Reminder through mobile messaging application improves outpatient attendance and medication adherence among patients with depression: An open-label randomised controlled trial

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ABSTRACT

Introduction: Non-attendance and medication adherence are longstanding concerns in psychiatric outpatient settings. This study aimed to determine effectiveness of reminders using mobile messaging applications (messaging apps) in improving outpatient attendance and medication adherence among patients with depression.

Methods: This was a parallel, open-label randomised controlled trial with participants recruited from psychiatric outpatient services of a teaching hospital in Kuala Lumpur and a secondary hospital in Melaka. Adults (≥18 years) diagnosed with major depressive disorder; capable of reading and understanding English or Bahasa Malaysia; prescribed with at least one antidepressant and owns a smart phone were subsequently randomly assigned (1:1) to receive treatment reminders (intervention) or standard treatment without reminders (control), using a computergenerated randomisation programme. The intervention group received two reminder categories: Outpatient appointment reminders (a day before appointment); and medication reminders (weekly basis). Participants were followed-up over two months. We utilised Montgomery-Asberg Depression Rating Scale (MADRS) to measure the severity of depression; and Brief Adherence Rating Scale (BARS) to assess medication adherence. Primary outcomes were outpatient attendance rates and medication adherence assessed at two months. Secondary outcomes included changes in depression severity within each group at two months; comparison of changes in depression severity between both groups; preferences of participants towards treatment reminders, and reasons for non-attendance among participants. This trial was registered with the National Medical Research Registry, NMRR-19-3466-52001.

Results: Between February and April 2020, 183 participants were randomised to each group, of whom 179 reached study endpoint (91 [98.9%] of 92 in intervention group and 88 [96.7%] of 91 in control group). All recruited participants (n=183) were analysed using intention-to-treat approach. At two months, intervention group has significantly higher outpatient attendance rates (76.8%) than control group (56.4%) (p=0.002), and reported higher medical adherence

percentage (mean difference 23.1, [95%CI 0.4, 35.8]; p<0.001). There was also significant difference in the MADRS score change between both groups (mean difference 3.4, [95%CI 0.4, 6.3]; p=0.025). Treatment reminders preferences among participants varied; forgetfulness was the most commonly reported reason (53%) for missing outpatient appointments.

Conclusion: Reminders through mobile messaging applications significantly improved outpatient attendance and medication adherence among patients with depression. Our findings support the use of messaging apps for treatment reminders in psychiatric outpatient settings. However, concerns regarding confidentiality require careful measures to be taken.

KEYWORDS:

Medication adherence, Depression, Outpatients, Mental health services, Mobile applications, Randomised controlled trial

INTRODUCTION

Non-attendance has been a longstanding issue within the healthcare system in Malaysia and is more likely to occur in the psychiatric setting compared to other specialties in medicine.¹ For psychiatric patients, non-attendance predicts higher risk of relapse and readmission.¹ A recent systematic review identified reasons for outpatients non-attendance include transportation issues, forgetfulness, poor risk perception and opportunity costs.²

Non-adherence to medication is another area of concern, associated with poorer prognosis and incremental differences of treatment cost. The rate of non-adherence among patients with depression ranged from 40% to $66.9\%^{3.5}$, with forgetfulness being the main reason for non-adherence in majority.⁶ Antidepressants were also found to have the highest proportion (74.5%) of reporting forgetfulness as reason, among all psychotropic medications.⁵

Individuals with depressive symptoms had shown 12% reduction in memory functioning.⁷ The nature of depression, such as lack of motivation, being pessimistic towards

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treatment and recovery could further contribute to nonattendance and medication non-adherence. Considering the above, reminders might not only benefit depressed individuals in terms of tackling forgetfulness, but also encourages treatment adherence.

Many studies have proven the efficacy of different reminder forms - such as phone calls, emails and short message service (SMS) - with disparities in cost-efficiency and staff dependence. However, studies on reminders utilising mobile messaging applications (messaging apps) to improve psychiatric outpatient attendance and medication adherence are relatively few. With the continuously increasing penetration of smartphones among Malaysians,⁸ 97.3% of Malaysian internet users are using messaging apps in January 2021.⁹ suggesting this to be the most efficient method for reminders delivery.

The primary objective of this study was to assess outpatient attendance rates and medication adherence of intervention and control group. Secondary objectives included determining changes in depression severity within each group between baseline and two months; comparing changes in depression severity between both groups; identifying preferences of participants towards treatment reminders, and exploring reasons for missing outpatient appointments among patients with depression.

