Original Investigation

Mobile Telephone Text Messaging for Medication Adherence in Chronic Disease
A Meta-analysis

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IMPORTANCE Adherence to long-term therapies in chronic disease is poor. Traditional interventions to improve adherence are complex and not widely effective. Mobile telephone text messaging may be a scalable means to support medication adherence.

OBJECTIVES To conduct a meta-analysis of randomized clinical trials to assess the effect of mobile telephone text messaging on medication adherence in chronic disease.

DATA SOURCES MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL (from database inception to January 15, 2015), as well as reference lists of the articles identified. The data were analyzed in March 2015.

STUDY SELECTION Randomized clinical trials evaluating a mobile telephone text message intervention to promote medication adherence in adults with chronic disease.

DATA EXTRACTION Two authors independently extracted information on study characteristics, text message characteristics, and outcome measures as per the predefined protocol.

MAIN OUTCOMES AND MEASURES Odds ratios and pooled data were calculated using random-effects models. Risk of bias and study quality were assessed as per Cochrane guidelines. Disagreement was resolved by consensus.

RESULTS Sixteen randomized clinical trials were included, with 5 of 16 using personalization, 8 of 16 using 2-way communication, and 8 of 16 using a daily text message frequency. The median intervention duration was 12 weeks, and self-report was the most commonly used method to assess medication adherence. In the pooled analysis of 2742 patients (median age, 39 years and 50.3% [1380 of 2742] female), text messaging significantly improved medication adherence (odds ratio, 2.11; 95% CI, 1.52-2.93; $P < .001$). The effect was not sensitive to study characteristics (intervention duration or type of disease) or text message characteristics (personalization, 2-way communication, or daily text message frequency). In a sensitivity analysis, our findings remained robust to change in inclusion criteria based on study quality (odds ratio, 1.67; 95% CI, 1.21-2.29; $P = .002$). There was moderate heterogeneity ($I^2 = 62\%$) across clinical trials. After adjustment for publication bias, the point estimate was reduced but remained positive for an intervention effect (odds ratio, 1.68; 95% CI, 1.18-2.39).

CONCLUSIONS AND RELEVANCE Mobile phone text messaging approximately doubles the odds of medication adherence. This increase translates into adherence rates improving from 50% (assuming this baseline rate in patients with chronic disease) to 67.8%, or an absolute increase of 17.8%. While promising, these results should be interpreted with caution given the short duration of trials and reliance on self-reported medication adherence measures. Future studies need to determine the features of text message interventions that improve success, as well as appropriate patient populations, sustained effects, and influences on clinical outcomes.

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Adherence is defined as the extent to which a patient correctly follows a prescribed therapy. Adherence is the medically preferred term because it reflects active involvement of the patient and a therapeutic alliance between the patient and his or her physician.[1] This term is in contrast to compliance, which reflects more unidirectional connotations.[1,2] Adherence to long-term therapies in developed countries is typically reported to be approximately 50% at 1 year after initiation of therapy, with worse rates in lower socioeconomic groups and in developing countries.[3,4] Poor adherence has been linked to successive hospitalizations, increased need for medical interventions, morbidity, and mortality.[5] In addition, medication nonadherence results in increased health care cost, with estimates from North America of approximately $100 billion being spent annually and $2000 spent per patient per year in excess physician visits.[6]

Interventions that improve adherence may have far greater effect on the health of a population than any improvement in specific medical treatment.[7] A review article by Haynes et al[8] concluded that almost all interventions that were effective for long-term care were complex and not widely effective. There is widespread need for convenient and feasible innovations to help patients remain adherent to medications.[9] In recent years, mobile health (mHealth) has emerged as a strategy to improve the implementation of evidence-based medicine and support public health by using mobile digital devices.[10] The usefulness of this medium has been explored to improve treatment adherence. Electronic reminders can be delivered in various forms. The use of mobile apps (software applications) requires specialized devices (smartphones, tablet computers, or personal digital assistants).[11] Other media for reminders are pagers or dedicated devices for audiovisual reminders. However, their availability within usual health care is low and presents a challenge for translation into routine clinical practice.

Mobile telephone text messaging may be a more feasible platform to deliver electronic reminders in practice. The technology is old and therefore can be delivered to any existing mobile telephone. Subscription to mobile telephones is ever increasing. According to one estimate, there were approximately 7 billion mobile subscribers by the end of 2014, roughly corresponding to the global population.[12] This technology is increasingly used by people from all socioeconomic classes,[13,14] age groups,[13] and continents.[15]

In recent times, text messages have been widely used as a reminder and support in various health programs. While previous reviews have shown favorable effects of text messaging, only narrative reviews of text messages without meta-analysis[16,17] and a meta-analysis[18] that included a diverse range of electronic interventions (text messages, audiovisual reminders, pagers, and beepers) have been published to date. The aim of this review was to estimate the effect of text messaging on medication adherence in adults with chronic medical disorders. Secondary aims were to describe and examine the effect of characteristics of text message interventions, including frequency of messaging, interactivity, and customization, and to describe perceptions and acceptability to participants.

