**Mobile Messaging Assisted Treatment (MMAT) for Patients with Methamphetamine Use Disorder: A Preliminary Randomized Controlled Trial**

**Introduction:**

 Methamphetamine (MA) is a psychostimulant with high abuse potential. It can cause numerous physical and psychological harms (Darke, Kaye, McKetin, & Duflou, 2008). MA can increase dopamine release and block dopamine reuptake, resulting in an increased concentration of dopamine in synaptic clefts, especially in the brain’s reward system. MA-produced neurotoxic effects on monoaminergic neurons may relate to various psychiatric symptoms, such as depression (Glasner-Edwards et al., 2009), psychosis (Grant et al., 2012), and suicidality (Kuo et al., 2011). Furthermore, MA use can also cause serious adverse physical effects, such as the deterioration of oral health (i.e., caries, tooth fracture, gingivitis, and periodontitis) (Padilla & Ritter, 2008), cardiovascular disease (i.e. cardiomyopathy, myocardial ischemia, arrhythmia) (Kaye, McKetin, Duflou, & Darke, 2007), cerebral hemorrhage (McGee, McGee, & McGee, 2004), and blood-borne virus transmission (Gonzales, Marinelli-Casey, Shoptaw, Ang, & Rawson, 2006; R. A. Rawson et al., 2008; Vogt et al., 2006). Chronic MA use can also detrimentally affect other areas of life (e.g., high-risk sexual activity, criminal activity, and decreased academic performance). Additionally, MA use imposes a considerable burden on social service agencies and criminal justice systems in many countries due to legal offenses and other risky behaviors (Sheridan, Bennett, Coggan, Wheeler, & McMillan, 2006). Thus, the development of effective treatments for patients with MA use disorder has garnered substantial attention.

 Addiction is a chronic, relapsing condition. Long-term MA use results in neuroadaptation of the brain’s reward systems, which causes dependence, loss of control, compulsive use, and neurotoxicity (Moszczynska & Callan, 2017). In people with chronic MA use, structural changes to the brain, including decreased cortical and hippocampal volumes, may cause pervasive neuropsychological impairment to prospective memory, decision-making ability, and cognitive flexibility (Thanos et al., 2017). Effective pharmacotherapies for MA dependence lack supporting evidence; however, psychosocial interventions, such as the Matrix Model program (Shoptaw, Rawson, McCann, & Obert, 1994), cognitive behavioral therapy (Lee & Rawson, 2008), relapse prevention (Matsumoto et al., 2013), and contingency management (Roll et al., 2006), have demonstrated success. Completion of treatment or remaining in continued care has been shown to significantly reduce MA use and improve quality of life (R. A. Rawson et al., 2004). Despite current evidence demonstrating the therapeutic effects of psychosocial interventions, finding a approach to encourage patient adherence to treatment and provide immediate support to patients with active cravings for MA remain a real-world challenge. In response to these findings, researchers and therapists have mostly focused on developing and evaluating treatment programs that might reduce barriers to adopting interventions, improve patient compliance, increase treatment adherence and retention, and reduce patient dropout rates. The rapid development of various new technologies, such as mobile health (mHealth) systems, has substantially affected the health care field. Mobile phone messaging applications, such as short message service (SMS) and multimedia message service, not only provide immediate response for personalized, supportive care but also present convenient, cost-effective means of supporting self-management and improving patients' self-efficacy through treatment reminders or homework practices that restore therapeutic efficacy (Car, Gurol-Urganci, de Jongh, Vodopivec-Jamsek, & Atun, 2012; de Jongh, Gurol-Urganci, Vodopivec-Jamsek, Car, & Atun, 2012; Vodopivec-Jamsek, de Jongh, Gurol-Urganci, Atun, & Car, 2012). Delivering interventions through these technologies has several advantages, including therapeutic support availability at any time and location, low barriers to treatment, and high use and dissemination in at-risk populations (Fjeldsoe, Marshall, & Miller, 2009; Ohannessian, 2009).

