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REVIEW PAPER

A quantitative systematic review of the efficacy of mobile phone interventions to improve medication adherence

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Abstract

Aims. To evaluate the characteristics and efficacy of mobile phone interventions to improve medication adherence. Secondary aims are to explore participants' acceptability and satisfaction with mobile phone interventions and to evaluate the selected studies in terms of study rigour, impact, cost and resource feasibility, generalizability and implications for nursing practice and research.

Background. Medication non-adherence is a major global challenge. Mobile phones are the most commonly used form of technology worldwide and have the potential to promote medication adherence.

Design. Guidelines from the Centre for Reviews and Dissemination were followed for this systematic review.

Data Sources. A comprehensive search of databases (PubMed, Web of Science, CINAHL, PsycInfo, Google Chrome and Cochrane) and bibliographies from related articles was performed from January 2002–January 2013 to identify the included studies.

Review Methods. A quantitative systematic review without meta-analysis was conducted and the selected studies were critically evaluated to extract and summarize pertinent characteristics and outcomes.

Results. The literature search produced 29 quantitative research studies related to mobile phones and medication adherence. The studies were conducted for prevention purposes as well as management of acute and chronic illnesses. All of the studies used text messaging. Eighteen studies found significant improvement in medication adherence.

Conclusion. While the majority of investigators found improvement in medication adherence, long-term studies characterized by rigorous research methodologies, appropriate statistical and economic analyses and the test of theory-based interventions are needed to determine the efficacy of mobile phones to influence medication adherence.

Keywords: medication adherence, mobile phone, nursing, short message service (SMS), text messaging

Why is this research or review needed?

- Medication non-adherence is a major global challenge and leads to increased morbidity and mortality.
- Mobile phones are the most commonly used form of technology worldwide and have significant potential to promote health-related behavioural change and self-management of acute and chronic disease.
- Mobile phone interventions have been conducted to improve medication adherence with the recent advent of mobile health.

What are the key findings?

- A comprehensive systematic review found that 18 of 29 studies using text messaging improved medication adherence.
- Negative studies tended to have more basic and repetitious content with a simple medication reminder, while positive studies delivered a variety of educational and motivational content with 'tailored' or 'personalized' SMS.
- Text messaging interventions are feasible and acceptable with the majority of studies reporting high participant satisfaction (>80%) in receiving text messages for health management.

How should the findings be used to influence policy/practice/research/education?

- Nurses will be instrumental in developing strategies to include mobile health resources to promote medication adherence with patients and their caregivers in clinical practice and research settings.
- Further research is recommended to determine the efficacy of different mobile health approaches over time and to explore topics on patient acceptance, clinical outcomes, cost-effectiveness and theory supporting medication adherence behaviour.
- Many opportunities exist in discovering the value and potential of mHealth initiatives to improve medication adherence for health promotion and chronic disease management.

Introduction

Medication non-adherence is a major global challenge [World Health Organization (WHO) 2003]. More than half of Americans with chronic diseases do not take any or all of their medications correctly (Osterberg & Blaschke 2005). In developing countries with limited resources and access to health care, medication non-adherence is assumed to have even greater magnitude and impact (WHO 2003). A strong association between medication adherence and clinical outcomes such as rehospitalization, morbidity and mortality has been demonstrated in observational studies (Smith *et al.* 2006). In addition, medication non-adherence results in an estimated $290 billion in US healthcare costs (New England Health Institute 2009).

Behavioural change interventions have attempted to promote medication adherence over many decades as reported in a Cochrane review of 83 studies; however, even the most efficacious interventions did not result in large improvements in adherence and treatment outcomes (Haynes *et al.* 2008). The factors that influence medication adherence behaviour are complex and unique to each individual, thereby requiring numerous multifactorial strategies to remove barriers and promote adherence (Brown & Bussell 2011). In the recent decade, novel behavioural interventions have introduced the use of technology by applying mobile health (mHealth) solutions to enhance adherence. Mobile health can facilitate the implementation of these behavioural strategies to provide meaningful impact on primary and secondary prevention of chronic diseases.

Technology may provide a practical and inexpensive means to promote medication adherence. The evolution of mHealth has taken shape in the past decade and refers to the use of mobile devices that are used to promote health. Mobile phones are the most commonly used form of technology worldwide (International Telecommunication Union 2011) and have the greatest potential to influence large populations. mHealth has '... the potential to advance research, prevent disease, enhance diagnostics, improve treatment, reduce disparities, increase access to health services and lower healthcare costs in ways previously unimaginable' (Nilsen *et al.* 2012, p. 6). The growth of mobile phones over the past decade has been astounding with worldwide mobile phone subscriptions growing from 12·4 million to 5·9 billion in 2011 with global penetration of 87% of individuals, including 79% in the developing world (International Telecommunication Union 2011).

Applying mobile phones in health care is a relatively young field of research with intervention studies being published just within the past decade. Text messaging (TM) interventions using short message service (SMS) have been most widely applied, while some investigators have tested interventions using a mobile phone application ('app') (Meltzer *et al.* 2008). Previous reviews have described the breadth of research that has been conducted with mobile phones (Haynes *et al.* 2008, Fjeldsoe *et al.* 2009, Krishna *et al.* 2009, Ingerski *et al.* 2011, Wei *et al.* 2011, de Jongh *et al.* 2012, Militello *et al.* 2012). Recently, there has been

a transition in mHealth, global health and funding agencies to move beyond the exploration phase of research (e.g. pilot studies, proof-of-concept) into an era of evidence-based interventions that are evaluated with the same rigour as other public health strategies (Labrique *et al.* 2013).

The review

Aims

The major aim of this systematic review was to evaluate the efficacy of mobile phone interventions to improve medication adherence and to describe the characteristics of the interventions. Secondary aims were to explore acceptability and satisfaction of mobile phone interventions and to evaluate the selected studies in terms of study rigour, impact, cost and resource feasibility, generalizability and implications for nursing practice and research. The PICO (Population, Intervention, Comparison, Outcome) question for this research study was, 'Among those who take medications for prevention or treatment of acute/chronic illness, do mobile phone text messages improve medication adherence compared with those who do not receive text messages (when applicable)?'

Design

Guidelines from the Centre for Reviews and Dissemination (CRD) were followed to develop this quantitative systematic review without meta-analysis (CRD 2008). The core principles and methods from the CRD guidelines for conducting a systematic review of health interventions were followed (CRD 2008).

Search methods

A comprehensive search was conducted to identify all studies that included the key review question of whether mobile phone interventions can support medication adherence in health promotion and disease management. Studies from all countries published in English were included in the review. To this end, a search was performed on PubMed, Web of Science, CINAHL, PsycInfo, Google Chrome and Cochrane databases to identify research publications related to this topic. In addition, bibliographies from related articles were reviewed to identify additional articles. All full-text manuscripts from January 2002–January 2013 were identified by the first and second authors (LGP and JHE), including bibliographies of the chosen articles and related reviews. Key terms were used alone and in combination with each other including 'mobile phone', 'cellular phone', 'text messages', 'text messaging', 'short message service', 'SMS', 'mobile phone application', 'medication' and 'medication adherence'.