MATERIALS AND METHODS

Study design

This is an open-label randomised controlled trial conducted in two psychiatric outpatient settings of different states in Malaysia: University Malaya Medical Centre (UMMC), a university hospital located in Kuala Lumpur; and Hospital Melaka (HM), a secondary hospital located in state of Malacca, approximately 150km away from Kuala Lumpur. The study was conducted between February and June 2020.

Ethical approvals for the study were obtained from Medical Research Ethics Committee of UMMC (MREC ID: 20191127-8047) and Medical Research and Ethics Committee of the Ministry of Health Malaysia, through the National Medical Research Registry (NMRR) (NMRR ID: NMRR-19-3466-52001).

Participants

Participants were 18 years old and above, newly diagnosed patients with major depressive disorder (MDD) according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria, capable of reading and understanding either English or Bahasa Malaysia, prescribed with at least one antidepressant, owns a smart phone and consented to partake in the study. Participants were excluded from the study if they were diagnosed with severe medical condition(s), which might affect their cognitive function and physical ability to travel to hospital independently; or other major psychiatric disorders with psychotic symptoms and/or severe cognitive impairment. Written informed consent was obtained from all participants, and each of them was followed up for two months.

Randomisation and Procedures

Upon recruitment, participants were required to fill up the Socio-Demographic Questionnaire and Treatment Reminder Preference Questionnaire. Baseline depression severity were then assessed using Montgomery-Asberg Depression Rating Scale (MADRS) before they were randomly assigned (1:1) to intervention or control group. Participants were randomised through block randomisation (size of 8) and random number generation using a computer-generated randomisation programme.

The intervention group received both reminder types: i) Medication adherence - at one week after last outpatient appointment and weekly thereafter; ii) Outpatient appointment - at one day before appointment. Reminders were delivered through their preferred mobile messaging applications as indicated, which comprised of either WhatsApp, WeChat, Telegram or Line. The control group did not receive any reminders. Throughout the two months of follow-up, attendance of each participant was tracked through the electronic medical record system in UMMC, and daily manual attendance records in HM. For the intervention group, those who had missed their appointments would be reminded once for rescheduling. The control group would not receive any reminder under similar circumstances.

At two months after randomisation, all participants were assessed with MADRS and Brief Adherence Rating Scale (BARS) during their outpatient appointment.

Outcomes

The primary outcomes were outpatient attendance rate and medication adherence (BARS percentage), assessed at two months. Outpatient attendance rate was calculated by dividing number of appointments attended by number of appointments scheduled within study period. Missed appointments were coded as absent, and participants who missed their appointments were contacted through phone to enquire regarding reasons for non-attendance. Appointments cancelled by psychiatrists or rescheduled ahead of time were excluded from analysis.

Brief Adherence Rating Scale (BARS) is a clinicianadministered adherence assessment tool. It comprises three questions and a visual analogue scale to assess proportion of doses taken in the past month (0–100%). BARS demonstrated good sensitivity (73%) and specificity (74%) in identifying non-adherent outpatients.¹⁰

Secondary outcomes assessed at two months include MADRS score difference from baseline within each group; comparison of MADRS score difference between both groups; preferences regarding treatment and medication reminders; and reasons missing outpatient appointments.

Montgomery-Asberg Depression Rating Scale (MADRS) is a clinician-administered scale for depression severity assessment, particularly sensitive in evaluating treatment effects. It includes ten items rated on a 0 to 6 scale, yielding a total score from 0 to 60. Usual cut-off points are 0 to 6 for normal; 7 to 19 for mild depression; 20 to 33 for moderate depression; 34 and above for severe depression. MADRS has