Recently, numerous researchers have used communication technology (e-mail, SMS, and videoconferencing) to enroll patients into treatment programs, access patients during treatment periods, provide substance use interventions, deter risky behaviors, and promote adherence to treatment (Car et al., 2012). Whittaker et al. (2019) reviewed 26 studies that investigated text message–based smoking cessation interventions and revealed that supplementing smoking cessation interventions with text messaging was more effective than smoking cessation interventions alone (RR 1.59, 95% CI 1.09 to 2.33; I2 = 0%, 4 studies, 997 participants) (Whittaker et al., 2019). Tofighi et al. (2017) conducted a systematic review to assess the acceptability, feasibility, and clinical impact of text messaging interventions for individuals with illicit drug and alcohol dependence (Tofighi, Nicholson, McNeely, Muench, & Lee, 2017). It included 11 randomized control trials (two for opiate, four for alcohol, three for MA, and two for polysubstance abuse) and found that most studies demonstrated improved clinical outcomes, medication adherence, and engagement with peer support groups. Text messaging interventions also had a positive influence on multiple therapeutic targets such as appointment attendance, motivation, self-efficacy, relapse prevention, and social support.

During treatment, mobile intervention also has the potential to immediately address patients’ needs when they are out of the clinic and experience cravings or have a high risk of relapse. However, few studies have examined the effects of text messaging–supplemented treatment on MA use disorder. Reback et al. (2012) conducted a 2-week, uncontrolled pilot study of an intervention designed to reduce high-risk sexual behavior and MA use among out-of-treatment men who have sex with men (N = 52) (Reback et al., 2012). Results derived from self-report data showed that at follow-up, participants had significantly reduced their frequency of MA use (*p* < .01) and condomless sex while using MA (20.9% vs. 44.2%, *p* < .01), and significantly increases were noted in abstinence from MA use (13.3% vs. 48.9%, *p* < .001) and length of time since last use (*p* < .01). Moore et al. (2013) examined the feasibility of using text messaging to track MA use and promote adherence to antiretroviral treatment among people diagnosed as having HIV who use MA (Moore et al., 2013). When sent a reminder message and asked to reply, participants in the intervention group were significantly more likely to respond that they “took” versus “didn't take” their medication (*M* = 19.08, *SD* = 9.3 vs *M* = 1.23, *SD* = 2.1; *t*= −6.52,  *df* = 12, *p* < .001). In reply to text messages asking participants if they had used MA in the previous 24 h, participants were more likely to send a “no” versus “yes” response (18.2 days, 62.2% vs 3.1 days, 10.7%; *t* = 10.3, *df* = 20*,* *p* < .001). Additionally, Kioleian et al. (2013) developed a text messaging intervention and demonstrated its feasibility and potential as an adjunct to cognitive behavioral group therapy for people who use MA (Keoleian, Stalcup, Polcin, Brown, & Galloway, 2013).

 In Taiwan, approximately 82.1% of adults have access to the internet and 96.8% own mobile phones (Lin, Wu, You, Hu, & Yen, 2018). The near-ubiquitous ownership of mobile phones provides a practical opportunity to integrate mobile health technology with treatment delivery services. This study aimed to extend current research by investigating the role of mHealth systems, which could deliver SMS and videoconferencing, on therapeutic outcomes during outpatient treatment among people who use MA. The primary aim was to compare treatment retention and the results of urine drug tests between experimental and control groups. Participants in the experimental group received text messages consisting of treatment reminders about clinic visits and psychotherapy attendance, as well as psychoeducative messages and videoconferencing with case managers once every 2 weeks to discuss MA use problems and how to deal with them. The control group comprised patients who received treatment as usual (TAU). The hypothesis was that the group of patients who received mobile messages would have better treatment retention and more negative drug urine test results compared with patients receiving TAU. The secondary aim of this study was to explore the feasibility of and patient satisfaction with mobile messaging to improve treatment efficacy.

**Methods:**

**Study Design:**

This study utilized a randomized-controlled design followed by the CONSORT STATEMENT 2010. MMAT served as the experimental group. Both experimental and control group members received standard treatment as provided by the facility. Dependent variables used in this study were: (1) retention, and (2) results of drug urine test. Each group will be followed for six months. Approval by the Institutional Review Board (IRB-18-017) was obtained, and subjects were given an explanation of the study and an opportunity to provide informed consent. The study was powered to detect statistically significant an odds ratio of 0.75(α= 0.05, power 0.80, and 20 participants per group), comparing the intervention arms pooled together with the control group.

**Inclusion Criteria for Participants**

 The inclusion criteria were (a) a diagnosis of MA abuse or dependence as defined by the DSM-IV-TR (b) age between 18 and 65 years, (c) no initial diagnosis of severe physical or mental illness, such as schizophrenia or bipolar I disorder, at survey baseline, and (d) a willingness to participate in standard outpatient treatment for 1 year. Subjects who were unwilling to participate in this study, were incarcerated during the study period, or were hospitalized due to physical or mental illness were considered to have dropped out of the study.

