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TEXT MESSAGING INTERVENTIONS FOR PROMOTING MEDICATION ADHERENCE: A REVIEW OF THE LITERATURE

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ABSTRACT

We reviewed the literature on the use of mobile phone text messaging as an intervention to promote medication adherence. A literature search was conducted of the PubMed, CINAHL, PsycInfo, EMBASE and Cochrane databases, supplemented by grey literature hand searches. These searches returned 1752 results and the final selection consisted of 14 studies published between 2009 to 2013 with a randomized controlled trial (RCT) design, which were reviewed in detail. The studies were conducted in 10 different countries, on patients suffering from five different diseases, or discharged from the emergency department, or healthy volunteers seeking preventive treatment. There was great variability in intervention design and the adherence outcome was defined and measured in multiple ways, making direct comparison amongst studies difficult. Overall, the effectiveness of text messaging interventions on medication adherence was mixed and some methodological flaws were identified which need to be addressed in future research. We also conducted a preliminary exploration of other types of interventions available to promote medication adherence. We pooled data from these studies to examine the average improvement in medication adherence across different types of interventions. Comparisons of average improvements across the eight types of interventions suggested that text messaging was the second most effective type of intervention (after behavioural interventions). While this finding augurs well for the development of text messaging as an intervention to enhance medication adherence, it must be interpreted with caution due to methodological limitations

KEYWORDS: Biomedical Technology, Medication Adherence, Randomized Controlled Trial, Review, Text Messaging

INTRODUCTION

Medication adherence can be defined as *'the extent to which the patient follows medical instructions'* (World Health Organization, 2003). This definition, however, is limited due to its inadequacy in describing the different therapeutic behaviors that reflect adherence to the range of interventions to treat chronic diseases (e.g. seeking medical attention, filling prescriptions, taking medication appropriately) and its connotation that the patient is a passive recipient of expert advice (WHO, 2003). Traditionally, other terms used interchangeably with adherence include, most commonly, *'compliance'*, but also *'persistence'* and *'concordance'* (Hugtenburg et al, 2013; National Council on Patient Information and Education, 2007). The differences between these terms were increasingly acknowledged. Hugtenburg and colleagues (2013) have provided a comprehensive discussion on the topic, and offered an improved definition of adherence that many researchers have adopted: *'the extent to which patients' medication intake behaviour corresponds with the recommendations of the health care provider'* (Hugtenburg et al, 2013). However, there continues to be a lack of consensus on the definition and operationalization of adherence. Similarly, as "adherence" has multiple definitions,

'adherence behavior' is assessed in multiple ways. Depending on the type of disease and intervention, adherence behaviors may include attending follow-up appointments and executing behavioural modification strategies (WHO, 2003). For the purposes of this study, we have focused on patients' adherence to taking prescribed pharmaceuticals only.

Each of the different methods used to measure adherence has strengths and weaknesses (Balkrishnan et al, 2007; WHO, 2003). As with any self-reported measures, individual ratings, interviews and questionnaires used to assess adherence are prone to subjectivity and social desirability biases. More objective measures, such as pill counts, may suffer from counting inaccuracies and/or patients may throw away pills to show adherence. A recent innovation is a range of electronic monitoring devices which record the time and date of each instance of opening and closing of the medication container. However, opening and closing the medication containers may not reflect the actual taking of medication.

Rates of patient medication adherence are often reported to be poor. Poor medication adherence may compromise the quality of treatment outcome, or worsen disease progression leading to complications, re-hospitalizations, emergency department visits, or death (Balkrishnan et al, 2007; Castano et al, 2012). Adherence rates for patients with chronic diseases in developed countries have been estimated to be 50% (WHO, 2003; Balkrishnan et al, 2007). These rates are likely to be even lower in developing countries (WHO, 2003).

Poor adherence may be due to a number of factors. It may be unintentional, for example, patients forgetting to take medication or not knowing how to take medication; it may also be intentional, for example, patients refusing to take medication because of side effects, drug dependency, masking of other diseases, reduced long-term efficacy, stigma associated with certain medications, or lack of knowledge and trust in the medication and its effects (Hugtenburg et al, 2013).

Interventions to improve adherence may include ways to make taking medication easier, or to increase patients' motivation to take medication (Van Dulmen et al, 2008). Ideally, interventions need to be tailored to the potential causes of non-adherence (Balkrishnan et al, 2007; Hugtenburg et al, 2013). For example, a reminder system might be used for patients who forget (Van Dulmen et al, 2008).

Technological solutions may represent one way to remove barriers to medical adherence, by using technology to provide reminders to patients to take their medication (Van Dulmen et al, 2008). Different reminder methods have been reported, including by telephone (Rinfret et al, 2013), pager (Safren et al, 2003; Simoni et al, 1999), and most recently, text messaging through mobile phones. Text messaging is low cost, instant, and has become an increasingly popular way of communicating health messages (Pop-Eleches et al, 2011; Suffoletto et al, 2012).