Inclusion criteria for this review were intervention studies that supported medication adherence via a mobile phone (i.e. TM, app) in health prevention or management of acute or chronic conditions. Medication use was measured by objective or subjective data in all studies to evaluate the efficacy of the interventions. Studies that used two modalities were included if the primary mode of intervention was mobile phones. All patient populations and languages were considered. All study designs including randomized controlled trials (RCT), quasi-experimental studies and observational cohort studies were included in this review to capture the breadth of research that has been conducted as mHealth is a relatively new field. Pilot studies in mHealth were also included because they have been informative to understand the feasibility and acceptability of using mobile phones in health promotion and management.

Studies were excluded if the interventions were predominantly conducted via Internet, email, traditional landline telephones or other electronic devices (two-way TM pagers, personal digital assistants, medication alarms) alone or in conjunction with mobile phones. Studies that used co-interventions such as Internet-based communication along with TM were excluded. Studies that were based on calling patients on their mobile phones were also excluded as one of the key features of mHealth interventions is having less 'intrusive' methods of communicating with patients. Studies using mobile phones to communicate health data to healthcare providers (e.g. glucose levels) were excluded if medication use was not explicitly addressed. Last, more timely studies that were reported in journal abstracts or research conferences were excluded because they were not full-text articles and did not provide sufficient data.

Search outcome

A comprehensive electronic search produced 29 studies: 19 RCTs, two quasi-experimental studies, six pilot studies with no comparison group, one retrospective observational cohort study with matched control and one parallel two-cohort study with randomization (Figure 1). Qualitative studies or other types of studies (case series, case reports, cross-sectional studies, case–control studies) were not found. All of the studies used TM as the primary intervention. No studies using mobile phone apps met the inclusion criteria.

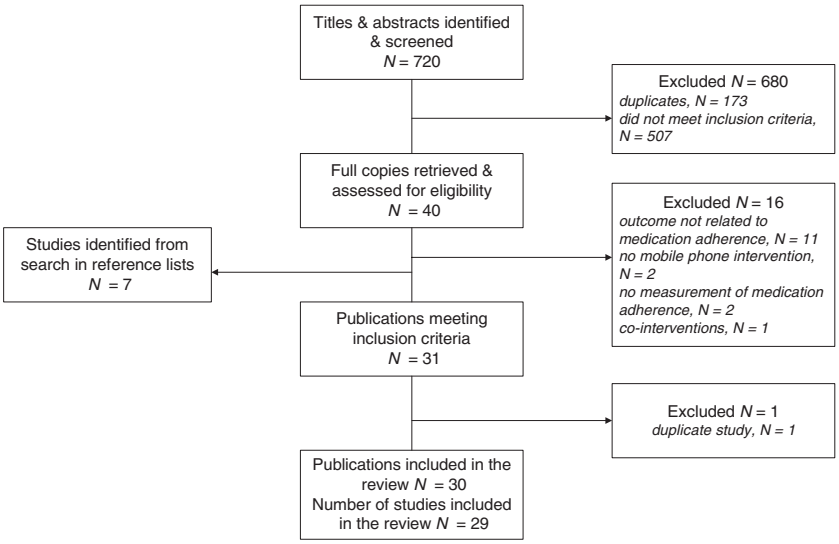

Figure 1 Flow chart of study selection process.

Quality appraisal

Quality assessment of the studies was conducted under the guidelines of the Cochrane Effective Practice and Organisation of Care Group (2012) (supplementary files). Risk of bias was assessed among the diverse study designs that were included in this review. The assessment was completed by independent review of two researchers (LGP and KD). The two reviewers discussed any items that were scored discordantly until agreement was reached. There were significant methodological differences between the studies. Narrative synthesis was performed as it was not possible to pool results with a meta-analysis. No studies were excluded on the basis of quality.

Data abstraction

Data were abstracted from each eligible study including location, target condition, duration of study, design, sample characteristics, exposure of experimental and control groups, measures of medication adherence and results (Table 1). In addition, frequency, tracking (two-way messaging) and response rate, message content and satisfaction reports were recorded (Table 2). Supplemental data on methodologies were abstracted, such as sample size calculations, effect size calculations, attrition, cost-analyses and application of theory.

Synthesis

The eligible studies differed substantially in the medical conditions, patient populations, interventions and measurement of medication adherence. Therefore, each study was examined in the context of the medication adherence outcomes and patient-reported satisfaction.

Results

Overall, 18 of the 29 studies were efficacious in improving medication adherence rates or biomarkers after receiving text messages ($P < 0{\cdot}05$), while 11 studies reported no difference (Table 1). The interventions differed substantially across studies with a variety of message content and dosing (frequency, duration). Table 2 describes the studies' tracking, message content and participants' satisfaction with the TM interventions.

Noteworthy trends were observed between the positive and negative studies. Among the negative studies, text messages tended to have more basic and repetitious content with a simple medication reminder. In contrast, positive studies delivered text messages with a variety of educational and motivational content that may have engaged more participants, thus leading to better outcomes. In addition, positive effects on medication adherence occurred in all eight studies that applied 'tailored' or 'personalized' messages. Descriptions of interventions that authors used to describe their studies as offering 'tailored' or 'personalized' messages generally meant that the text messages used the participant's name, clinical condition or participant-chosen content.

Among the 29 selected studies, the range of chronic disease processes that were treated varied from HIV/AIDS (7), diabetes (6), asthma (3), schizophrenia (2), hypertension (1), general chronic diseases (1), acne (1), atopic dermatitis (1), systematic lupus erythematosus (1) and immunosuppression after paediatric liver transplant (1). One study

Table 1 Studies on mobile phones and medication adherence.

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/ or biomarker)
Arora (2012) US	Diabetes 3 weeks	Proof-of-concept; $N = 23$; 45·4 ± 7·5; Male & female	SMS with health messages and triggers to promote knowledge, healthy eating, exercise, self-efficacy and med adherence	Morisky Medication Adherence Scale (MMAS)	Significant improvement on MMAS score (3·5–4·75).
Boker (2012) US	Acne 12 weeks	RCT; $N = 40$; 22·7 ± 5·7; Male & female	EG: SMS on med reminders for 2 different gels for acne treatment CG: No SMS	Med tube with MEMS, clinical evaluation of acne	No significant difference in mean adherence rates between EG and CG (33·9% vs. 36·5% respectively; $P = 0·5$). Self-reported adherence (responses received) for EG was 74·4%. Both groups had similar clinical improvement of acne.
Castano (2012) US	Oral contraceptive pills 6 months	RCT; $N = 962$; EG 20·8 ± 2·5 CG 20·4 ± 2·7; Female	EG: SMS with educational content CG: Routine care	Self-report on continued OCP use, missed pills, interruptions in med use, use at last intercourse	Significant difference in mean adherence rates between EG and CG (75% vs. 54% respectively; $P = 0·003$) if follow-up occurred while intervention was ongoing. Adherence was not different between groups after 187 days, 5–8 months or more.
Cocosila (2009) Canada	Prevention of colds: Vitamin C use 1 month	RCT; $N = 102$; 23·8 ± 7; Male & female	EG: SMS med reminders CG: No SMS	Self-reported pill counts	No significant difference in missed pills during last week of trial between EG and CG (2·5 ± 1·5 vs. 3·3 ± 2·2 respectively). Both groups increased Vitamin C adherence: 1·3–4·5 (246%) for EG, 1·6–3·7 (131%) for CG.
da Costa (2012) Brazil	HIV/AIDS 4 months	RCT; $N = 21$; 34·6 ± 6·9; Female	EC: SMS general health message CG: No SMS	Self-reported adherence, pill counting and MEMS	No significant differences in adherence between EG and CG. Self-report 100% vs. 84·62% respectively; $P = 0·24$. Pill counts 50% vs. 38·46% respectively; $P = 0·60$. MEMS 75% vs. 46·15%, respectively; $P = 0·19$.
Dick (2011) US	Diabetes 1 month	Feasibility and usability pilot; $N = 18$; 55 (38–72); Male & female	'Personalized' SMS on med, blood sugar, foot care, appointment, or administrative	Self-report on number of med doses missed in periods before, during and 1 month	Significant decrease in number of reported missed med doses from a mean of 1·9 per week at baseline to 0·6 during the study period ($P = 0·003$) and 0·8 at 1 month follow-up ($P < 0·001$).