	Total (n=183)	Intervention group (n=92)	Control group (n=91)	p value
Age, years				
Mean (SD)	29.4 (11.7)	30.5 (13.0)	28.3 (10.2)	0.618*
Median (IQR)	25 (13)	25 (17)	25 (11)	
Gender				
Male	61 (33.3%)	33 (35.9%)	28 (30.8%)	0.464**
Female	122 (66.7%)	59 (64.1%)	63 (69.2%)	
Ethnicity				
Malay	126 (68.9%)	60 (65.2%)	66 (72.5%)	0.271**
Chinese	33 (18.0%)	17 (18.5%)	16 (17.6%)	
Indian	14 (7.7%)	7 (7.6%)	7 (7.7%)	
Others	10 (5.5%)	8 (8.7%)	2 (2.2%)	
Marital status				
Single	116 (63.4%)	58 (63.0%)	58 (63.7%)	0.909**
Married/ partnership	59 (32.2%)	29 (31.5%)	30 (33.0%)	
Divorced	5 (2.7%)	3 (3.3%)	2 (2.2%)	
Widowed	3 (1.6%)	2 (2.2%)	1 (1.1%)	
Occupation				
Employed	66 (36.1%)	36 (39.1%)	30 (33.0%)	0.205**
Self-employed	8 (4.4%)	3 (3.3%)	5 (5.5%)	
Unemployed	16 (8.7%)	5 (5.4%)	11 (12.1%)	
Retired	6 (3.3%)	5 (5.4%)	1 (1.1%)	
Homemaker	14 (7.7%)	5 (5.4%)	9 (9.9%)	
Student	73 (39.9%)	38 (41.3%)	35 (38.5%)	
Education level				
Primary	3 (1.6%)	1 (1.1%)	2 (2.2%)	0.779**
Secondary	42 (23.0%)	19 (20.7%)	23 (25.3%)	
Post-secondary	16 (8.7%)	9 (9.8%)	7 (7.7%)	
Higher	122 (66.7%)	63 (68.5%)	59 (64.8%)	
Travel distance (house to hospital), km				
<5	41 (22.4%)	21 (22.8%)	20 (22.0%)	0.354**
5 – 10	41 (22.4%)	16 (17.4%)	25 (27.5%)	
10 – 15	60 (32.8%)	31 (33.7%)	29 (31.9%)	
>15	41 (22.4%)	24 (26.1%)	17 (18.7%)	

Table I: Baseline socio-demographic characteristics of participants

Table II: Comparison of outcome measures between intervention and control group

	Intervention group (n=92)	Control group (n=91)	Mean difference (95% CI)	t-statistic (df)	Z-statistic	p value
Primary outcomes						
Attendance percentage						
Mean (SD)	76.8 (35.3)	56.4 (44.5)				
Median (IQR)	100 (50)	67 (100)			-3.161	0.002*
BARS percentage						
Mean (SD)	60.2 (43.1)	37.1 (44.0)	23.1 (0.4, 35.8)	3.59 (181)		<0.001**
Secondary outcome						
Mean of MADRS score change (SD)	9.4 (10.8)	6.0 (9.1)	3.4 (0.4, 6.3)	2.27 (181)		0.025**

SD=Standard deviation; IQR=Interquartile range. *Mann-Whitney test **Independent t-test. CI: Confidence interval; df: Degrees of freedom; BARS: Brief Adherence Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale.

Table III: MADRS score changes within both groups

	Mean of MADRS score (SD)		Mean of MADRS score change	p value*
	Baseline	Two months	(95% CI)	
Intervention group	32.7 (10.1)	23.3 (12.4)	9.4 (7.2, 11.6)	<0.001
Control group	32.6 (9.5)	26.5 (12.1)	6.0 (4.1, 7.9)	<0.001

SD=Standard deviation. *paired t-test. CI: Confidence Interval; MADRS: Montgomery-Asberg Depression Rating Scale.

Variables	n (%)
Agreement towards reminders	
Yes	180 (98.4)
No	3 (1.6)
Reason agreeing	
To avoid forgetting	54 (29.5)
Being forgetful	43 (23.5)
Convenience	30 (16.4)
Being health-conscious	2 (1.1)
Feeling of concern	2 (1.1)
Others	4 (2.2)
No specific reason	45 (24.6)
Not applicable – opted for "Disagree"	3 (1.6)
Concerns regarding confidentiality	5 (1.0)
Present	80 (43.7)
Absent	103 (56.3)
Timing for reminders (throughout the day)	
Morning	74 (40.4)
Afternoon	31 (16.9)
Evening	50 (27.3)
Office hours	5 (2.7)
Anytime	20 (10.9)
No preference	3 (1.6)
Day for appointment reminders, prior to appointment	5 (1.0)
One day	38 (20.8)
Two days	36 (20.8)
Three days	29 (15.8)
One week	26 (14.2)
One week, along with one day	19 (10.4)
Two days, along with one day	6 (3.3)
Others	24 (13.3)
No preference	5 (2.7)
	5 (2.7)
Frequency of medication reminders	10 (5 5)
Monthly	10 (5.5)
Fortnightly	4 (2.2)
Weekly	59 (32.2)
Twice per week	14 (7.7)
Daily	20 (10.9)
Once in between appointments	9 (4.9)
No preference	4 (2.2)
Not required	63 (34.4)
Preferred mobile messenger application	4.50 (07.1)
WhatsApp	160 (87.4)
Telegram	13 (7.1)
WeChat	1 (0.5)
WhatsApp or Telegram	5 (2.7)
WhatsApp or WeChat	1 (0.5)
Not applicable – opted for "Disagree"	3 (1.6)