A search of the Cochrane database identified two recent reviews: The first review examined the use of mobile phone text messaging in promoting adherence to antiretroviral therapy in patients with Human Immunodeficiency Virus (HIV) (Horvath et al 2012). The second review explored mobile phone text messaging for preventive health care (Vodopivec-Jamsek et al, 2012). However, neither review specifically examined the use of text messaging in improving medication adherence in general, which is the aim of the present study.

METHOD

Search Method

We conducted a search of the PubMed, CINAHL, PsycInfo, EMBASE and Cochrane databases for published

papers, supplemented by grey literature hand searches, for the period from 2009 until the second week of December 2013. We used the following search terms: ("text messaging" OR "mobile phone" OR "health technology") AND ("medication" OR "treatment" OR "discharge instruction" OR "prescription") AND ("adherence" OR "compliance" OR "reminder"). The filters applied include human participants, English language, and availability of at least an abstract. A hand search of the reference lists of the review articles returned from the search above was also conducted.

A separate search was also conducted of PubMed with the search terms "interventions" AND "medication adherence" to determine other types of interventions designed to promote medication adherence. However, the purpose of this latter search was only to explore the different types of interventions available and their associated effect sizes. This additional search was not the primary focus of the current review and will not be discussed in detail in this paper.

Inclusion Criteria

We included all studies with a randomized controlled trial (RCT) design where the primary focus of the study was to examine the effectiveness of an intervention using text messaging as a way of promoting or enhancing patients' medication adherence. Studies were selected if the primary outcome was adherence in some form of medication or drug treatment. We included studies conducted in all clinical settings, with all types of diseases, all types of medications or drug treatment. Studies conducted in all countries, with participants from all ethnicities were included.

Exclusion Criteria

Studies were excluded if: (1) they had a non-RCT design, (2) text messaging was one of many types of interventions investigated as part of a large multi-modal intervention study, (3) medication adherence was not the primary outcome of the study, (4) adherence was for a non-pharmaceutical form of treatment, for example, physiotherapy appointment, cognitive behavioral therapy; (5) the intervention was designed for health care staff, not patients; (6) pediatric participants, (7) the article had no abstract or full text available, (8) article was not in English.

Review Procedure

The search of text message intervention RCTs and the hand search of reference lists were done by HL, while the search of other types of interventions available was done by RD. Selection of articles was done by firstly reviewing the relevance of the articles' titles; if relevance was not clear from the title, the abstract was examined. A list of abstracts from shortlisted articles was compiled by HL, then passed to GL to review and determine the final list of articles. The full text of each article on the final list was then downloaded and read in detail to extract information for the present review.

Analysis

Data were pooled (i) from the final selected list of text message intervention studies and (ii) from the list of other types of adherence-building interventions available. We calculated average effect sizes of the intervention and control groups of the text message intervention studies, and algebraically estimated mean effect sizes based on sample sizes of each study to calculate mean adherence improvements.

A meta-analysis was not conducted due to the heterogeneity of methodologies employed across studies.

RESULTS AND DISCUSSIONS

Search Results

The PubMed search for text message intervention studies to promote medication adherence returned 1752 results. HL reviewed the titles and/or abstract and selected 92 articles. Of these, 19 review articles were identified and were used to ensure completeness. Only papers with prospectively collected primary source data were used. The most common reason for exclusion was that the study did not use a RCT design. Following review by GL, the final selection consisted of 11 articles. Three more articles from the hand search of the reference lists of reviews were selected. A total of 14 RCTs were reviewed in detail.

Study Characteristics

The 14 selected RCTs are summarized in Tables 1 and 2. All studies were published between 2009 and 2013. The studies were conducted in 10 different countries: United States (4), Africa (1), Kenya (2), Nigeria (1), New Zealand (1), The Netherlands (1), Spain (1), Denmark (1), Canada (1), France (1).

The 14 RCTs targeted a combined total of 2663 adult participants, and included different diseases and contexts: patients discharged from the Emergency Department (1 study), and patients with human immunodeficiency virus (5 studies), asthma (2 studies), type II diabetes (1 study), acne vulgaris with facial involvement (1 study) and schizophrenia (1 study). In addition, three studies involved preventive interventions in healthy adult participants. The total sample size of each study ranged from 23 patients to 538 patients, with approximately equal numbers of patients in the intervention and control groups.

Types of Text Messaging Interventions

All of the text messages in the studies (see Table 1) were reminders for the patient to take their medications, except for one study in which the text messages were statements to promote adherence by counteracting the beliefs associated with non-adherence, for example, *'taking your preventer every day protects you from asthma symptoms'* (Petrie et al, 2012). The medication reminder texts were sent along with a positive message in some studies (Mbuagbaw et al, 2012, Pop-Eleches et al, 2011). Some reminders were interactive (Suffoletto et al, 2012; Cocosila et al, 2009) or required the patient to respond (Lester et al, 2010; Hardy et al, 2011; Boker et al, 2012; Maduka et al, 2013); others did not require interaction (Pop-Eleches et al, 2011). The frequency with which the text messages were delivered varied, from once a week (Mbuagbaw et al, 2012; Lester et al, 2012) to a few times a day (Suffoletto et al, 2012) or matching patients' dosing frequencies (Hardy et al, 2011). The duration of the text messaging interventions also varied, from a few days (Suffoletto et al, 2012) to 48 weeks (Pop-Eleches et al, 2011) or 12 months (Lester et al, 2010).