Table 1 (*Continued*).

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/ or biomarker)
Dowshen (2012) US	HIV/AIDS 24 weeks	Pilot, pre-post design; $N = 25$; $23 \pm 3{\cdot}1$; Male & female	'Personalized' SMS as med reminder	VAS and AIDS Clinical Trial Group (ACTG) questionnaire 4-day recall Viral load and CD4 cell count at baseline, 12 and 24 weeks	Significant increase in VAS at 12 and 24 weeks (baseline: 74·7; week 12: 93·3, $P < 0{\cdot}001$; week 24: 93·1, $P < 0{\cdot}001$). Significant improvement in ACTG questionnaire (baseline: 2·33; week 12: 3·24, $P = 0{\cdot}002$; week 24: 3·19, $P = 0{\cdot}005$). No significant difference in CD4 cell count or viral load between baseline and 12- or 24-week follow-up. Small-to-moderate effect size (Cohen's $d = -0{\cdot}51$ to 0·22).
Foreman (2012) US	Chronic oral med(s) 8 months	Retrospective observational cohort analysis; $N = 580$; EG $64{\cdot}8 \pm 11{\cdot}9$ CG $63{\cdot}7 \pm 13{\cdot}7$; Male & female	EG: choice of SMS on refill, renewals, transfer, order shipment, general or specific med reminder CG: matched 1:1 on med class, then propensity matching score	Proportion of days covered (PDC) Change in PDC from baseline to postintervention	Significant overall mean PDC higher for EG compared with CG (0·85 vs. 0·77 respectively; $P < 0{\cdot}001$). Significant overall mean PDC change higher for EG compared with CG (0·01 vs. −0·07 respectively; $P < 0{\cdot}001$).
Franklin (2003) Scotland	Diabetes 12 months	RCT; $N = 92$; CIT 12·7 (10·5–14·8) CIT + SMS 14·1 (11·7–15·6) IIT + SMS 12·6 (11·2–15·4); Male & female	EG: 'Personalized' motivational SMS with 'Sweet Talk' CG: Standard of care	VAS	Significant difference in VAS between conventional insulin therapy (CIT) patients and CIT with Sweet Talk ($P = 0{\cdot}04$). No difference between CIT with Sweet Talk and intensive insulin therapy patients (IIT) ($P = 0{\cdot}90$).
Granholm (2012) US	Schizophrenia or schizoaffective disorder 12 weeks	Feasibility and usability pilot; $N = 55$; $48{\cdot}7 \pm 9{\cdot}1$; Male & female	'Personalized' SMS to target med adherence, socialization or auditory hallucinations	Self-report	Significant improvement in adherence, but only for individuals who were living independently.
Hardy (2011) US	HIV/AIDS 6 weeks	Parallel group RCT; $N = 25$; $42{\cdot}7 \pm 6{\cdot}5$; Male & female	SMS group: 'Personalized' SMS with med reminders Beeper group: med reminders	Self-report (7-day recall), pill count, MEMS and composite adherence score (combining MEMS, pill count and self-report)	Significant differences in mean adherence between groups when measured by MEMS (mean difference: $33{\cdot}4 \pm 9{\cdot}1$, $P = 0{\cdot}002$) and composite score ($27{\cdot}1 \pm 9{\cdot}2$, $P = 0{\cdot}01$). No significant difference by pill count ($13{\cdot}7 \pm 9{\cdot}1$, $P = 0{\cdot}15$) or self-report ($20{\cdot}2 \pm 10{\cdot}3$, $P = 0{\cdot}07$).
Hou (2010) US	Oral contraceptive pills 3 months	RCT; $N = 82$; EG: 22 (18–31) CG: 22 (18–30); Female	EG: SMS med reminders CG: No SMS	Electronic monitoring device to store OCP (SIMPill) and paper diary	No significant difference in missed OCP per cycle between EG and CG ($4{\cdot}9 \pm 3{\cdot}0$ vs. $4{\cdot}6 \pm 3{\cdot}5$, respectively; $P = 0{\cdot}60$).

Table 1 (*Continued*).

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/ or biomarker)
Lester (2010) Kenya	HIV 12 months	RCT; $N = 538$; 36·7 ± 8·5; Male & female	EG: SMS med reminders CG: Standard of care	Self-reported adherence and plasma HIV-1 viral RNA load suppression	Significant difference in adherence rates between EG and CG (RR for non-adherence 0·81, 95% CI 0·69–0·94; $P = 0·006$). Significant difference in suppressed viral loads between groups (RR for virological failure 0·85, 95% CI 0·72–0·99; $P = 0·04$).
Lewis (2012) US	HIV 3 months	Proof-of-concept; $N = 52$; 38 (25 to over 60); Male	'Tailored' frequency of SMS med reminders depending on weekly assessment of adherence	Self-report of missed doses and clinical outcomes (viral load and CD4 count)	Significant difference in number of missed med days for participants from baseline to follow-up (1·90 ± 1·22 vs. 0·94 ± 1·09, Cohen's $d = 0·83$; $t(16) = 2·22$, $P = 0·04$). Significant reduction in viral load from baseline to follow-up ($P = 0·01$; Cohen's $d = -0·40$) and CD4 counts ($P = 0·04$; Cohen's $d = 0·21$).
Marquez Contreras (2004) Spain	Hypertension 6 months	RCT; $N = 67$; 57 ± 10·6; Male & female	EG: SMS med reminders and health info CG: Standard of care	Pill counts and blood pressure recordings	No significant difference in mean percentage of adherence between EG and CG (91·9% ± 11·5% vs. 88·1% ± 20·8%, respectively; P = NS). No significant difference in blood pressure control between EG and CG (64·7% vs. 51·5% respectively; P = NS).
Mbuagbaw (2012) Cameroon	HIV 6 months	RCT; $N = 200$; EG: 41·3 ± 10·1 CG: 39·0 ± 10·0; Male & female	EG: SMS with motivational and reminder components CG: Standard of care	VAS, self-report, pharmacy refill data (PRD)	No significant difference in VAS between groups (RR 1·06, 95% CI 0·89–1·29; $P = 0·54$) or self-reported missed doses (RR 1·01, 95% CI 0·87–1·16; $P = 0·99$). No difference in PRD between groups (mean difference 0·1, 95% CI 0·23–0·43; $P = 0·62$). EG achieved adherence of 90% at 6 months (RR 1·14, 95% CI 1·01–1·29; $P = 0·03$).
Miloh (2009) US	Immunosuppression posttransplant 13 ± 1·5 months	Quasi-experimental; $N = 41$; Median age 15 (2–27); Male & female	SMS med reminders	Mean tacrolimus SD, clinical outcomes (rejection)	Significant decrease in tacrolimus level SD before compared with during the study (3·46–1·37 mcg/L ($P < 0·005$). Significant reduction in acute cellular rejection before compared with during the study (12–2, $\chi^2 = 5·08$; $P = 0·02$).