Methods

This review was written and detailed in accord with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement and the Cochrane Collaboration reporting items for systematic reviews and meta-analyses.[19]

Literature Search

A computerized literature search of MEDLINE, EMBASE, CINAHL, PsycINFO, Cochrane Central Register of Controlled Trials, and trial registries (clinicaltrials.gov and ANZCTR [http://www.anzctr.org.au/]) was conducted using Medical Subject Headings and keywords. The keywords included (1) *intervention* (*text messaging*, *text messages*, *short message service*, *mobile phone*, and *cellular phone*) and (2) *medication use* (*adherence*, *nonadherence*, *compliance*, *noncompliance*, *refuse*, *refusal*, *treatment refusal*, and *patient compliance*). No restriction on publication date was applied. The electronic database was last searched on January 15, 2015.

Study Eligibility

We included trials based on the following criteria: (1) the trial studied adult patients (≥18 years) with chronic disease, (2) the patients received a mobile telephone text message intervention designed to promote medication adherence, (3) the design was a randomized clinical trial (RCT) with at least 4 weeks' follow-up, and (4) the trial reported quantitative measures of the effect of text messaging on medication adherence. We excluded studies based on the following criteria: (1) the primary intervention under consideration was not limited to text messages, (2) the focus was solely disease management or education and did not report medication adherence or reported only surrogate outcomes (eg, CD4 cell count or glycated hemoglobin level), and (3) the study involved psychiatric, military, or institutionalized patients. The latter criterion was to avoid the potential influence of psychosocial or institutional controls on adherence.

Data Extraction

Two of us (J.T. and R.K.) independently screened all identified titles and abstracts from the literature search using a predefined protocol. We reviewed reference lists of relevant articles for additional publications. Full texts of screened articles were reviewed for inclusion criteria and study quality. Disagreements were resolved through discussion or in consultation with a third independent reviewer (C.K.C.). If more than 1 publication of an original trial was identified, such articles were assessed together to maximize data collection. We extracted data on study characteristics, text message characteristics, and outcomes.

We used the *Cochrane Handbook for Systematic Reviews of Interventions*[20] guidelines for trials with multiple intervention arms. When reported, we used the overall intervention effect. Otherwise, we combined trial arms (ie, text message vs non–text message arms). We did not follow the alternative strategy of selecting a single pair of interventions because that can result in loss of information and introduce bias if the arm with positive results is preferentially included for analysis. For example, for the trial by Lv et al,[21] we combined control and tra-

ditional arms and treated this group as a non-text message intervention arm. For trials reporting multiple follow-ups, the final follow-up corresponding to the study duration was used.

Assessment of Study Quality

Two of us (J.T. and R.K.) independently assessed the risk of bias of included studies, with any disagreements resolved by discussion and a third opinion (C.K.C.) to reach consensus. We assessed the methodological risk of bias of included studies in accord with the *Cochrane Handbook for Systematic Reviews of Interventions*,[19] which recommends reporting of the following individual elements for RCTs: random sequence generation, randomization sequence concealment, masking, completeness of outcome data, selective outcome reporting, and other sources of bias. Each item is judged as being at high, low, or unclear risk of bias. Studies were deemed to be at highest risk of bias if they were scored as being at high or unclear risk of bias for the sequence generation or randomization concealment domains.

Statistical Analysis

We used a software program (Comprehensive Meta-analysis, version 2.2.064; Biostat) for statistical analyses.[22] We used the mean effect size approach to pool estimates, which has been used by others.[18] The effect size was weighted as per the study sample size. We used individual patient data when available. If only aggregate data were available, we used estimates of treatment difference and their variance.[23] We calculated the odds ratio (OR) for each primary study and used random-effects models to pool estimates. We also calculated Cohen *d* as a magnitude of the effect size. Cohen *d* values of 0.2, 0.5, and 0.8 are generally considered as small, medium, and large effect sizes, respectively.[24] We used the I^2 statistic to assess heterogeneity. An I^2 statistic exceeding 50% with $P < .05$ was interpreted as representing substantial heterogeneity.[25] We assessed publication bias using funnel plot symmetry and Egger regression intercept. If publication bias exists, the funnel plot is asymmetric, with Egger test $P < .05$. We used the trim-and-fill method by Duval and Tweedie[26] to impute the missing studies. We performed subgroup analysis based on study and text message characteristics.