The control groups in all studies but one (Hardy et al, 2011) had no exposure to text messages as part of the intervention. In the study by Hardy and colleagues, the control group used a beeper. In some studies, the control groups were exposed to 'standard care' (Lester et al, 2012; Montes et al, 2012) or 'usual care' (Mbuagbaw et al, 2012; Petrie et al, 2012), but these terms were not always clearly defined.

Definition and Measurement of Adherence

The outcome 'adherence' was defined in multiple ways, including: '*the extent to which patients take medications*

as prescribed by their health care provider' (Strandbygaard et al, 2010); *'how well patients follow their prescribed regimen'* (Vervloet et al, 2012); or in study-specific ways: *'that patient had picked up prescription within 24 hours and had no pills left on the day of intended completion of prescription'* (Suffoletto et al, 2012). The variability of how adherence was defined in each study made comparisons across multiple studies difficult. In seven out of 14 studies reviewed, no explicit definition of adherence was found anywhere in the article. Our review reinforced the point made by Balkrishnan and colleagues (2007), and Strandbygaard and colleagues (2010), that studies to date have not had a consensus on how adherence should be defined nor what constitutes an adequate level of adherence.

Some studies defined adherence using a cut-off percentage of the minimum proportion of participants who took the prescribed dosage at a given time, for example, at least 80% (Strandbygaard et al, 2010; Petrie et al, 2012), 90% (Pop-Eleches et al, 2011), 95% (Lester et al, 2010, Maduka et al, 2013). This setting of thresholds to determine dichotomous 'good' versus 'poor adherence', or 'adherent' versus 'non-adherent' patients creates unnecessary challenges as adherence measures the extent of medication taking behaviour which is best measured using a continuous scale (Balkrishnan et al, 2007; WHO, 2003).

Poor adherence may include taking too much or too little of the prescribed medication, discontinuing medication prematurely, refusing to fill pharmacy prescriptions, taking medication at the wrong time or in an ineffective way (Van Dulmen et al, 2008; Hugtenburg et al, 2013). However, the studies reviewed typically assumed that non-adherence was related only to taking an inadequate amount of medication (e.g. missed pills) and therefore did not address the other types of prescription deviation.

In addition to being defined in different ways, adherence was also measured in multiple ways, including: picking up the prescription; number or percentage of doses taken within a defined time period; percentage of participants who took the prescribed dosage; calculating a percentage of the actual dosage taken divided by the expected dosage taken in the time period according to prescription; number or percentage of pills missed; number of pharmacy refills. The most common way adherence was examined was by the percentage of the actual versus expected dosage taken in a time period according to prescription; this measure was used in half of the studies reviewed. Some studies used a mixture of the criteria above to measure adherence.

These adherence outcomes were measured most commonly using self-reported measures (11 studies), pill count at follow-up visits (2 studies), electronic monitoring systems (6 studies) such as Medication Event Monitoring System (MEMS) or Real Time Medication Monitoring system (RTMM), or a combination of these methods (4 studies).

Intervention Outcomes

Overall, results were mixed regarding the effectiveness of the use of text messaging to enhance medication adherence (Table 2). Eight studies reported a clear positive outcome in adherence, with intervention participants achieving significantly higher adherence (Maduka et al, 2013; Petrie et al, 2012; Vervloet et al, 2012; Cocosila et al, 2009; Strandbygaard et al, 2010; Hardy et al, 2011) and/or a significantly higher percentage of 'adherent' participants (Lester et al, 2012; Petrie et al, 2012) or a significant improvement in Morisky Green Adherence Questionnaire (MAQ) score (Montes et al, 2012) compared to controls. In five of these eight studies , the positive outcomes were based solely on self-reported measures (Maduka et al, 2013; Petrie et al, 2012; Lester et al, 2012; Cocosila et al, 2009; Montes et al, 2012).

However, in Hardy and colleagues' (2011) study, the positive outcomes were found only in electronically-monitored data, arguably a more objective, robust measure than self-report.

Five studies reported a clear negative outcome in adherence (Suffoletto et al, 2012; Boker et al, 2012; Ollivier et al, 2009; Hou et al, 2010; Mbuagbaw et al, 2012). In these studies there was no significant difference between intervention and control participants in all measures of adherence employed, which were self-reported measures of pills taken or missed, and electronically-monitored opening/closing of medication containers. In two of these five studies the negative outcomes were based solely on electronically-monitored data (Boker et al, 2012; Ollivier et al, 2009).

Two studies that compared methods of measuring adherence found that adherent outcomes differed according to the type of measurement method used (Hardy et al, 2011; Hou et al, 2010). In the study by Hardy and colleagues, the percentage of increase in adherence in the intervention group over the control group was significant only when measured by electronically-monitored data, The same outcome did not reach statistical significance when measured by self-reported data. Hou and colleagues reported that the number of missed pills per cycle was significantly higher in electronically-monitored data compared to participant diary data.