Table 1 (*Continued*).

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/ or biomarker)
Montes (2012) Spain	Schizophrenia 3 month of SMS; follow-up at month 6	RCT; *N* = 254; EG 38·6 ± 10·2 CG 40·6 ± 11·5; Male & female	EG: SMS med reminders CG: Standard of care	Morisky Green Adherence Questionnaire (MAQ)	Significant change in MAQ total score between EG and CG (25% vs. 17·5% respectively). Mean changes in MAQ total score from baseline to month 3 were −1·0 (95% CI −1·02 to −0·98) for EG and −0·7 (95% CI −0·72 to −0·68) for CG (*P* = 0·02). Significant change remained 3 months after SMS with mean changes in MAQ total score −1·1 (95% CI −1·12 to −1·08) for EG and −0·8 (95% CI −0·81 to −0·78) for CG (*P* = 0·04).
Ollivier (2009) France	Malaria 1 month	RCT; *N* = 424; 26·4 (no SD); Male	EG: SMS med reminders CG: Standard health info	MEMS	No significant difference in med adherence between groups. Decreased adherence rate in both groups (EG 94·6% to 67·6% and CG 95·2% to 65·8%).
Ostojic (2005) Croatia	Asthma 16 weeks	RCT; *N* = 16; 24·6 ± 6·5; Male & female	EG: SMS on med therapy and clinic follow-up CG: No SMS	Use of asthma med; pulmonary function test (FEV1% and mean FEV1); daily symptoms; home PEF (peak expiratory flow); clinical records (office visits, hospitalizations, med changes)	No significant difference in daily use of inhaled med between groups (steroids, *P* = 0·57; beta 2-agonists, *P* = 0·38). EG used 20% higher doses compared with CG. Significant increase in FEV1% predicted in EG (*P* = 0·01) compared with CG (*P* = 0·50). No change in mean FEV1 or forced vital capacity. PEF variability significantly different between groups (*P* = 0·049), although not absolute PEF. Significantly higher symptom scores in CG for cough (*P* = 0·05) and night symptoms (*P* = 0·05).
Pena-Robichaux (2010) US	Atopic dermatitis 6 weeks	Pilot, pre-post design; *N* = 25; 30·5 ± 13·4; Male & female	SMS med reminders (3 per week) and educational messages (4 per week)	Self-report	Significant improvement in mean number of days/week of adherence from pre- to postintervention among 72% of participants (3·8 ± 2·4 vs. 6·0 ± 1·7 respectively; *P* < 0·001).
Petrie (2012) New Zealand	Asthma 18 week SMS intervention; up to 9-month follow-up	RCT; *N* = 216; included 16–45 year olds; Male & female	EG: 'Tailored' SMS based on illness and med beliefs CG: No SMS	Self-report	Significant difference in mean adherence across all time points (6, 12 and 18 weeks; 6 and 9 months) between EG and CG (57·8% ± 27·1 vs. 43·2% ± 26; *P* = 0·003). Significant difference in proportions of mean adherence of 80% or above between EG and CG (25·9% vs. 15·3%; *P* = 0·03).

Table 1 (*Continued*).

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/ or biomarker)
Pop-Eleches (2011) Kenya	HIV 4 months	RCT; $N = 431$; Average age of 5 groups: 36·2 (no SD); Male & female	EG: SMS med reminders: daily vs. weekly, short vs. long CG: No SMS	MEMS	Significant difference in proportion of >90% adherence rate between EG and CG receiving weekly SMS (53% vs. 40% respectively; $P = 0.03$) and less likely to have treatment interruptions exceeding 48 hour (81% vs. 90%, $P = 0.03$). No differences between groups receiving daily SMS. No differences between groups receiving short messages ($P = 0.24$) or long messages with encouraging messages ($P = 0.24$).
Shetty (2011) India	Diabetes 1 year	Pilot RCT; $N = 215$; EG 50·1 ± 9·9, CG 50·5 ± 8·3; Male & female	EG: 'Personalized' SMS CG: Standard of care	Fasting plasma glucose (FPG), 2 hour postprandial plasma glucose (2 h PG) and HbA1C; Adherence to med, diet and activity prescriptions	Significant decrease in mean FPG (185 + 57 mg/dL to 166 + 54, $P < 0.002$) and 2 hour PG (263 + 84 mg/dL to 220 + 67, $P < 0.002$) in EG. Significant change from baseline in 2 h PG between EG and CG (14·1–34·6% vs. 13·6–19·7% respectively; $P < 0.007$). Significant change from baseline in HbA1C between groups (30·8–55·1%, 31·8–48·5% respectively; $P < 0.007$). Med prescriptions 'were followed satisfactorily by both groups.'
Strandbygaard (2010) Denmark	Asthma 3 months	RCT; $N = 26$; EG: 34·4 CG: 30·7 (no SD); Male & female	EG: SMS med reminders CG: No SMS	Med dose-count on the discos Seretide®, pharmacy reports	Significant absolute difference in mean adherence rate between groups of 17·8% ($P = 0.02$). Significant increase in mean adherence rate in EG (77·9% to 81·5%, mean change = 3·5%; $P = 0.52$). Significant decrease in mean adherence rate in CG (84·2% to 70·1%, mean change = −14·2%; $P = 0.01$).
Suffoletto (2012) US	Oral antibiotic use from emergency department Duration of antibiotic use, up to 2 weeks	RCT; $N = 200$; 33 ± 12; Male & female	EG: SMS query about prescription pickup and dosage taken with educational feedback based on responses CG: Standard of care	Self-report	No significant difference in adherence between EG and CG (57% vs. 45% respectively; $P = 0.16$). No difference in proportion of those who had filled prescriptions in first 24 hours between EG and CG (78% vs. 69% respectively; $P = 0.26$) or proportion of those who had no pills left (68% vs. 59% respectively; $P = 0.30$).

Table 1 (*Continued*).

First author, year, Country	Target condition and duration of study (months)	Design, sample size, mean age (SD or range), gender	Exposure of experimental and control groups	Measures of med adherence	Results (med adherence and/or biomarker)
Ting (2012) US	Systematic lupus erythematosus 14 months	RCT; $N = 41$ (subset with med adherence); 18·6 ± 2·5; Male & female	EG: SMS on med reminders CG: Standard of care	Self-report, blood levels of HCQ and pharmacy refill reports	No significant difference in self-reported adherence between EG and CG (80% for both). 25% had sufficiently high HCQ blood levels; 29% had undetectable levels. 32% were adherent over 80% of the time by pharmacy refill. Small effect size (Cohen's $d < 0{\cdot}25$) on adherence.
Vervloet (2012) Netherlands	Diabetes 6 months	RCT; $N = 104$; EG: 54·9 ± 6·6 CG: 54·6 ± 6·9; Male & female	EG: RTMM system with electronic med dispensers and customized SMS only if dispenser not opened CG: RTMM without SMS	RTMM electronic monitoring system	No significant difference in missed doses between EG and CG (15% vs. 19% respectively; $P = 0{\cdot}07$). No difference in days without dosing between groups ($P = 0{\cdot}28$). EG took significantly more doses within agreed time period than CG (57% vs. 43% respectively; $P = 0{\cdot}003$).
Zolfaghari (2012) Iran	Diabetes 3 months	Quasi-experimental; $N = 77$; EG 51·1 CG 53·7 (no SD); Male & female	EG: educational SMS CG: telephone contact at least twice a week for first month, then weekly	Self-report HbA1C	Significant improvement of med adherence $P < 0{\cdot}001$, diet adherence $P < 0{\cdot}001$ and physical activity $P < 0{\cdot}001$. Significant changes in HbA1C for EG ($P < 0{\cdot}001$) and CG ($P < 0{\cdot}001$) but no differences between groups ($P = 0{\cdot}19$).