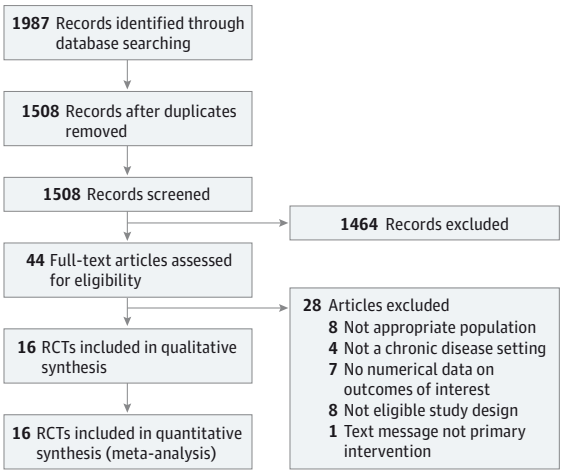
There are no clear guidelines or criterion standard recommendations on how to assess medication adherence or define adherence outcomes.[27,28] Our primary analysis was to examine the effects of text message interventions on medication adherence. We defined adherent patients as those individuals determined to be adherent as defined by the individual included trials. For trials that reported multiple measures of adherence, we selected the most objective measure of adherence according to a predefined hierarchy (ie, electronic monitoring over pill count over self-recall, as well as a continuous scale over a dichotomized scale.[18]

Results

Study Characteristics

We assessed 44 full-text articles for eligibility and identified 16 RCTs[21,29-43] (**Figure 1**, **Table 1**, and eTable 1 in the Supplement) involving 2742 patients that met our inclusion criteria.

Figure 1. Study Selection Process



RCTs indicates randomized clinical trials.

The median sample size was 97 (range, 21-538). The median age of participants was 39 years (age range, 31-64 years), and 50.3% (1380 of 2742) were female. The studies evaluated various chronic diseases, including human immunodeficiency virus (HIV) infection,[29,30,32,34,35,37] cardiovascular disease (CVD),[31,36,38,41,43] asthma,[21,39] allergic rhinitis,[42] diabetes mellitus,[40] and epilepsy.[33] The median intervention duration was 12 weeks (range, 4-48 weeks).

Self-recall was the most commonly used method to assess adherence,[21,31-34,36,38,41,42] followed by medication event monitoring system[29,30,36,37] and pill count.[29,30,43] Adherence outcome data were reported in 12 studies[21,29,31-35,37,38,41-43] as proportion of patients adherent and in 4 studies[30,36,39,40] as proportion of medication doses taken as prescribed. The adherence cutoff was defined at 95% in 6 HIV trials and 1 CVD trial, at 90% in 1 HIV trial, at 80% in 1 CVD trial, and at 80% in one hypertension trial. The control arm in 15 studies was standard therapy. Only 1 study[30] compared the text message intervention with a control arm (using additional 1-way pager or beeper).

Text Message Characteristics

There was considerable variation in the text message intervention characteristics (**Table 2**). Fifteen studies sent text messages at a fixed predetermined frequency. One study[40] used real-time medication monitoring in which patients were sent a text message reminder only if the participant failed to open the medication dispenser. Five studies[30,31,36,38,41] incorporated personalization into their messages. For example, the trial by Khonsari et al[31] used the following personalization: [Mr or Ms] [patient name], please take [medicine quantity] tablet of [medication name] at [time]. Eight studies used a 2-way communication strategy, which was mandatory in 4 studies[30,32,36,41] and encouraged in 4 studies.[21,33-35] The message content was predominantly medication reminders[31,33-43] but also included medical educational information[21,33,35-37,43] or nonmedical general topics[29,30,32] (eg, jokes, Bible verses, humor,

Table 1. Characteristics of the Randomized Clinical Trials Using Text Messaging to Promote Medication Adherence