The study by Pop-Eleches and colleagues (2011) reported mixed findings. They found a significantly higher percentage of 'adherent' participants in the intervention group relative to the control group, but only when the text messages were delivered weekly, and not when they were delivered daily (Pop-Eleches et al, 2011). However, in all other studies, no clear pattern was observed between frequency of text messages delivered and medication adherence.

Duration of Intervention and Follow-up

The duration of intervention in the 14 studies ranged from a few days post-discharge (Suffoletto et al, 2012) to 12 months (Lester et al, 2012) or 48 weeks (Pop-Eleches et al, 2011). No clear pattern of adherence emerged when comparing shorter and longer interventions.

However, one important issue to consider is whether (and if so, for how long) the participants had been on the medication prior to the intervention. In our reviewed studies, participants' medication history varied (Table 1). In four of the 14 studies reviewed, participants had not been taking the medication for which adherence was measured. Of the remaining studies, in which participants had prior exposure to the medication, this exposure ranged from less than three months to more than one year. Two studies with healthy volunteers reported, respectively, that 42%, and 62%, of the participants had prior exposure to the medication concerned. Some studies focused on 'non-adherent' participants but the criteria for non-adherence varied among studies. Overall, no consistent pattern emerged between prior exposure to medication and adherence outcomes.

The length of the follow-up period after completion of the intervention was rarely reported. It is possible that most of these studies did not have a follow-up phase after the intervention had been completed and that this explains the lack of follow-up data. Three studies did report a follow-up period: approximately one week (Suffoletto et al, 2012), three months (Montes et al, 2012), and five months (Petrie et al, 2012). Suffoletto and colleagues' study obtained a negative outcome. Petrie and colleagues' study yielded a positive outcome, however, it was based on data at the endpoint of the intervention rather than at subsequent follow-up. In Montes and colleagues' study, the intervention group sustained significant improvements in scores on an adherence questionnaire, compared to controls, at both three and six months follow-up.

Receiving reminder texts was not a significant predictor in adherence scores at six months, but it was at three months (Montes et al, 2012).

Attrition

Another important methodological issue in these studies is attrition. Eysenbach and colleagues (2005) described two types of attrition: (1) participants who dropped out of the study or who were lost to follow-up; and (2) participants who remained in the study but stopped using the intervention. The 14 studies we reviewed had an average drop-out rate of 16.98% of eligible participants after randomization (range 1.18% - 39.02%). A high drop-out rate produces selection bias, as unmotivated participants are under-represented in the sample. The intention-to-treat (ITT) analysis is one way of overcoming this bias. In ITT, drop-out participants are included in the analysis so that the results reflect the total number of participants at randomization. Ten of the 14 studies adopted the ITT approach.

The high rate of attrition is likely to be due to a variety of reasons. One possibility could be that the adherence interventions were not tailored to the needs of participants (Verbrugghe et al, 2013; Van Dulmen et al, 2008; Hugtenburg et al, 2013). Eysenback and colleagues (2005) have suggested that rate of attrition is likely to be higher if participants perceive that the intervention is not producing benefits to themselves, is too complex, is not consistent with personal values or needs, is an experiment on a limited basis, or if its effects are not visible to others. Future research should address these factors when designing an intervention (e.g. by conducting focus groups, and pilot studies of trial interventions) in efforts to develop interventions which are meaningful to patients and might, thereby, reduce attrition rates.

Other Types of Intervention to Promote Medication Adherence

Apart from text messaging interventions, we also explored other types of interventions reported in the literature to enhance medication adherence. Our PubMed search returned 748 results and 48 studies were examined (Table 3). The studies were a mixture of RCT and non-RCT designs. Other types of interventions designed to promote medication adherence include the use of electronic reminders, pagers, Interactive Voice Response (IVR) systems, a support person or group, financial incentives, educational interventions and behavioural interventions (for example, teaching cognitive behavioural skills and offering counselling to patients with depression). Table 3 summarizes the average, and the range, of improvement in medication adherence for each type of intervention. A comparison of the estimated effect sizes suggests that behavioural interventions appear to be the most effective in improving medication adherence, followed by text messaging interventions. The use of a support person (or group) and financial incentives also appear to be effective; however, the estimates were based on a small number of studies.

Limitations

Our systematic review has some limitations. Firstly, we were unable to conduct a meta-analysis on the data available due to the varied (and in some cases, lack of) definitions of adherence and different measurements of the concept across studies. Secondly, the majority of the studies reviewed did not report measures of effect sizes; the effect sizes we reported here are estimates calculated based on the information available in the articles reviewed. Thirdly, we did not conduct formal assessments of the methodological quality of the studies reviewed. Finally, a small number of studies were reviewed. Our search terms included ‘adherence’ and ‘compliance’. Since adherence had also been used interchangeably with ‘persistence’ and ‘concordance’ (although ‘compliance’ was more common), we could perhaps expand our search terms to include ‘persistence’ and ‘concordance’ in order to be more comprehensive.