2 h PG, 2 hour post prandial plasma glucose; CG, control group; CIT, conventional insulin therapy; EG, experimental group; FPG, fasting plasma glucose; FEV1, forced expiratory volume; HbA1C, Haemoglobin A1C; HCQ, hydroxyl-chloroquine; IIT, intensive insulin therapy; MAQ, Morisky Green Adherence Questionnaire; MMAS, Morisky Medication Adherence Scale; med, medication; MEMS, Medication Event Monitoring System; NS, non-significant; OCP, oral contraceptive pill; PDC, proportion of days covered; PEF, peak expiratory flow; PRD, pharmacy refill data; RCT, randomized controlled trial; RR, relative risk; RTMM, Real Time Medication Monitoring; SD, standard deviation; SMS, short message service (text message); VAS, Visual Analogue Scale.

Table 2 Tracking, message content, satisfaction of SMS interventions.

First author & year	Frequency of SMS	Tracking (2-way SMS) & response	Message content	Satisfaction
Arora (2012)	Daily (9 am, 12 pm and 6 pm); frequency of med reminders was 3 per week	Yes, 2-way response was only an option with trivia SMS (one per week) 35% response to trivia SMS	SMS on 5 domains: educational/motivational, med reminders, healthy living challenges, diabetes trivia and links to free diabetes management tools.	High satisfaction (90–100%) in helpfulness of SMS to take meds, enjoying SMS, wanting to continue SMS and recommending to others.
Boker (2012)	Twice daily, tailored to participant preference and time of med use	Yes 74% replied that they had taken their med (although it did not coincide with MEMS data)	SMS started with participant's name but content identical (med reminder).	33% starting ignoring SMS after 2 weeks. 26% found SMS to be 'annoying.'
Castano (2012)	Daily; time selected by participant and could be changed on website	Yes, 12 of 180 (0·07%) of messages were 2-way for quality control purposes Response rate not reported	47 educational messages on 6 domains (risks, benefits, side effects, use, effectiveness and mechanisms of action) that were repeated up to 4 times, 12 2-way messages for quality control.	Participants satisfied with number (91%), content (91%) and length (91%) of messages.
Cocosila (2009)	Dosing weaned down over 1 month	Yes 44%	Virtual friend named 'Tim'. SMS divided into reminding-basic, reminding-reinforcing and reminding-correcting.	Not reported
da Costa (2012)	Every Sat, Sun and alternate working days sent 30 minutes before last required med dose in a day	No	'The UNIFESP informs: take good care of your health.'	Timing: 27% – should be closer to time of med intake. Content: 91% – SMS did not need to be changed, 9% – Yes, change the content of SMS daily. Usefulness: 64% – SMS helped them to remember the time to take meds. 45% – SMS provided incentive to take care of health or take meds; 27% – felt like someone cared about them.
Dick (2011)	Timing and frequency of delivery selected by participant	Possible for participant to respond 80% responses	Recommendations for self-care including med adherence, foot care and blood sugar monitoring.	94% of participants said that SMS helped them to avoid missing meds, 94% strongly agreed that the system was easy to use and 89% increased the frequency of foot self-examinations.

Table 2 (*Continued*).

First author & year	Frequency of SMS	Tracking (2-way SMS) & response	Message content	Satisfaction
Dowshen (2012)	Daily at time(s) selected by participant	Yes 48% responses	Participants designed personalized SMS reminder at the beginning of study. Examples included: 'Don't forget!,' 'Reminder,' 'Superman calling you,' 'Time for fruit cocktail.'	81% of participants said that they would like to continue to receive SMS after the end of the study and 95% indicated that SMS helped them 'very much' to miss fewer doses of meds.
Foreman (2012)	Type and frequency of message selected by participant	No N/A	For those who elected med reminders, the general daily reminder read, 'Take your medications today.' Option of dosage specific reminders.	Not reported
Franklin (2003)	Daily or twice daily	No, hotline number provided if needed	Tailored SMS from database (examples): 'Don't 4get 2 inject!', 'Do you have any 'carb counting' questions for the DiaBTs doctors or dietitians?'	97% liked frequency (daily or twice daily), 20% complained about receiving the same message repeatedly.
Granholm (2012)	Monday through Saturday in random order in morning, afternoon and evening; time within a 2-hour window selected by participant	Yes Question 1: Mean = 86% ± 19%, Median = 93%. Questions 2–3: Mean = 85% ± 21% and 85% ± 30%. Median = 94% and 98%	First question: 'Did you take your meds today?' Next 2 questions depending on response, 'Do meds help you stay healthy?' or 'How can you remember?'	Participant were asked each Friday, ''How helpful were the text messages this week?'' Overall, mean = 3·15 ± 0·84; median = 3·42 (moderately to very helpful). Participants who had more experience with the SMS intervention increased the likelihood of reporting the intervention was helpful.
Hardy (2011)	Daily reminder matching med dosing frequency	Yes Weeks 0–3: median response rate 0·78. Weeks 3–6: response rate 0·62	Choice of following categories: news, weather, celebrity news, humour, jokes, Bible verses, word of the day, baseball, basketball, or football (able to change at weeks 3 and 6).	Nine of 10 participants reported that they enjoyed receiving a content-tailored reminder SMS. Only 1 participant, whose content was Bible verses, said that the content helped motivate her in some way to take meds.
Hou (2010)	Daily	No	'Please remember to take your birth control pills.'	SMS reminder was useful with a median score of 8 on a 0–10 scale. 66% said that the SMS reminded them more

Table 2 (*Continued*).

