional outcomes warrant emphasis, notably hospitalization rates and associated costs. Exploration of tele-pharmacy initiatives for broader mental health conditions, especially schizophrenia, is recommended.

Conclusion

This research demonstrated that newly diagnosed patients with major depressive disorder receiving personalized in-person pharmaceutical care counseling together with orientation to a depression-specific smartphone application exhibited improved medication adherence. Furthermore, notable enhancements in overall depressive symptoms were observed.

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Conflict of Interest: None

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Ethics Statement: None

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