CONCLUSIONS AND FUTURE RESEARCH

In summary, we reviewed the literature on the use of text messaging interventions to promote medication adherence. This is a rapidly expanding field of research, partly attributable to the increasingly common use and ownership of mobile phones in many countries. We identified and reviewed 14 RCTs, all of which were published in the last four years (2009-2013). The studies were conducted in 10 different countries with healthy adult participants, discharged emergency department patients, or patients suffering from five different types of diseases. Although we reviewed only 14 studies, there was a lot of variability in the intervention design and measurement of outcomes. The text messages varied in their content and frequency of delivery. Adherence was not always clearly defined, and where it was defined, it was defined differently and measured in one or multiple ways across studies, at variable time points. Not surprisingly, these studies have reported mixed results for medication adherence outcomes. The heterogeneous design and measurement of outcomes made it difficult to compare across studies and to determine the effectiveness of the interventions.

A number of methodological weaknesses are evident in the reviewed studies. Self-reported measures were a popular way to measure adherence, despite evidence that significant differences were observed between self-reported data and electronically-monitored data when measuring exactly the same variable (Hardy et al, 2011; Hou et al, 2010). Self-reported measures tend to carry a social desirability bias. For example, in Hou and colleagues study (2010), the number of missed pills was significantly lower when self-reported than when electronically-monitored. Self-reported measures have the potential to make adherence levels appear to be higher than they actually may be. A majority of the positive outcomes in the studies reviewed were based on self-reported measures, whereas the negative outcomes were more evenly split between electronically-monitored and self-reported outcomes. A detailed investigation of the advantages and disadvantages of using different methods to measure adherence is needed in future research. Given our findings, and given the burgeoning number of studies of text message interventions to enhance medication adherence, we strongly recommend that future intervention studies employ multiple measures of adherence, including both self-reported and objective and/or monitoring methods, and compare and report results between the two. Other common flaws in the current studies include poor description of the control group and of 'usual care', and contaminated exposure to the intervention material in the control group. In addition, not all studies reported follow-up data, so the long-term efficacy of text messaging interventions remains unclear. Although ITT analysis was used to reduce bias in the studies with high attrition rates, future studies needs to consider ways of reducing attrition.

Text message reminders have the potential to improve medication adherence by providing cheap, instant, tailored prompts to patients. However, until various methodological limitations are addressed in better designed and more carefully controlled studies, the extent to which the promising findings from current studies can be generalized to other patient groups and to other disease categories remains unclear.

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APPENDIECS

Table 1: Methodological Features of 14 Reviewed RCT Studies

Study	Setting	Sample	Intervention	Duration of Intervention	Definition and Measurement of Adherence
Cocosila et al (2009)	An unidentified Canadian University, Canada	N=102 participants (aged 18 or above) from a Canadian University n=52 intervention n=50 control 42% participants took vitamin C previously	Intervention: Interactive text reminders to take vitamin C, with reinforcing or correcting feedback, depending on acknowledgement. First two weeks, one reminder text per day, feedback every two days. Final two weeks, one reminder text every two days, feedback every three days Control: No exposure to text messages	1 month	Not explicitly defined Measured by self-reported total number of Vitamin C pills missed in the final week of study Dosage was one pill per day therefore the no. of pills taken is calculated by 7 – no. of missed pills
Ollivier et al (2009)	Military base, France	N=424 soldiers returning from Côte d'Ivoire n=202 intervention n=222 control No prior exposure to malaria chemoprophylaxis	Intervention: Daily text medication reminder to take malaria chemoprophylaxis delivered at midday Control: No exposure to text messages	28 days	Defined as 'taken a doxycycline pill on a given day'. If not, they were considered 'non-adherent' on that day Measured by: 1. Proportion of 'fully adherent' participants who took one pill every day for the duration of the study 2. Average no. of pills taken 3. Daily % of adherent participants Measured using electronically-monitored data (MEMS)
Hou et al (2010)	Planned Parenthood Clinic, Boston, USA	N=82 women taking the oral contraceptive pill, mean age 22 years n=41 intervention n=41 control	Intervention: Daily reminder text to take oral contraceptive pill sent at participants' chosen time	3 months	Not explicitly defined Measured by comparison of two methods: 1.Rate of missed