First author & year	Frequency of SMS	Tracking (2-way SMS) & response	Message content	Satisfaction
				than 50% of the time to take their meds. 86% of women said that they would continue or consider using the reminder system. 97% would recommend or consider recommending it to others.
Lester (2010)	Weekly	Yes; Response was either: 'Sawa' (fine) or 'Shida' (problem) fine (65%), problem (3%), no response (32%)	'Mambo?' (How are you?)	98% reported wanting to continue the SMS programme. 98% would recommend the programme to a friend. In focus groups, patients reported that they felt 'like someone cares.'
Lewis (2012)	Daily for non-adherent; weekly for adherent	Yes Not reported	Non-adherent: 'Stop, drop and pop. Take your meds now.' Adherent: 'He shoots! He scores! Perfect med adherence. Great job!'	93% reported 'always' reading the messages; 76% reported 'liking' the messages; and 39% and 29% reported the messages being 'very' or 'somewhat' helpful respectively.
Marquez Contreras (2004)	2 SMS per week on random days Mon–Fri between 11 am–2 pm	No	SMS to encourage a dherence and educate on lifestyle. Examples: 'Do not stop taking your blood pressure medicine even when you are taking other medicines or have another illness.'	Not reported
Mbuagbaw (2012)	Weekly	No, phone number was provided if help needed 48 of 101 EG patients used feedback option	Motivational messages with a reminder component. Example: 'You are important to your family. Please remember to take your medication. You can call us at this number: +237 xxxx xxxx.'	91% – SMS helped them to remember to take their meds, 35% – did not want to continue receiving SMS. 12% – SMS excellent, 30% – very good, 21% – good, 17% – average, 5% – bad, 16% – very bad.
Miloh (2009)	Once or twice daily matching med dosing times	Yes, if patient did not respond within 15–60 minutes, SMS sent to caregiver Not reported	'Take [name of med] at [set time]. To confirm intake, press REPLY, type CARE 1 and press SEND.'	Not reported
Montes (2012)	Daily; participant selected either 11 am or 2 pm	No	'Please remember to take your medication.'	Not reported

Table 2 (*Continued*).

First author & year	Frequency of SMS	Tracking (2-way SMS) & response	Message content	Satisfaction
Ollivier (2009)	Daily	No	'Remember to take your doxycycline pill at midday.'	Overall satisfaction with reports that SMS was very useful, generalizable and was not laborious.
Ostojic (2005)	Weekly	EG sent SMS to researcher (PEF values) daily – 99% compliant	SMS on adjustments of therapy and recommended follow-up with monitoring physician.	SMS were convenient and non-intrusive.
Pena-Robichaux (2010)	Daily; time between 7–9 am or 4–6 pm selected by participant	No	SMS with med reminders with alternating educational content and option of additional 'fun' SMS or 'hook' with choice of forecast, sports scores or celebrity gossip.	Participants rated the SMS system a mean score of 7·1 ± 2·4 (scale from 1–10). 88% – SMS were helpful, 92% – educational SMS were helpful, 84% – want to continue the system, 84% – would recommend the SMS programme to a friend, 72% – willing to pay a small monthly fee for service.
Petrie (2012)	weeks 1–6: 2 daily weeks 7–12: 1 daily weeks 13–18: 3 per week	No	SMS based on baseline scores on Brief Illness Perception Questionnaire and level of med belief ratings. Example med SMS: 'Your preventer medication is not addictive.'	Not reported
Pop-Eleches (2011)	Daily compared with weekly at 12 pm	No	Short message: 'This is your reminder.' Long message: 'This is your reminder. Be strong and courageous, we care about you.'	Not reported
Shetty (2011)	Frequency chosen by participant; median frequency was 2 SMS per week	No	Content chosen by participant. SMS on medical nutrition therapy, physical activity, med reminders and general healthy living habits.	Not reported
Strandbygaard (2010)	Daily at 10 am	No	'Remember to take your asthma medication morning and evening. From the Respiratory Unit.'	Perception of receiving daily SMS was positive, although majority found 10 am as unsuitable. EG reported SMS became comparable to a simple alarm clock on a mobile phone after some weeks.

Table 2 (*Continued*).

First author & year	Frequency of SMS	Tracking (2-way SMS) & response	Message content	Satisfaction
Suffoletto (2012)	One hour after antibiotic prescribed and 24 hours after participant response	Yes 67% replied to the antibiotic pickup question	Initial SMS: 'Welcome to the IMPACT antibiotic study. Text back 'yes' when you have picked up your prescription for [Antibiotic].' If no reply, extra SMS. 24 hours after response: 'IMPACT antibiotic study: How many doses of [Antibiotic] did you take between [0:00 PM] yesterday and [0:00 PM] today?'	91% reported SMS was at least somewhat useful to remind them to pick up their antibiotics. 52% reported it was very useful. 97% reported that SMS was at least somewhat useful to remind them to take their antibiotics, with 61% who reported it was very useful.
Ting (2012)	Once daily med – 8 am; twice daily med – 8 am and 8 pm	No	Example: 'Take ur HCQ now,' 'It's time 4ur meds.'	Participants initially gave informal positive feedback at follow-up clinic visits.
Vervloet (2012)	SMS only if dispenser not opened (reminded for 36% of all prescribed doses)	No	'Have you taken your medication yet? Please take your medication as prescribed by your health care provider.'	EG reported more awareness of med use compared with CG ($P = 0{\cdot}04$). Accuracy in taking med was not significant ($P = 0{\cdot}10$). 83% – 'It is good to know I am reminded if needed,' 75% – 'SMS reminders support me in med use,' 18% – 'I do not react to the SMS reminders,' 21% – 'SMS reminders are disturbing,' 66% – 'SMS reminders are useful.'
Zolfaghari (2012)	6 SMS every week (except holidays)	No	Messages set in 3 priorities: diet adherence, med adherence and stress management.	Not reported

CG, control group; EG, experimental group; med, medication; N/A, not applicable; PEF, peak expiratory flow; SMS, short message service (text message).

addressed antibiotic use for management of acute infections treated in the emergency department. Prevention studies included use of oral contraception (2), Vitamin C to prevent colds (1) and chemoprophylaxis to prevent malaria (1).

Among the RCTs, the sample sizes ranged from 16 to 962 participants. Seventeen of the 29 studies (59%) had sample sizes of approximately 100 patients or less. The majority of studies included younger populations, although one focused specifically on older adults who were eligible for Medicare benefits (mean age of SMS cohort was 64·8 SD 11·9) (Foreman *et al.* 2012). The age range of participants was 11–78 years. Five studies included participants with a mean age over 50, which is a positive step forwards in establishing the generalizability of mobile phone interventions. The majority of the studies included individuals from

both genders. There were five studies that were gender-specific including three studies focused on women (Hou *et al.* 2010, Castano *et al.* 2012, da Costa *et al.* 2012) and two studies on men (Ollivier *et al.* 2009, Lewis *et al.* 2012). The majority of investigators recruited a convenience sample from varied sites (e.g. clinics, hospitals, pharmacies and registries of prescription drug plans). A few used advertisements in local newspapers and magazines as well as university and local websites.

Thirteen studies sent messages that were strictly medication reminders. The remaining studies used content other than medication reminders such as education, motivation, prescription-related information, tips on disease self-management, generic messages or a combination of messages that included medication reminders. Several studies in this review used TM to enhance social support and remind patients to take their medication while communicating concern and providing assistance (Franklin *et al.* 2003, Cocosila *et al.* 2009, Miloh *et al.* 2009, Lester *et al.* 2010, Pop-Eleches *et al.* 2011). One study on prevention of colds with Vitamin C among a young adult population sent interesting and light-hearted messages at random times from a virtual friend named 'Tim' (Cocosila *et al.* 2009). In an HIV intervention study, researchers in Kenya typically sent a weekly bulk message to 273 participants asking 'Mambo?' (How are you?) and research participants responded back either 'Sawa' (Doing well) or 'Shida' (I have a problem) (Lester *et al.* 2010). Healthcare providers called participants who responded with the latter text, and at the end of the study, participants reported that they felt that someone cared about them (Lester *et al.* 2010). In contrast, other investigators in Kenya who targeted adults with HIV tested the effect of short vs. long messages and found no significant influence on adherence to antiretroviral medications after providing a longer message that offered social support (Pop-Eleches *et al.* 2011).