**Recruitment and Enrolment**

 The study population was recruited from outpatients of the Addiction Unit at Jianan Psychiatric Center. The study was introduced as an adjuvant treatment for MA use disorder. Those who were willing enroll in this study were given an information sheet and asked to provide contact details. After informed consent was obtained, case managers scheduled further visits for this study. All study procedures were approved by the ethical committee review board of Jianan Psychiatric Center.

**Randomization and Allocation**

 This study was a randomized controlled trail, and a quantitative approach was used to collect and analyze data. Comprehensive interviews of all participants were conducted by well-trained psychiatrists for the purpose of gathering demographic data (name, age, sex, marital status, educational level, employment status) and drug use history (age at first use, duration of use, number of unique events in a criminal record, current dose in the previous month). Diagnostic interviews were also performed to confirm a diagnosis of substance use disorder. Severity of MA use was defined by the number of DSM-5 criteria that a participant met (2–3 criteria: mild, 4–5 criteria: moderate, ≥6 criteria: severe) (Galanter, Kleber, & Brady, 2015). Eligible patients were randomly assigned to one of the two groups on the day of enrollment after baseline measurements by researchers. Participants were divided into groups using permuted-block randomization with a 1:1 allocation ratio to achieve balanced sample sizes. The participants were blinded to individual group assignment.

**Intervention**

During the 6 months of participation, the mobile messaging–assisted treatment (MMAT) group received treatment reminders by text message every week that coincided with their treatment schedule. Psychoeducational messages consisted of 80 messages based on the early recovery group treatments in the Matrix Model, which focuses on (a) how to stop the addiction cycle, (b) identifying external triggers (c), identifying internal triggers (d), mutual-help activities (e), body chemistry in recovery (f), common challenges in early recovery (g) thinking, feeling and doing, and (h) 12-step wisdom (R. A. a. Rawson, Obert, McCann, & Ling). Participants had videoconferencing sessions with case managers once every 2 weeks to discuss MA use problems and facilitate changes in their behavior. All participants were required to attend relapse prevention group therapy sessions once per week for a total of 8 weeks and attend OPD follow-up sessions for 6 months. Treatment retention, psychotherapy session attendance, and the results of monthly urine tests were analyzed used as outcome measurements. Feasibility and participant satisfaction were also assessed through a Mobile Phone Use Questionnaire that was developed for the purpose of this study and used to reveal patients’ experiences with using mobile phones for MA use disorder treatment. This study started from 1st July, 2018 to 1st July 2019.

**Statistical Analysis**

Descriptive statistics, *M* ± *SD* for quantitative variables, and frequencies and percentages for categorical variables were calculated for all sociodemographic, clinical, and psychosocial variables. Differences in all characteristics of the study groups were examined using a one-way analysis of variance (ANOVA) and chi-squared test. All data were subjected to an intention-to-treat analysis. Missing data were assumed to be missing completely at random. The criterion for significance was set a priori as a = 0.05. SPSS 21.0 was used for all analyses. A one-way ANOVA was used to examine the difference between objectively measured adherence values of clinical data gathered at follow-up between the two groups. A matched paired t test was performed to compare the two groups’ response rates regarding psychotherapy appointment attendance and drug urine test results. Pearson’s correlation test was applied to evaluate significant trends. The number of days in treatment from the initiation until either the patient quit or the end of the 6-month follow-up period was used to calculate cumulative retention in treatment using the Kaplan–Meier method with a log-rank test. Variables that were significantly associated with retention in the Kaplan–Meier analysis were included in the Cox regression multivariate analyses and presented as odds ratios with 95% CIs. Regression analysis (logistic regression, linear regression) was used to analyze the differences between potential predictor variables (age, sex, education, employment, severity by DSM-5 criteria) and the proportion of negative urine samples. A *p* value of <.05 was considered statistically significant.

**Possible benefits and risks:** It is supposed to be benefits for participants who received MMAT better treatment retention and more negative drug urine test results compared with patients receiving TAU. Since MMAT is delivered through individual communication devices, the possibility of stigmatization while others know participants with MA use is considered as risks.