		62% used contraceptive pill previously Currently on pill >1month excluded	Control: No exposure to text messages		pills, measured using electronically-monitored data (SIMPill) 2.Self-reported diary of daily pill taking
Lester et al (2010)	Three HIV Clinics, Kenya	N=538 HIV patients (aged 18 or above) on antiretroviral therapy for the first time n=273 intervention n=265 control	Intervention: Weekly interactive texts about health status and reminders about phone-based support Control: standard care	12 months	Defined as 'taken >95% of provided pills at both 6 and 12 month follow up visits' Measured by self-reports of how many pills the patient missed in the past 30 days.
Strandbygaard et al (2010)	Enrolled through advertisements in free newspaper, Copenhagen, Denmark	N=26 patients with asthma (aged 18-45) on discos Seretide for 4 weeks n=12 intervention n=14 control	Intervention: Medication reminder text sent daily at 10am Control: no text reminders	8 weeks	Defined as 'the extent to which patients take medications as prescribed by their health care provider'. 'Non-adherence' as 'insufficient intake of the prescribed medicine' Adherence rate cut-off at 80% Measured by % medicine taken via a medicine dose count on the discos Seretide inhaler device at clinical visits
Hardy et al (2011)	Boston Medical Center, Boston	N=23 HIV infected patients (aged 18 or above) on antiretroviral therapy for at least 3 months and <85% adherent n=12 intervention n=11 control	Intervention: personalized interactive medication reminder text delivered daily matching their dosing frequency, beeps every 15 mins until text is acknowledged Control: medication reminder beeper which beep once at each expected time for a dose, beeping does not repeat and no acknowledgement needed.	6 weeks	Not explicitly defined Measured by 1. Self-report (SR), 7 day recall 2. Difference between no. of prescribed doses and no. of missed doses, divided by no. of prescribed doses – measured by pill count (PC) 3. Electronically-monitored data (MEMS) A composite

					adherence score (CAS) is calculated based on the above three measures
Pop-Eleches et al (2011)	Chulaimbo Rural Health Center (CRHC), Nyanza Province, Kenya	N=428 patients (aged 18 or above) on antiretroviral therapy for less than 3 months n=70 short daily text n=72 long daily text n=73 short weekly text n=74 long weekly text n=139 control	Four Intervention Groups from 2x2 design of short (reminder) vs long texts (reminder plus support message), and frequent (daily) vs non-frequent (weekly) texts. All texts are one-way and non-interactive. Control: No exposure to text messages.	48 weeks	Defined as 'taking twice-daily medication at least 90% per 12-week period' Measured by no. of actual medication bottle opening divided by total no. of prescribed medication bottle opening per 12-week period Measured using electronically-monitored data (MEMS)
Boker et al (2012)	Two university-affiliated dermatology clinics in Dallas and Davis, USA. Also from advertisement posted around the medical campus and on Craigslist.com	N=40 patients (aged 12-35) with mild to moderate facial acne suitable for treatment with topical medications No prior experience with medication	Intervention: personalized interactive medication reminder texts sent twice daily at anticipated time of medication use or patient's preferred time. Control: no text reminders	12 weeks	Not explicitly defined Measured by: 1. Actual no. of opening/closing events for each medication tube divided by expected no. of opening/closing events over 12 weeks, using electronically-monitored data (MEMS) 2. Self-reports of medication taking (via returned texts)
Mbuagbaw et al (2012)	HIV/AIDS Management Clinic, Cameroon, Africa	N=200 HIV positive patients (aged 21 or above) on antiretroviral therapy for at least 1 month n=101 intervention n=99 control	Intervention group: Weekly text sent every Wednesday at 9am with a medication reminder, a positive message, and helpline number, in addition to usual care (antiretroviral therapy counselling and home visits). Control group:	6 months	Not explicitly defined Measured during interviews: 1. Visual Analogue Scale (VAS) 2.No. of missed doses 3.No. of pharmacy refills

			Usual care only. No exposure to text messages.		
Montes et al (2012)	56 outpatient psychiatric centres throughout Spain	N=254 patients (aged 18-65) with schizophrenia on a single oral antipsychotic medication, who are clinically stable with change in severity or new treatment in the last 6 months n=100 intervention n=154 control	Intervention: medication reminder texts sent daily at either 11am or 2pm Control: no text reminders, standard care	3 months	Not explicitly defined Measured by scores on the Morisky Green Adherence Questionnaire (MAQ), a self-report measure of the failure of patients to take prescriptions due to forgetfulness, carelessness, stopping treatment when they feel like it.
Petrie et al (2012)	Recruited through asthma medication flyers and emails to members of a targeted marketing website, New Zealand	N=147 patients (aged 16-45) with asthma, currently 'non-adherent' (not defined) n=73 intervention n=74 control	Intervention: texts with messages that counteract beliefs associated with medication non-adherence, sent twice daily (weeks 1-6), then once daily (weeks 7-12), then three per week (weeks 13-18). Control: Usual care	18 weeks	Not explicitly defined 'Optimally adherent' defined as >80% adherent measured through self-reports over telephone questionnaire
Suffoletto et al (2012)	ED, Western Pennsylvania	N=200 patients (aged 18 or above) prescribed oral antibiotics at discharge n=100 intervention n=100 control	Intervention group: Interactive text messages about prescriptive pickup and dosage taken. Feedback provided. One to four texts per day, depending on response. Control group: Printed discharge instructions only. No exposure to text messages.	1-2 days post discharge	Defined as 'a patient who reported that s/he (1) picked up prescription within the first 24 hours of discharge; and (2) had no pills left on the day of intended completion of prescription' Measured by self-reports over telephone questionnaire
Vervloet et al (2012)	40 Mediq pharmacies, The Netherlands	N=104 patients (aged 18-65) with type II diabetes on oral anti-diabetic medication with insulin for at least 1 year and <80%	Intervention: medication reminder texts sent at each time period they chose to take their prescribed doses	6 months	Defined as 'how well patients follow their prescribed regimen' Measured by