Eight studies described their interventions as personalized or tailored. For example, one small pilot study with a younger HIV/AIDS population sent personalized messages that were developed by the participants at the beginning of the study (e.g. 'Superman calling you,' 'Take it or die') (Dowshen *et al.* 2012). A visual analogue scale and a 4-day recall of medication administration showed significant changes in scores from baseline (74·7 at baseline to 93·1 at 24 weeks, $P < 0{\cdot}001$), although the investigators could not document a significant change in CD4 cell count or viral load (Dowshen *et al.* 2012).

The content of messages using the Mobile Assessment and Treatment for Schizophrenia (MATS) programme was tailored in real-time and incorporated cognitive behavioural therapy (Granholm *et al.* 2012). The response to the first text message ('Did you take your meds today?') triggered a second level of questions that led to a final message with encouragement or advice on medication adherence (Granholm *et al.* 2012). In this study, medication adherence improved significantly over 12 weeks, but only for individuals who were living independently ($P = 0{\cdot}018$) (Granholm *et al.* 2012).

While the majority of studies delivered messages once or twice daily, the frequency of delivery was optional (Dick *et al.* 2011, Shetty *et al.* 2011, Foreman *et al.* 2012). Only two studies tapered the frequency of messages through the duration of the intervention at 4 and 8 weeks (Cocosila *et al.* 2009, Petrie *et al.* 2012). The timing of delivery was commonly tailored to the participants' preferences or coincided with medication dosing.

Frequency of TM was tailored real-time in a study with diabetic patients via an innovative Real Time Medication Monitoring (RTMM) system that used an electronic medication dispenser. Customized reminders were sent only if the dispenser was not opened (Vervloet *et al.* 2012). Overall, the TM group took significantly more doses within the agreed time period than the control group (57% vs. 43%, $P = 0{\cdot}003$); however, there were no differences in missed doses between the groups (15% vs. 19%, $P = 0{\cdot}065$) (Vervloet *et al.* 2012).

The majority of studies delivered one-way messaging, while nine of the 28 studies had participants respond with two-way messaging. Two-way messaging allows for confirmation of text messages with a time-stamped response and is a means of engaging patients' involvement. The two-way response rates ranged from 35% to 86%. One study used 12 of 180 messages (0·07%) as two-way for quality control purposes (Castano *et al.* 2012). Along with daily medication reminders, other investigators offered weekly trivia questions that allowed participants to respond; however, the weekly two-way messaging response rate was only 35% (Arora *et al.* 2012).

Accurate measurement of medication adherence is imperative when applying an intervention. The discrepancy between self-reported and electronically monitored medication use was evident in some studies (Hardy *et al.* 2011, Dowshen *et al.* 2012). Self-report was the sole measure to report medication adherence in ten studies, while three studies used pharmacy data solely or in combination with other measurements (Foreman *et al.* 2012, Mbuagbaw *et al.* 2012, Ting *et al.* 2012). Other interventions ranged from exclusively using monitoring systems to reporting adherence through multiple measures (up to five).

In eight studies, adherence data were stored through electronic monitoring devices [Medication Event Monitoring System (MEMS), dose counts on inhalers] or real-time wireless communication to servers (SIMPill, RTMM system). Other objective forms of medication adherence included manual pill counts, biomarkers and health outcomes (e.g. haemoglobin A1C, viral loads, transplant rejection). Seventeen studies used biomarkers and health outcomes to assess medication adherence, while less than half of the (13) studies applied multiple methods to measure medication adherence.

The majority of studies included an evaluation of participant satisfaction that is described in Table 2. A few studies had a brief statement on participant feedback, while most studies reported participants' satisfaction using a format of percentages or Likert scales. Overall, the majority of studies reported high participant satisfaction (>80%) in receiving text messages for health management. The lowest satisfaction scores in reminding participants to take their medications included 64% of Brazilian women with HIV/AIDS (da Costa *et al.* 2012). In a study of clinic patients with atopic dermatitis, Boker *et al.* reported that 33% starting ignoring messages after 2 weeks and 26% found the messages to be 'annoying' (2012).

Discussion

The majority of interventions (18 of 29) were efficacious in improving medication adherence. These data are vital because non-adherence to medication regimens has remained a consistent and well-documented problem in health care. Mobile phones may be a useful adjunct to standard education and counselling about medications, thereby promoting the complex behaviour of medication adherence. The groundwork for using mobile phones to improve medication adherence has been explored through these studies, yet the possibilities of mHealth are abundant. The opportunities that exist with applying mobile phones in health interventions are exciting because mobile phones are so commonly used, widely accepted, easily accessible and affordable. To inform future research on improving medication adherence from mobile phone interventions, the selected studies in this review will be evaluated in the following section in terms of study rigour, impact, cost and resource feasibility, generalizability and implications for nursing practice and research.

More rigorous study designs and research methodologies will be important in future studies. Reporting accurate sample size calculations, effect sizes, measurement and statistical analyses is essential to move the science of mHealth forwards. Among the RCTs, 11 of the 20 studies included a sample size calculation. Some researchers reported that inaccurate and incomplete sample size calculations may have potentially affected their study results (Ostojic *et al.* 2005, Cocosila *et al.* 2009). Effect sizes were reported in only six studies. Statistical significance was generally provided by P values, while confidence intervals were rarely reported, indicating a lack of reporting on statistical precision. A closer examination of the studies that did not reach statistical significance revealed several study design limitations that may have influenced the results. In addition to inaccurate sample size calculations and measurement issues, the use of additive or interactive effects may have compromised the results. For example, investigators in a study of oral contraceptives realized that 88% of their patients used other co-interventions such as alternative alarm systems (e.g. alarm clocks or mobile phone alarms) (Hou *et al.* 2010).

The application of quality assessment tools will identify potential biases and allow a systematic evaluation of the internal and external validity of the studies under review. A risk of bias assessment of the current studies is presented in the supplementary tables. As expected, the non-RCT studies showed the highest risk of bias with the fewest criteria met. Of the nine criteria, there was a range of 1–7 criteria met among the 29 studies. Five of the nine criteria were satisfied by the majority of studies; however, there were other criteria that were less frequently met or unclear (i.e. blinding, free of other bias given a non-RCT design). The quality of these studies is difficult to evaluate given the variety of rigour among the studies. For example, six pilot studies with no control group clearly had the highest risk of bias compared with other studies. The inclusion of pilot studies was still valuable because each study added to the growing evidence of the strengths and limitations of TM interventions to promote medication adherence in this young field of research. Although the collective rigour is moderately weak, there is potential to build stronger confidence in future mHealth studies with more rigorous designs that account for potential biases as recommended in Cochrane EPOC (Cochrane Effective Practice & Organisation of Care Group 2012).

Regarding accurate measurement, a mixed methods approach with electronic devices, biomarkers and self-report is an important component in strengthening rigour of a study protocol in data collection and corroborating data. In addition, in studies with frequent follow-up visits, more sophisticated statistical models will be valuable to assess change over time without being influenced by missing data. The spectrum of evaluation methods in mHealth

research will need to include alternative study designs and methodologies to provide timely information in a rapidly evolving field (Nilsen *et al.* 2012).