Table IV: Preferences	towards	reminders	usina	mobile	messaging	application

high inter-rater reliability and validity, as its scores correlated well with scores on Hamilton Rating Scale for Depression (HAM-D), a standard rating scale for depression.¹¹

Statistical Analysis

The sample size for this study was calculated using the formula as below, taking $\alpha = 0.05$, $\beta = 0.2$ and the expected proportion from previous study by Branson et al. (12)

n=
$$\theta[\frac{\pi_t (1 - \pi_t) + \pi_c (1 - \pi_c)}{(\pi_t - \pi_c)^2}]$$

The smallest sample size to detect a difference between two groups was 154.

Data collected was analysed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, N.Y., USA). The intention-to-treat approach was used to include all participants who were recruited and randomly assigned into analysis. For those who missed their appointments or were withdrawn from study, their MADRS scores and BARS percentage were imputed as the last observed value, as per last observation carried forward (LOCF) method. All statistical tests were two-tailed with alpha value of 0.05. The main study parameters analysed include: i) Outpatient attendance rate of both groups compared using Mann-Whitney test; ii) Brief Adherence Rating Scale (BARS) percentage of both groups, along with MADRS score difference between both groups compared using independent t-test; iii) MADRS score difference from baseline within each

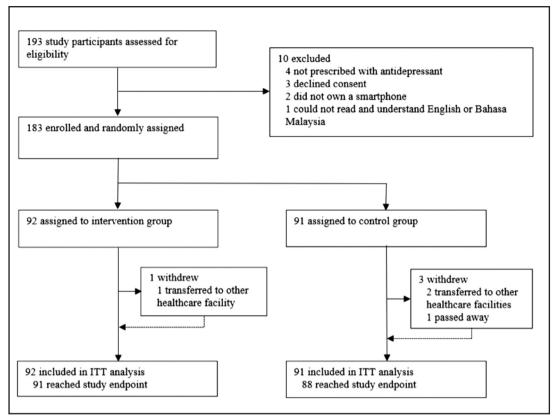


Fig. 1: Disposition of study participants.

group compared using paired t-test. Descriptive statistics were used to summarise data from Treatment Reminder Preference Questionnaire and reasons for non-attendance.

RESULTS

Between February and June 2020, from the 193 participants were assessed for eligibility in the study. 183 were recruited and 179 reached the study endpoint after two months of follow-up. All recruited participants were included for analysis, in accordance with intention-to-treat approach as shown in Figure 1.

Baseline socio-demographic data of both groups were comparable (Table I), with most participants being Malay females with higher education.

Attendance rate of intervention group (76.8%) was significantly higher than control group (56.4%) (p=0.002) (Table II). Similarly, the medication adherence (assessed using BARS) of intervention group (60.2%) was much higher than control group as well (37.1%) (p<0.001) (Table II).

For the secondary outcomes, MADRS scores had increased significantly in both groups after two months of treatment (p<0.001). The intervention group reported mean score change of 9.4 (95%CI 7.2, 11.6); while the control group reported mean score change of 6.0 (95%CI 4.1, 7.9) (Table III). Mean difference of the MADRS score change between the two groups was significant (p=0.025) at 3.4 (95%CI 0.4, 6.3) (Table II).

Our descriptive analyses show that 98.4% of participants preferred receiving reminders, with over half (53%) being concerned about forgetfulness. 43.7% (n=80) expressed concerns regarding confidentiality. 87.4% selected WhatsApp as their preferred mobile messaging application for reminders delivery (Table IV).

Forgetting the appointment was stated as the most common reason (31.0%, n=18) for participants to miss their outpatient appointments, followed by issues related with the national lockdown (20.7%) and personal issues (13.8%).