		adherent in pharmacy refills n=56 intervention n=48 control	Control: no text reminders		1. No. of days without dosing 2. % missed doses 3. % doses taken within agreed time period, and within predefined standardized time windows (1-4 hours) Measured using electronically-monitored data (RTMM) and self-reported questionnaire
Maduka et al (2013)	Tertiary health care institution, Nigeria	N= 104 HIV positive patients on highly active antiretroviral therapy for at least 3 months and <95% adherent	Intervention: Twice per week (Monday, Thursday mornings) interactive text messages with adherence-related information, medication reminder, and telephone numbers available for more information, delivered over 4 months along with monthly adherence counselling session Control: standard care – educational messages, occasional warnings/questioning of adherence	4 months	Defined by '>95% in no. of doses taken divided by no. of doses prescribed' Measured using self-reported measure of the no. of pills the patient missed in the past 7 days.

Note: I = Intervention, C = Control, $p<0.05$ in bold.

Table 2: Main Outcomes of the 14 Reviewed RCT Studies

Study	Adherence Outcome Key Findings	Net Effect on Adherence	Limitations	Intention to Treat Analysis
Cocosila et al (2009)	Measurement time points: baseline, 1-month (endpoint) • No. of vitamin pills taken for intervention group increased from 1.3 (baseline) to 4.5 (1-month), control group increased from 1.6 (baseline) to 3.7 (1-month). Mean % increase I>C, **p=0.001** • % self-reported increase in adherence, I(94%)>C(67%) • No difference between no. of missed pills at 1-month, I(2.5) vs C(3.3), p=0.134	Positive	1. Limited external validity to outpatients 2. Self-reported measure	Yes

Ollivier et al (2009)	Measurement time points: baseline, day 28 (endpoint) • Daily % of adherent participants decreased from 94.6% (baseline) to 67.6% (day 28) for intervention group; and 95.2% (baseline) to 65.8% (day 28) for control. • No differences between I and C in the daily % of adherent participants at baseline and day 28, p>0.05.	Negative	1. High no. of participants lost to follow-up (80% remained) 2. Contamination of intervention and control group due to shared information	No
Hou et al (2010)	Measurement time points: weeks 1, 2, 3 at each monthly cycles 1, 2, 3 • Overall rate of missed pills per cycle measured electronically: I(4.9) vs C(4.6), p>0.05; measured by self-reports: I(1.4) vs C(1.1) p>0.05 • No. of missed pills increased over time, p=0.020, but did not differ between groups, p=0.580	Negative	1. Use of alternative reminders (e.g. alarm clocks) in both groups, with higher usage among control participants, C 68% > I 36%, p=0.003. 2. Rate of missed pills per cycle recorded in SIMPill was higher than diary, **p<0.001** for both I and C. 3. Possible under-estimation of missed pill rate due to participant manipulation of SIMPill	Yes
Lester et al (2010)	Measurement time points: 6 months, 12 months • % 'adherent' participants: I (62%) > C (50%), **p=0.006**, after adjusting for baseline covariates **p=0.003** • Number needed to treat (NNT) for adherence was 9, 95% CI 5.0-29.5	Positive	1. Intervention participants forwarding their weekly text messages to control participants	Yes
Strandbygaard et al (2010)	Measurement time points: week 0 baseline, week 4 randomization, week 12 follow-up • Intervention group adherence rate at 4 weeks (77.9%) and 12 weeks (81.5%), p=0.520 • Control group adherence rate at 4 weeks (84.2%) and 12 weeks (70.1%), **p=0.010** • I-C difference in adherence rate at 12 weeks: 17.8%, **p=0.019**	Positive	1. Small sample size 2.Short follow-up period 3. Possibility of dose dumping-participants empty medication device prior to assessment visits	Yes
Hardy et al (2011)	Measurement time points: 3 weeks, 6 weeks • Adherence % at 3 weeks, as measured by SR (I-C mean difference = 12.2, p=0.137), PC (I-C mean difference = 15.7, p=0.144), MEMS (I>C mean difference = 28.1, **p=0.012**), CAS (I>C mean difference = 24.8, **p=0.018**). • Adherence % at 6 weeks, as measured by SR (I-C mean difference = 20.2, p=0.069), PC (I-C mean difference = 13.7, p=0.153), MEMS (I>C mean difference = 33.4, **p=0.002**), CAS	Positive	1. Small sample size 2. No clinical outcome data (e.g. CD4 count) was collected 3. Short follow up period (6 weeks) 4. No data on how many reminder beeps patients heard before attending their phone.	No