Source	Chronic Disease	Sample Size (Intervention Duration)	Experimental Arm vs Control Arm	Participant Age, Mean (SD), y	Female Sex, %	Setting/Country	Participant Characteristics
Márquez Contreras et al,[43] 2004	HT	n = 67 (6 mo)	TM vs standard care	56.2 (10.2) for IG and 59.4 (10.9) for CG	45	Outpatient/Spain	Uncontrolled HT on monotherapy regimen
da Costa et al,[29] 2012	HIV	n = 21 (4 mo)	TM vs standard care	36.1 (9.1) for IG and 34.6 (6.9) for CG	100	University clinic/Brazil	Stable patients with HIV
Hardy et al,[30] 2011	HIV	n = 23 (6 wk)	TM vs beeper	42 (8) for IG and 44 (4) for CG	47	HIV clinic/United States	On ART regimen >3 mo with self-reported adherence <85%
Khonsari et al,[31] 2015	CAD	n = 62 (8 wk)	TM vs standard care	Median (range), 57.9 (12-64)	14.5	Hospital inpatient/Malaysia	Patients admitted to the hospital for management of ACS
Lester et al,[32] 2010	HIV	n = 538 (12 mo)	TM vs standard care	36.7 (8.5) for IG and 36.6 (7.9) for CG	65	HIV clinic/Kenya	Initiated ART for the first time
Lua and Neni,[33] 2013	Epilepsy	n = 136 (3 mo)	TM vs standard care	31 (12)	49	Hospital outpatient clinic/Malaysia	On regular treatment regimen for epilepsy
Lv et al,[21] 2012	Asthma	n = 71 (12 wk)	TM vs traditional care vs standard care	36.2 (11.1) for IG and 38.8 (12.0) for CG	42	Hospital respiratory department/China	Asthma diagnosed >3 mo and positive bronchodilator provocation test result
Maduka and Tobin-West,[34] 2013	HIV	n = 104 (4 mo)	TM vs standard care	36.6 (11.7) for IG and 35.3 (9.0) for CG	56.7	Hospital outpatient clinic/Nigeria	HIV positive on HAART regimen for ≥3 mo
Mbuagbaw et al,[35] 2012	HIV	n = 200 (6 mo)	TM vs standard care	41.3 (10.3) for IG and 39.0 (10.0) for CG	73.5	Hospital clinic/Cameroon	On ART regimen >1 mo
Park et al,[36] 2014	CAD	n = 90 (30 d)	TM vs TM vs standard care	Median (range), 59.2 (35-83)	24	Hospital inpatient/United States	Admitted for STEMI, NSTEMI, or PCI
Pop-Eleches et al,[37] 2011	HIV	n = 428 (48 wk)	TM vs standard care	36.3	66	HIV clinic/Kenya	Initiated antiretroviral therapy <3 mo
Quilici et al,[38] 2013	CAD	n = 521 (1 mo)	TM vs standard care	64 (10) for IG and 64 (14) for CG	24	Hospital inpatient/France	Coronary stenting for ACS (aspirin resistance excluded by platelet function testing)
Strandbygaard et al,[39] 2010	Asthma	n = 26 (12 wk)	TM vs standard care	Range, 18-45	46	Newspaper advertisement/Denmark	Asthma history and positive methacholine test result
Vervloet et al,[40] 2012	Diabetes mellitus	n = 104 (6 mo)	RTMM-TM vs standard care	54.9 (6.6) for IG and 54.6 (6.9) for CG	45	Pharmacies/the Netherlands	Oral diabetic for >1 y and/or insulin >6 mo and known adherence <80% based on pharmacy dispensing data
Wald et al,[41] 2014	CVD	n = 303 (6 mo)	TM vs standard care	Median (range), 60 (54-68) for IG and 41 (49-69) for CG	46	Primary care clinic/London, England	Patients receiving blood pressure and lipid-lowering therapy for prevention of CVD
Wang et al,[42] 2014	Allergic rhinitis	n = 50 (30 d)	TM vs standard care	35.7 (8.8) for IG and 31.0 (10.8) for CG	60	Outpatient/China	Allergic rhinitis history and positive skin prick test result

Abbreviations: ACS, acute coronary syndrome; ART, antiretroviral therapy; CAD, coronary artery disease; CG, control group; CVD, cardiovascular disease; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HT, hypertension; IG, intervention group; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; RTMM, real-time medication monitoring; STEMI, ST-segment elevation myocardial infarction; TM, text message.

etc). With respect to frequency; the most common pattern was a daily text message in 8 studies,[21,30,31,36-39,42] followed by a weekly text message in 3 studies.[32,35,37] Only 1 study[41] used a variable frequency pattern, with daily send for 2 weeks, followed by alternate days for 2 weeks, and then weekly for the remainder of the study duration. Four studies[31,36,40,41] matched message send times with the time of patients' medication doses. The sending of messages was managed by automation or computer programs in 10 studies.[29-33,36,38,40,41,43]

Meta-analysis of the Intervention Efficacy

In the pooled analysis of 2742 patients, text message interventions significantly improved medication adherence (OR, 2.11; 95% CI, 1.52-2.93; $P < .001$) (**Figure 2**). The weighted mean effect size (Cohen d) was 0.41 (95% CI, 0.23-0.59). Text message interventions were similarly effective when analyses were restricted to text message studies[31,32,34,35,37,40-42] reporting outcomes by intent to treat (OR, 2.25; 95% CI, 1.51-3.37; $P < .001$; Cohen d, 0.45) (eFigure 1 in the Supplement) or by per-protocol analysis (OR, 1.65; 95% CI, 1.07-2.53; $P = .02$; Cohen d, 0.28) (eFigure 2 in the Supplement). We did not find significant effects of text messages on adherence in subgroup analysis based on text message characteristics and study variables (**Table 3**). There was moderate heterogeneity ($I^2 = 62\%$) across clinical trials. Publication bias was detected by funnel plot asymmetry (eFigure 3 in the Supplement) and Egger regression coefficient (1-tailed $P = .02$). Using trim-and-fill imputation for missing studies, the point estimate was reduced but remained positive, with an OR of 1.68 (95% CI, 1.18-2.39; $P < .05$).