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**Reference**

Car, J., Gurol-Urganci, I., de Jongh, T., Vodopivec-Jamsek, V., & Atun, R. (2012). Mobile phone messaging reminders for attendance at healthcare appointments. *Cochrane Database Syst Rev*(7), Cd007458. doi:10.1002/14651858.CD007458.pub2

Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug Alcohol Rev, 27*(3), 253-262. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18368606>. doi:10.1080/09595230801923702

de Jongh, T., Gurol-Urganci, I., Vodopivec-Jamsek, V., Car, J., & Atun, R. (2012). Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database Syst Rev, 12*(12), Cd007459. doi:10.1002/14651858.CD007459.pub2

Fjeldsoe, B. S., Marshall, A. L., & Miller, Y. D. (2009). Behavior change interventions delivered by mobile telephone short-message service. *Am J Prev Med, 36*(2), 165-173. doi:10.1016/j.amepre.2008.09.040

Galanter, M., Kleber, H. D., & Brady, K. (2015). *The American Psychiatric Publishing textbook of substance abuse treatment* (Fifth edition. ed.). Washington, DC: American Psychiatric Publishing.

Glasner-Edwards, S., Marinelli-Casey, P., Hillhouse, M., Ang, A., Mooney, L. J., & Rawson, R. (2009). Depression among methamphetamine users: association with outcomes from the Methamphetamine Treatment Project at 3-year follow-up. *J Nerv Ment Dis, 197*(4), 225-231. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19363377>. doi:10.1097/NMD.0b013e31819db6fe

Gonzales, R., Marinelli-Casey, P., Shoptaw, S., Ang, A., & Rawson, R. A. (2006). Hepatitis C virus infection among methamphetamine-dependent individuals in outpatient treatment. *J Subst Abuse Treat, 31*(2), 195-202. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16919748>. doi:10.1016/j.jsat.2006.04.006

Grant, K. M., LeVan, T. D., Wells, S. M., Li, M., Stoltenberg, S. F., Gendelman, H. E., . . . Bevins, R. A. (2012). Methamphetamine-associated psychosis. *J Neuroimmune Pharmacol, 7*(1), 113-139. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/21728034>. doi:10.1007/s11481-011-9288-1

Kaye, S., McKetin, R., Duflou, J., & Darke, S. (2007). Methamphetamine and cardiovascular pathology: a review of the evidence. *Addiction, 102*(8), 1204-1211. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17565561>. doi:10.1111/j.1360-0443.2007.01874.x

Keoleian, V., Stalcup, S. A., Polcin, D. L., Brown, M., & Galloway, G. (2013). A cognitive behavioral therapy-based text messaging intervention for methamphetamine dependence. *J Psychoactive Drugs, 45*(5), 434-442. doi:10.1080/02791072.2013.847995

Kuo, C. J., Tsai, S. Y., Liao, Y. T., Conwell, Y., Lin, S. K., Chang, C. L., . . . Chen, W. J. (2011). Risk and protective factors for suicide among patients with methamphetamine dependence: a nested case-control study. *J Clin Psychiatry, 72*(4), 487-493. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20868632>. doi:10.4088/JCP.09m05360gry

Lee, N. K., & Rawson, R. A. (2008). A systematic review of cognitive and behavioural therapies for methamphetamine dependence. *Drug Alcohol Rev, 27*(3), 309-317. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18368613>. doi:10.1080/09595230801919494

Lin, M. P., Wu, J. Y., You, J., Hu, W. H., & Yen, C. F. (2018). Prevalence of internet addiction and its risk and protective factors in a representative sample of senior high school students in Taiwan. *J Adolesc, 62*, 38-46. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/29149653>. doi:10.1016/j.adolescence.2017.11.004

Matsumoto, T., Imamura, F., Kobayashi, O., Wada, K., Ozaki, S., Takeuchi, Y., . . . Adachi, Y. (2013). Evaluation of a relapse-prevention program for methamphetamine-dependent inmates using a self-teaching workbook and group therapy. *Psychiatry Clin Neurosci*. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/24102922>. doi:10.1111/pcn.12084

McGee, S. M., McGee, D. N., & McGee, M. B. (2004). Spontaneous intracerebral hemorrhage related to methamphetamine abuse: autopsy findings and clinical correlation. *Am J Forensic Med Pathol, 25*(4), 334-337. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15577524>.

Moore, D. J., Montoya, J. L., Blackstone, K., Rooney, A., Gouaux, B., Georges, S., . . . Tmarc Group, T. (2013). Preliminary Evidence for Feasibility, Use, and Acceptability of Individualized Texting for Adherence Building for Antiretroviral Adherence and Substance Use Assessment among HIV-Infected Methamphetamine Users. *AIDS research and treatment, 2013*, 585143-585143. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/24078868>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3776360/>. doi:10.1155/2013/585143

Moszczynska, A., & Callan, S. P. (2017). Molecular, Behavioral, and Physiological Consequences of Methamphetamine Neurotoxicity: Implications for Treatment. *J Pharmacol Exp Ther, 362*(3), 474-488. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/28630283>. doi:10.1124/jpet.116.238501