	(I>C mean difference = 27.1, **p=0.009**).			
Pop-Eleches et al (2011)	Measurement time points: four 12-week period, weeks 0-48 • Compared to control (40%), % 'adherent' participants was higher in weekly texts (53%, **p=0.030),** but similar in daily texts (41%, p=0.920), long texts (47%, p=0.240) and short texts (47%, p=0.240)	Mixed	1. Bottle openings may not reflect dose taking behaviour 2. Measured adherence in only one tablet not the entire regime 3. No clinical outcome measured (e.g. HIV-RNA determinations)	Yes
Boker et al (2012)	Measurement time points: 6 weeks, 12 weeks • Electronically-monitored adherence rates over 12 weeks: I (33.9%) vs C (36.5%), p=0.500 • Self-reported adherence rates for the intervention group was 74.4%	Negative	1. Small sample size 2. Twice daily texts were too frequent 3.Reported opening of closing of tube may not accurately reflect medication application	No
Mbuagbaw et al (2012)	Measurement time points: baseline, 3 months, 6 months • No. of participants with >95% adherence (measured by VAS) at 3mo (**I<C p=0.029**), 6mo (I vs C, p=0.542) • No. of participants with >90% adherence (measured by VAS) at 3mo (I vs C, p=0.094), 6mo (**I>C p=0.027**) • Missed doses reported, 3mo (I vs C, p=0.622), 6mo (I vs C, p>0.999) • No. of pharmacy refills, 3mo (I vs C, p=0.139), 6mo (I vs C, p=0.617)	Negative	1.Adherence rates may not be the same over longer periods 2.Possible exposure to other reminder methods in control group	Yes
Montes et al (2012)	Measurement time points: baseline, 3 months (endpoint), 6 months (follow-up) • Improvements in total MAQ score at 3 months: I (25%) > C (17.5%), **p=0.020** • More patients from intervention (37%) achieved a 'good adherence' score than control (22.7%). • Improvements in total MAQ score at 6 months was maintained **p=0.040** • Drop in affirmative responses to MAQ after 3 months • Receiving reminder texts was a significant predictor in improved MAQ score at 3 months, but not at 6 months	Positive	1. May not generalize to other types of patients, e.g. less stable, on several drugs 2. Other factors (e.g. drug experience, side effects) associated with adherence not examined 3. Self-reported measure 4. No blinding was used 5. Patients on medication early morning or late evening could not benefit from fixed-time texts	Yes
Petrie et al (2012)	Measurement time points: 6 weeks, 12 weeks, 18 weeks (endpoint), 6 months and 9 months (follow-up) • Self-reported adherence: I(57.8%)>C (43.2%) **p=0.003** • >80% adherent: I(25.9%)>C (10.6%) **p=0.034**	Positive	1. Large dropout rate, 93 participants remained at final follow up 2. Participants limited to <45 years old, not generalizable to older populations 3.Self-reported measures	No
Suffoletto et al (2012)	Measurement time points: up to 3 days post prescription completion	Negative	1.Self-report 2.28% missing data at <14 days	Yes

	• % Adherent, I(57%) vs C (45%), p=0.160 • % Filled prescription within first 24 hours, I(78%) vs C (69%), p=0.260 • % No pills left at completion, I(68%) vs C (59%), p=0.300		3.Other factors (e.g. health literacy, depression, cognitive impairment) associate with non-adherence not measured 4. Group size imbalances in disease categories	
Vervloet et al (2012)	Measurement time points: RTMM data daily plus questionnaire at 6 months • No. of days without dosing: I(11.9) vs C(13.8), p=0.283 • % missed doses: I(14.5) vs C(19.2), p=0.065 • % doses taken within agreed time period I(56.7) > C(43.2), **p=0.003** • % doses taken within standardized windows I>C, **p=0.002 – p=0.007** • Within 15 min, 30 min, 60 min of text sent, extra 26.9%, 34.5%, 46.2% forgotten doses were taken respectively	Positive	1. Small sample size 2. Possible language issues 3. Differences in recruitment response rates between pharmacies 4. Did not compare against automated reminders	Yes
Maduka et al (2013)	Measurement time points: baseline, monthly counselling visits, and at the end of 4 months • Self-reported adherence at 4 months follow-up: I (76.9% 'adherent') > C(55.8%'adherent'), **p=0.022,** Cohen's w = 0.224 • Median CD4+ cell count at baseline: I-C, p>0.05, at 4-months I (578.0 cells/ml) > C (361.5 cells/ml), **p=0.007**	Positive	1. Self-reported measures 2. Possible interactions of intervention and control patients outside hospital	Yes

Table 3: Interventions for Medication Adherence, Other Than Text Message Reminders, with Pooled Estimated Effect Sizes

Intervention to Improve Medication Adherence	Number of RCT's	Number of Participants	Follow-up Period	Range of Improvement in Medication Adherence (with Respect to Control Group)	Average Improvement in Medication Adherence (with Respect to Control Group)
Text Messaging	14	2663	3 days – 12 months	0%-27.1%	8.7%
Education	10	7215	1 week – 12 months	0%-68.4%	4.8%
Electronic Medication Reminder Messages	12	1523	3 weeks - 12 months	0% -19%	8%
Pager	2	294	2 weeks – 9 months	0%-15%	3.6%
Behavioural Intervention	21	9483	1-12 months	0%-50.8%	17.7%
Interactive Voice Response	1	39020	6 months	0%	0%
Support (person or group)	3	1561	6 months-12 months	9% - 91%	53.0%
Financial Incentives	1	141	12 months	11.5%	11.5%