Table 2. Features of the Text Messaging Design Used in the Randomized Clinical Trials

Source	TM Frequency (No. of Days per Week/No. of TMs per Day/Message Send Method)	TM Content and Other Characteristics (Personalization/Frequency Tailoring/2-Way Communication)	Mobile Telephone Ownership/Incentives/ Additional Support	Outcome Measure/Outcome Ascertainment Method	Patient Feedback
Márquez Contreras et al,[43] 2004	Twice per week/random weekdays/between 11 AM and 14 PM/automated commercial platform	1-Way	Personal mobile telephone	Mean percentage compliance/adherent patients (>80% of medications taken)/pill count	Not reported
da Costa et al,[29] 2012	Weekends and alternate days during weekdays/automated send engine	1-Way TM/general content (covert)/"The UNIFESP informs: take good care of your health"	Personal mobile telephone	Proportion of patients adherent (>95% of medications taken)/self-recall, pill count, MEMS	80% Provided feedback/100% of respondents reported that messages helped them take medications/90% would like to continue receiving TMs
Hardy et al,[30] 2011	Daily/automated send engine (ARemind; Dimagi Inc)	2-Way personalized TM, patient had to respond with a TM when taking ART. If no response, the telephone would beep every 15 min until the patient acknowledges the TM/general content (weather, jokes, Bible verses, sports, news, humor)	Study provided a mobile telephone with an unlimited calling and texting plan	Proportion of doses taken/self-recall (7 d)/pill count (30 d)/MEMS	Most intervention participants reported they would continue using a program to help remind them to take medications/one-third of control participants objected to the beeper, which provoked curiosity from people around them and violated confidentiality
Khonsari et al,[31] 2015	Daily before every intake of medication/automated send	Personalized 1-way TM/content of reminder is [Mr or Ms] [patient name], please take [medicine quantity] tablet of [medication name] at [time]	Personal mobile telephone/telephone contact 1-2 times per week to TM group to confirm delivery of TM and remind patients about appointments	Proportion of patients adherent/self-report (MMAS 8 item)	93.5% Reported that TMs were useful, and >80% requested that TM reminders should be continued
Lester et al,[32] 2010	Weekly (Monday morning)/bulk TM service	Slogan is "*Mambo*?" (meaning "How are you")/response expected within 48 h is "*Sawa*" (doing well) or "*Shida*" (problem)	Personal mobile telephone/clinic called patients who said they had a problem or failed to respond within 48 h	Proportion of patients adherent (>95% of medications taken)/self-report	Most patients recommended continuing the TM program (data not shown in the primary results article)
Lua and Neni,[33] 2013	TM every fourth day delivered at 10 AM/computerized automated send (MEES modular service)	Epilepsy knowledge, medication adherence, clinic appointment reminder/2-way TM exchange is possible	Personal mobile telephone/support for simple comments is provided by research assistants	Mean adherence rate/self-recall (Malay MMAS 4 item)	Not reported
Lv et al,[21] 2012	Twice-daily TMs at 10 AM and 8 PM	Content is asthma education, medications, triggers, and acute attacks/2-way TM communication is possible	Personal mobile telephone/clinic investigators responded to patient queries	Mean adherence rate/self-report	6% Considered TMs inconvenient
Maduka and Tobin-West,[34] 2013	Twice a week (Monday and Thursday morning)/bulk TM service	Adherence-related information and reminder to take HAART/participants are encouraged to communicate	Personal mobile telephone/researchers offered counseling via telephone on an as-needed basis	Proportion of patients adherent (>95% of medications taken)/self-report (No. of pills missed in last 7 d)	Not reported
Mbuagbaw et al,[35] 2012	Weekly (Wednesday 9 AM)	Motivational TM with reminder component/ callback number is provided, but a reply TM is not mandatory	Personal mobile telephone	Proportion of patients adherent (>95% of medications taken)/visual analog scale/pharmacy refill data	Moderate (65%) level of satisfaction reported
Park et al,[36] 2014	Reminder sent daily matched to medication dose time/educational material sent Monday, Wednesday, and Friday at 2 PM/customizable commercial platform (CareSpeak; CareSpeak Communications)	Reminders and education/2-way, personalized, with a reply required from the participant/"John, take (medication name) (medication dose) at 9 AM, respond with 1"	Personal mobile telephone	Proportion of doses taken/MEMS/MMAS 8 item	Most reported moderate to strong satisfaction with the TM program and ease of use
Pop-Eleches et al,[37] 2011	Multiple-arm study (daily TM arm and weekly TM arm)/message sent at 12 PM	1-Way TM designed to address barriers to adherence/short message (simple reminder)/long message (additional support)	Study provided a mobile telephone to the participants and financial support for telephone credits and follow-up visit	Proportion of patients adherent (≥90% of medications taken)/MEMS	Not reported

(continued)

Risk of Bias and Sensitivity Analysis

We performed a sensitivity analysis based on the quality of studies. Fourteen studies described a randomization sequence generation technique that was at low risk of bias. Ten studies used a low-risk method for randomization concealment. Masking of study participants was not possible be-

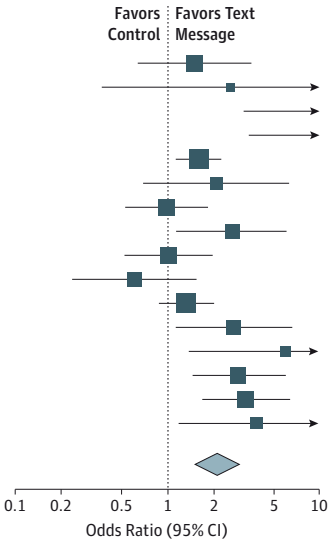
Table 2. Features of the Text Messaging Design Used in the Randomized Clinical Trials (continued)