Ohannessian, C. M. (2009). Does technology use moderate the relationship between parental alcoholism and adolescent alcohol and cigarette use? *Addictive Behaviors, 34*(6-7), 606-609. Retrieved from <https://pubmed.ncbi.nlm.nih.gov/19223123>

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2683900/>. doi:10.1016/j.addbeh.2009.01.001

Padilla, R., & Ritter, A. V. (2008). Meth mouth: methamphetamine and oral health. *J Esthet Restor Dent, 20*(2), 148-149. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18380848>. doi:10.1111/j.1708-8240.2008.00167.x

Rawson, R. A., Gonzales, R., Pearce, V., Ang, A., Marinelli-Casey, P., & Brummer, J. (2008). Methamphetamine dependence and human immunodeficiency virus risk behavior. *J Subst Abuse Treat, 35*(3), 279-284. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18329225>. doi:10.1016/j.jsat.2007.11.003

Rawson, R. A., Marinelli-Casey, P., Anglin, M. D., Dickow, A., Frazier, Y., Gallagher, C., . . . Zweben, J. (2004). A multi-site comparison of psychosocial approaches for the treatment of methamphetamine dependence. *Addiction, 99*(6), 708-717. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/15139869>. doi:10.1111/j.1360-0443.2004.00707.x

Rawson, R. A. a., Obert, J. L. a., McCann, M. J. M. A. a., & Ling, W. a. *The matrix model. Therapist's manual : intensive outpatient alcohol & drug treatment program* (Revised and expanded. ed.).

Reback, C. J., Grant, D. L., Fletcher, J. B., Branson, C. M., Shoptaw, S., Bowers, J. R., . . . Mansergh, G. (2012). Text messaging reduces HIV risk behaviors among methamphetamine-using men who have sex with men. *AIDS Behav, 16*(7), 1993-2002. doi:10.1007/s10461-012-0200-7

Roll, J. M., Petry, N. M., Stitzer, M. L., Brecht, M. L., Peirce, J. M., McCann, M. J., . . . Kellogg, S. (2006). Contingency management for the treatment of methamphetamine use disorders. *Am J Psychiatry, 163*(11), 1993-1999. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/17074952>. doi:163/11/1993 [pii]

10.1176/appi.ajp.163.11.1993

Sheridan, J., Bennett, S., Coggan, C., Wheeler, A., & McMillan, K. (2006). Injury associated with methamphetamine use: a review of the literature. *Harm Reduct J, 3*, 14. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16571134>. doi:10.1186/1477-7517-3-14

Shoptaw, S., Rawson, R. A., McCann, M. J., & Obert, J. L. (1994). The Matrix model of outpatient stimulant abuse treatment: evidence of efficacy. *J Addict Dis, 13*(4), 129-141. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/7734464>.

Thanos, P. K., Kim, R., Delis, F., Rocco, M. J., Cho, J., & Volkow, N. D. (2017). Effects of chronic methamphetamine on psychomotor and cognitive functions and dopamine signaling in the brain. *Behav Brain Res, 320*, 282-290. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/27993694>. doi:10.1016/j.bbr.2016.12.010

Tofighi, B., Nicholson, J. M., McNeely, J., Muench, F., & Lee, J. D. (2017). Mobile phone messaging for illicit drug and alcohol dependence: A systematic review of the literature. *Drug Alcohol Rev, 36*(4), 477-491. doi:10.1111/dar.12535

Vodopivec-Jamsek, V., de Jongh, T., Gurol-Urganci, I., Atun, R., & Car, J. (2012). Mobile phone messaging for preventive health care. *Cochrane Database Syst Rev, 12*(12), Cd007457. doi:10.1002/14651858.CD007457.pub2

Vogt, T. M., Perz, J. F., Van Houten, C. K., Jr., Harrington, R., Hansuld, T., Bialek, S. R., . . . Williams, I. T. (2006). An outbreak of hepatitis B virus infection among methamphetamine injectors: the role of sharing injection drug equipment. *Addiction, 101*(5), 726-730. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/16669906>. doi:10.1111/j.1360-0443.2006.01407.x

Whittaker, R., McRobbie, H., Bullen, C., Rodgers, A., Gu, Y., & Dobson, R. (2019). Mobile phone text messaging and app‐based interventions for smoking cessation. *Cochrane Database of Systematic Reviews*(10). Retrieved from <https://doi.org//10.1002/14651858.CD006611.pub5>. doi:10.1002/14651858.CD006611.pub5