DISCUSSION

This study demonstrated that reminders through mobile messaging applications are effective in improving outpatient attendance and medication adherence among patients with depression. At two months, the increase in outpatient attendance rate of intervention group was 20% higher than that of control group (p=0.002). Interestingly, this difference is higher than recent studies which utilised short message service (SMS) reminders among general psychiatric patients: Kunigiri et al. found 8% increment of attendance rate among adult patients;¹³ while Branson et al. reported 16% increment among adolescents.¹² This might be due to varying levels of non-attendance among patients with different diagnoses. For instance, Rajasuriya et al. had reported significant higher risk of non-attendance in patients with substance misuse disorders, anxiety disorders and organic disorders, including dementia.¹⁴ Another possibility would be the higher efficacy of messaging apps in delivering reminders compared to SMS,

which would require direct comparisons in future to confirm said hypothesis.

Messaging apps reminders were effective in improving medication adherence among participants, with 60.2% of mean BARS percentage in intervention group compared to 37.1% in control group (p<0.001). This finding is similar to a meta-analysis focused on patients with non-communicable diseases,¹⁵ which reported significant increase in adherence in groups receiving reminders compared to controls. Significant MADRS score changes at two months within each group (p<0.001) showed that antidepressant treatment would improve depressive symptoms overall. We have also discovered association between reminders and MADRS score improvement with a mean difference of 3.4 (95%CI 0.4, 6.3) (p=0.025), which could be explained by the synergistic effect of improved outpatient attendance and medication adherence in intervention group.

Expectedly, forgetfulness was identified as the most common reason for non-attendance in our study (31.0%). This finding is similar to that of primary care setting, which reported forgetting about the appointment or unawareness being the most common reason for non-attendance (37.6%) (16). Forgetting clinic appointments can be multifactorial including life events, perceived importance of follow-ups, and the aforementioned nature of depression.

Implementation of reminder system in psychiatric outpatient setting was well accepted by almost all participants (98.4%), however 43.7% raised concerns about confidentiality on the reminder system. While mental health awareness has greatly improved in recent years, stigmatisation still prevails in certain populations with poorer mental health literacy.^{17,18} Confidentiality issues should be discussed explicitly to address these concerns and improve trust of patients. Majority of participants (87.4%) selected WhatsApp as the preferred mobile messaging application for reminders, in concordance with WhatsApp being ranked as most used messaging app among Malaysian internet users (91.9%) in first quarter of 2021.⁹ Feedbacks of participants towards reminder deliveries were generally positive, with considerable variations in preferred time and frequency of reminders.

There were several limitations in this study. As we had sent out reminders manually without counterchecking, confirmation receipts for messages were not warranted in this study. The Brief Adherence Rating Scale (BARS) used in this study was only validated for oral antipsychotics use. However, the psychometric properties of BARS are well demonstrated,10 with our data contributing to the understanding towards its adaptability in assessing antidepressant adherence. As the intervention was designed to be one-way reminders, several treatment queries (submitted as replies) were unanswered. This raised the need for an interactive platform, preferably with a triaging system to address and encourage patient engagement. Lastly, as the second half of study period coincided with national lockdown due to Coronavirus disease 2019 (COVID-19), the national lockdown acted as potential confounder in this study.

Future research could be undertaken in wider context with patients diagnosed with other psychiatric conditions, while utilising the data here as reference. Larger sample size across diverse healthcare settings, such as district hospitals and community clinics, would greatly improve the generalisability. Besides, the association between treatment reminders and greater MADRS score improvement can be formally explored. A link between hospital appointment data and messaging apps could be devised for automated reminders, with an interactive approach for patient to confirm or reschedule the appointment. Triaging system alerting medical staffs to responses with crucial health information would be useful as well. Lastly, a postintervention feedback could be gathered to recognise and work on any issue that arises.

Treatment reminders and service response to non-attendance are vital parts of patient care for psychiatric outpatients. Utilising messaging apps for this purpose should be considered given its high penetration and proven effectiveness.

CONCLUSION

Our findings show that reminders through mobile messaging applications improved both outpatient attendance and medication adherence among patients with depression, resulting in greater improvement of depressive symptoms. Treatment reminders were generally well accepted and feasible in a psychiatric outpatient setting. However, potential issues such as confidentiality should be carefully handled while advocating reminder services.

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CONFLICT OF INTEREST

None to declare.

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