Source	TM Frequency (No. of Days per Week/No. of TMs per Day/Message Send Method)	TM Content and Other Characteristics (Personalization/Frequency Tailoring/2-Way Communication)	Mobile Telephone Ownership/Incentives/ Additional Support	Outcome Measure/Outcome Ascertainment Method	Patient Feedback
Quilici et al,[38] 2013	Daily TM/computer-generated reminders	Personalized TM reminder about aspirin intake	Personal mobile telephone	Proportion of patients adherent (≥95% of prescribed doses taken)/self-report/platelet function testing	High satisfaction (92% reported that TM support was valuable)
Strandbygaard et al,[39] 2010	Daily TM at 10 AM	Medication reminder ("Remember to take your asthma medication morning and evening. From the respiratory unit")	Personal mobile telephone	Proportion of doses taken	Overall perception of daily TM was positive/most reported the 10 AM time as unsuitable
Vervloet et al,[40] 2012	Real-time TM delivered only if participant fails to open dispenser	Reminder ("Have you taken your medications yet? Please take your medications as prescribed")	Personal mobile telephone	Proportion of doses taken within 4½ h of reminder	75% Reported that TM reminders were supportive
Wald et al,[41] 2014	Daily for 2 wk, then alternate days for 2 wk, then weekly for 6 mo/matched to medication dose time/automated send using a software application	Personalized 2-way TM ("Hello [name], have you taken your heart medication today?…")/participants are required to text back "yes" or "no"	Personal mobile telephone/telephone call to participants responding "no"	Proportion of patients adherent (>80% of prescribed doses taken)/self-report (doses missed over previous 28 d)	Not reported
Wang et al,[42] 2014	Daily TMs (7 AM on weekdays and 9 AM on weekends)/daily TMs sent by technician	Medication reminder ("Good morning. Budesonide once a day is effective. Please do not forget to take your medications")	Personal mobile telephone	Proportion of patients adherent (≥95% of prescribed doses taken)/self-report (doses missed over previous 30 d)	95% Of patients indicated they would like to participate in the ongoing TM program until the end of the study/TM timing not suitable (7 AM disrupted daily routines)

Abbreviations: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; MEES, mobile epilepsy education system; MEMS, medication event monitoring system; MMAS, Modified Morisky Adherence Scale; TM, text message; UNIFESP, Universidade Federal de São Paulo (Federal University of São Paulo, Brazil).

Figure 2. Meta-analysis of the Effect of a Mobile Telephone Text Message Intervention on Medication Adherence

Source	Statistics for Each Study: Odds Ratio	(95% CI)	*P* Value
Márquez Contreras et al,[43] 2004	1.508	(0.631-3.605)	.36
da Costa et al,[29] 2012	2.571	(0.371-17.831)	.34
Hardy et al,[30] 2011[a]	21.131	(3.161-141.237)	.002
Khonsari et al,[31] 2015[a]	12.273	(3.405-44.236)	<.001
Lester et al,[32] 2010	1.612	(1.144-2.271)	.006
Lv et al,[21] 2012	2.074	(0.686-6.251)	.20
Lua and Neni,[33] 2013	0.985	(0.535-1.812)	.96
Maduka and Tobin-West,[34] 2013	2.644	(1.135-6.160)	.02
Mbuagbaw et al,[35] 2012	1.026	(0.519-2.026)	.94
Park et al,[36] 2014	0.610	(0.236-1.585)	.31
Pop-Eleches et al,[37] 2011	1.330	(0.882-2.005)	.17
Quilici et al,[38] 2013	2.705	(1.109-6.596)	.03
Strandbygaard et al,[39] 2010	6.018	(1.368-26.466)	.02
Vervloet et al,[40] 2012	2.959	(1.448-6.046)	.003
Wald et al,[41] 2014	3.267	(1.686-6.331)	<.001
Wang et al,[42] 2014	3.857	(1.180-12.606)	.03
Overall	2.107	(1.517-2.926)	<.001



[a] The text message intervention significantly improved adherence (odds ratio, 2.11; 95% CI, 1.52-2.93; *P* < .001). The effect remained significant after excluding 2 studies with extreme outcomes (Hardy et al[30] and Kohnsari et al[31]) (odds ratio, 1.78; 95% CI, 1.35-2.35; *P* < .001).

cause of the nature of the intervention. Masking of outcome assessment was not clearly described in most studies. Almost half of the studies performed their primary analysis according to the principles of intent to treat. Overall, 10 studies were thought to be of high quality (eFigure 4 and eTable 2 in the Supplement). Text messaging improved adherence even when we included only high-quality studies[29,32-37,40-42] (OR, 1.67; 95% CI, 1.21-2.29; *P* = .002).

Text Message Acceptability

Participant feedback on text message acceptability was reported in 11 studies (Table 2). Most reported moderate to high

Table 3. Effect of Text Messaging on Medication Adherence in Subgroups Stratified by TM and Study Characteristics

Variable	No. of Studies or Substudies	Odds Ratio (95% CI)	*P* Value for Heterogeneity
Daily TM frequency[a]			
Yes	7	2.40 (1.37-4.16)	.50
No	10	1.88 (1.26-2.81)	
TM matched to medication dose time			
Yes	4	2.68 (1.42-5.05)	.77
No	12	1.93 (1.33-2.80)	
Personalization			
Yes	5	3.11 (1.68-5.73)	.14
No	11	1.81 (1.25-2.61)	
TM content			
Medical	12	2.12 (1.41-3.17)	.85
General nonmedical	4	2.29 (1.06-4.96)	
2-Way communication			
Yes	8	1.71 (1.08-2.71)	.17
No	8	2.77 (1.67-4.58)	
Sample size			
≤104	10	2.80 (1.78-4.40)	.07
>104	6	1.59 (1.03-2.44)	
Intervention duration, wk			
≤12	8	2.55 (1.50-4.33)	.38
>12	8	1.87 (1.20-2.92)	
Type of chronic disease			
Communicable	6	1.84 (1.08-3.14)	.51
Noncommunicable	10	2.32 (1.51-3.57)	
Outcome ascertainment method[b]			
Self-report	12	2.17 (1.44-3.26)	.34
MEMS	3	2.50 (0.97-6.46)	

Abbreviations: MEMS, medication event monitoring system; TM, text message.

[a] We defined daily text message frequency as at least 1 message per day. The study by Pop-Eleches et al[37] was split into a daily message arm and a weekly message arm for the subgroup analysis.

[b] The study by Márquez Contreras et al[43] reported outcomes based on pill count only.

levels of satisfaction with the program. They acknowledged text message support as a valuable reminder and expressed desire for continuation of the program. One study[21] that used twice-daily text message reminders had a small fraction (6%) of participants reporting messages as being intrusive and inconvenient. Participants in 2 studies[39,42] reported that morning hours (7 AM in the study by Wang et al[42] and 10 AM in the study by Strandbygaard et al[39]) were not suitable because they tend to disrupt routines.

Discussion

We identified 16 RCTs that investigated the effect of text messaging on medication adherence in patients with chronic disease. We found that text message interventions increased medication adherence, with an approximate doubling of the odds of patients' achieving adherence to their medication regimens. This increase translates into adherence rates improving from 50% (assuming this percentage as the baseline rate in patients with chronic disease from the literature in developing countries[3,7]) to 67.8%, or an absolute increase of 17.8%. Given the simplicity of the intervention and potential scalability, this finding suggests that text message–based interventions could have substantial potential to improve medication adherence in patients with chronic disease. Our findings are consistent with previous observations that text messaging can be a useful tool for behavioral change in disease prevention[44] and monitoring and management.[45,46] Our analyses indicated the presence of publication bias. However, even after taking this bias into account, the effect estimate was still significantly positive. There was also substantial heterogeneity noted, which is likely because of several reasons, including clinical heterogeneity (true variation of effect arising from variation in the characteristics of the text message interventions and variation in the patient populations). Nevertheless, there is also likely methodological heterogeneity, most likely arising because of variability in the ways outcomes were defined and measured in each study.

Improving medication adherence is a challenge. Various interventions targeting medication adherence have been reported, including patient education and counseling, allied health support (pharmacist-based or nurse-led interventions), use of reminders (beepers, pagers, smartphone apps, and automated telephone calls), packaged medications, and frequent clinic visits.[1] Successful strategies usually involve multimodal combinations. However, implementing such complex combination methods is resource intensive and may not

be feasible in routine clinical practice.[2] A systematic review by Kripalani et al[47] reported adherence outcomes of interventions broadly categorized as informational, behavioral, and combined interventions. Most effective informational interventions showed small to medium effect sizes (Cohen *d* range, 0.35-0.68) only when intensive counseling was offered over multiple sessions. Even behavioral interventions showed mixed success. Other techniques, such as specialized packaging, direct observed therapy, and cognitive behavior therapy, did not significantly affect adherence or clinical outcomes. The review by Haynes et al[8] concluded that interventions effective for long-term care are complex and require a combination of multiple approaches. Our meta-analysis showed a comparable effect size (Cohen *d*, 0.41; 95% CI, 0.23-0.59) of a mobile telephone text message intervention in enhancing adherence. The distinct advantages of text messaging over other interventions are simplicity and ease of administration, often in an automated fashion using a computerized program.

Another area of interest is the effect of text message characteristics. The characteristics of interventions in this meta-analysis varied substantially. While certain characteristics of text message–based programs such as increased message frequency and 2-way communication have been suggested to improve outcomes, we found no significant heterogeneity of effects across subgroups within this review. However, the results of a comparative analysis between these subgroups should be interpreted with caution and regarded as inconclusive because of sparse data available for analysis. However, some aspects are noteworthy. Interventions that delivered personalized messages showed a moderate effect size (Cohen *d*, 0.63; 95% CI, 0.29-0.96; $P < .01$), which suggests that sending a text message with one's preferred name may increase acceptance and participant engagement. There was no significant difference between daily text messages (Cohen *d*, 0.48; 95% CI, 0.17-0.79) compared with less frequent messaging (Cohen *d*, 0.35; 95% CI, 0.13-0.57), which is contrary to concerns raised in other studies[37,48] that daily reminders may lead to habituation and response fatigue. However, one possible explanation is that response fatigue may be a feature of longer-duration interventions, while the median length of studies in this review was 3 months.

Overall, the text message intervention had high acceptance rates. The patients in our meta-analysis were middle-aged (age range, 31-64 years), and 50.3% (1380 of 2742) were female. Most studies did not report the educational or socioeconomic status of the participants. Hence, there were insufficient data to determine whether these individual characteristics may be associated with variation in response.

While there has been mounting evidence largely in favor of texting interventions, many questions remain unanswered. There is a need for future high-quality studies to address more comprehensively what features of programs make them more effective. For example, is there greater benefit with more text message sophistication such as fixed-frequency or real-time medication monitoring, matched short message service with medication times, varied message content, personalization, and 2-way communication? Also, do text message–based interventions work better in some groups of patients compared with others? For example, do they vary based on participant characteristics such as nonadherence, cultural background, type of disease, educational level, and socioeconomic class? This information will help inform how best to formulate text message–based interventions for different patient cohorts.

One unique feature of text message interventions is the ability to offer confidential and unobtrusive support, which is an advantage of text messaging over other electronic reminders such as pagers or beepers. In the study by Hardy et al,[30] one-third of the control subjects objected to the use of beepers, which provoked curiosity from people around them and violated confidentiality. This concern was not reported in association with the text message intervention arm in any study, perhaps because of widespread use and recognition of conventional text message alert tones, which are less likely to arouse curiosity among peers. There is still a potential for problems in the case of unattended mobile telephones without password lock or smartphones with a message preview function, but these concerns can be managed with appropriate participant training.

There are several limitations of our meta-analysis. First, this study is subject to publication bias, although the effect of publication bias is likely small based on the fail-safe *N* test by Orwin.[49] This test provides an estimate of the number of missing studies. At a generally acceptable threshold of 0.1 for the effect size, this value was 34, which means that we would need to locate an additional 34 studies with a mean standard difference in means of 0 to bring the combined standard difference in means to below 0.1. Second, the adherence levels that defined patients as adherent varied among the studies. For example, these thresholds in HIV studies were 90% in the study by Pop-Eleches et al[37] vs 95% in the study by Lester et al;[32] and in CVD studies they were 80% in the study by Wald et al[41] vs 95% in the study by Quilici et al[38]. If the threshold is lowered, it can overestimate the effect of text messaging on adherence and vice versa. Third, many studies used self-reporting to determine the outcomes, which carries the possibility of recall bias and social desirability bias. Self-recall is commonly used to measure adherence owing to the convenience, the lack of a criterion standard, and the challenges of recording behaviors objectively. However, it tends to overestimate adherence, and there is no consensus on optimal recall periods (3 days, 7 days, or 1 month).[50] Social desirability bias may also be an important consideration in the studies included given their cultural diversity. Fourth, the RCTs identified in our meta-analysis had short intervention duration and follow-up (median, 12 weeks), and none of the studies reported data on adherence behavior beyond the end of the trial or completion of the intervention. The short duration of the trials suggests uncertainty about the duration of the effect, the time-effect relationship, and the continuation or decay of the effect after the intervention is withdrawn. While our meta-analysis identified a positive effect of text messaging on medication adherence in the short term, it is uncertain if this influence will translate into longer-term effects on adherence behavior or on clinical outcomes.

Conclusions

We found that mobile telephone text messaging increased adherence to taking medications among middle-aged patients with chronic disease. The ease of use, instantaneous relay of information, and boundless reach make it an attractive tool for public health. While our analyses indicate some heterogeneity across clinical trials, this finding is likely because of variation in the characteristics of the interventions studied and in the definitions of outcomes among the studies. These results should be interpreted with caution given that most trials were of short duration and that most used self-reported outcome measures. Hence, uncertainty remains about the effect size of text messages over longer periods and on objective measures of outcome. Future research on the benefit of different features of text message interventions, the longevity of the effect, and the influence on objective clinical measures of outcomes are needed to help better identify the role of text message interventions to improve medication adherence in chronic disease care.

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Study concept and design: Thakkar, Redfern, Chow.
Acquisition, analysis, or interpretation of data: All authors.
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Statistical analysis: Thakkar, Santo, Woodward.
Administrative, technical, or material support: Thakkar, Kurup, Thiagalingam, Redfern.
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