Among the studies, the highest attrition rate was 41% at a mean of 4 months in a year-long study of paediatric liver transplant patients (Miloh *et al.* 2009). Although there were no reported risk factor differences in patients who dropped out, the positive results of receiving text messages to improve adherence to immunosuppressant therapy among the experimental group may have been influenced by the higher adherence characteristics of the remaining patients overall (Miloh *et al.* 2009). Both the mean and median rates of attrition in all these studies were 15%.

The long-term impact of mHealth interventions is needed to document the efficacy and sustainability of these interventions on chronic disease management. The longest study period was 14 months, with the mean and median study durations being 21 and 16 weeks respectively. A major barrier in using mobile technology may be deterioration of interest as the novelty of the messages decreases over time. Factors that maintain engagement of participants remain unknown and serve as important gaps in research. The content of text messages may be a determining factor in patients' continued interest and persistence in using mobile phones to improve medication adherence. Messages varied widely in content among the studies, with some interventions giving the same daily reminder to take medications and other interventions using a variety of messages that varied in topic. Although more personable messages might appear to better engage users, the impact of such methods requires further study (Miloh *et al.* 2009, Pop-Eleches *et al.* 2011). Tailoring messages with personalized content, building on responses from participants and delivering messages in different languages may help to make a more customized programme that engages participants.

Future studies that focus on the impact of specific TM protocols and are age, gender and culture specific will develop our knowledge about culturally appropriate interventions (Strandbygaard *et al.* 2010). Research should be designed and interpreted in culture-specific contexts. For example, interventions that are targeted at health conditions associated with negative stigma such as HIV require consideration in maintaining confidentiality. In the study in Cameroon, a high proportion of participants disclosed their HIV status to their families during the course of the study (Mbuagbaw *et al.* 2012). In this study, 35% did not want to continue receiving messages at the end of the trial period, which might indicate the participants' sensitivity in receiving messages associated with their health status (Mbuagbaw *et al.* 2012).

Importantly, clinical outcomes that are tracked over time to determine efficacy and sustainability of TM interventions and health-related apps are fundamental to mHealth intervention design. The majority of research studies reviewed here demonstrated feasibility in supporting medication adherence as well as high acceptability and satisfaction among participants. Long-term studies are needed to provide and guide future intervention design, so that mHealth can be fully integrated into daily life.

In future studies, the cost of implementing a mobile phone intervention needs to be addressed from the providers' and participants' perspectives. Implementing cost-effective programmes for long-term participation will continue to be an important factor in achieving positive outcomes. Among the studies reviewed, some participants reported concerns about costs if they continued with the TM programme (Hardy *et al.* 2011). Providing options such as limiting two-way messaging to reduce costs for participants who have limited TM plans may be a consideration in future studies. Only five studies reported a cost-analysis of their medication adherence interventions. Cost-analyses will provide important information for policy makers and global funders, particularly in HIV research because reducing viral replication through antiretroviral therapy can decrease transmission of HIV to new partners (Lester *et al.* 2010). Use of mobile phones may offer a major prevention strategy in regions where HIV is endemic and other resources are limited. Another cost-analysis derived by a national pharmacy benefit manager found only a slight increase in pharmacy-related costs for the group who received text messages compared with the matched control group, although the differences were not statistically significant (Foreman *et al.* 2012). The total healthcare costs for these groups were not analysed but would be beneficial when determining the overall cost benefit of the intervention. Consideration of reimbursement models for medication adherence and mHealth interventions is also needed (Bosworth *et al.* 2011).

In terms of generalizability, it is difficult to generalize the positive findings of the studies to other populations given the differences in study design, group characteristics, comorbidities and intensity in managing medical conditions. Caution is necessary when extrapolating results from different patient populations and conditions such as applying findings from teenagers with diabetes administering insulin (Franklin *et al.* 2003) to older adults who are managing multiple chronic diseases with several different classes of medications (Foreman *et al.* 2012). Likewise, caution is necessary when extrapolating results with chronic disease populations to healthy individuals who are

practising primary prevention behaviours such as Vitamin C use (Cocosila *et al.* 2009). More studies in areas of health promotion as opposed to chronic disease management are needed as a literature search produced a few studies to date. Regarding the generalizability of the findings to older adults, several studies emerged from this review that successfully included older adults in using mobile phones for improved medication adherence. Mobile health resources may be offered as a supplement to the care of older adults, family members and caregivers as patients live with chronic diseases. Although penetration of mobile phones among older adults may be challenging due to the lack of familiarity with current technology, this is likely to change among individuals who regularly use TM or apps age (Petrie *et al.* 2012).

Sensitivity to literacy and languages will support mobile phone interventions that reach global populations and increase generalizability. Four studies in this review allowed participants to choose their language preference (Pop-Eleches *et al.* 2011, Arora *et al.* 2012, Castano *et al.* 2012, Mbuagbaw *et al.* 2012). The global reach of mHealth research is demonstrated in this review with 14 countries being represented, although 13 of the 29 studies were conducted in the USA. Valuable insight into mobile phone interventions in countries with few resources was provided by studies conducted in Kenya, Cameroon and India. Due to the ubiquitous nature of mobile phones across diverse populations, the modality of mobile technology may be generalizable across many more cultures.

This study offers several implications for nursing practice and research. Patients can be empowered to adhere to medication prescriptions through nursing practice. Prescription counselling often comes from nurses in hospital, outpatient or community settings. Developing strategies with patients and their caregivers to promote medication adherence may be key to successful self-management. Nurses can play an important role in keeping current with the growing number of available mHealth and telemedicine resources for patients. Nurses are encouraged to embrace an innovative and creative spirit to consider the potential of mobile technology to be a cost-effective and efficacious tool to improve medication adherence.

Many opportunities remain in building mHealth science. Future research may assess the impact on medication adherence and user fatigue from various message contents, frequency of reminders and text responses (Hardy *et al.* 2011). Moreover, integration of real-time feedback on disease management will be instrumental in designing future interventions (Granholm *et al.* 2012, Vervloet *et al.* 2012). Nurses can make a significant contribution to understanding the potential of mHealth by applying mixed methods study designs with quantitative and qualitative research as well as applying a theoretical framework to mHealth research related to medication adherence.

In this review, only five of 29 studies used theory to guide their research. The theories were Transtheoretical Model (Castano *et al.* 2012), Social Cognitive Theory (Franklin *et al.* 2003), Health Belief Model of Behavior Change (Mbuagbaw *et al.* 2012), Behavioral Learning Theory (Montes *et al.* 2012) and Theory of Planned Behavior (Suffoletto *et al.* 2012). It will be important for nurse scientists who design future studies to use a theoretical basis to explain the relationship between study variables. Other health behavioural theories may be developed that take into account the time-intensive, interactive and adaptive nature of mHealth interventions that demand more intra-individual dynamic regulatory processes (Riley *et al.* 2011).

Conclusion

The potential impact of mobile technology in disease prevention and management may be substantial. Research identified in this systematic review has introduced the use of mobile phones to support medication adherence among different patient populations. Future research is required to substantiate these early findings and to provide data on long-term follow-up in a variety of patient populations. Applying appropriate statistical approaches combined with rigorous theory-based interventions may provide important insights into the efficacy and acceptance of mHealth by patients related to medication use and the factors that mediate its efficacy. Future studies are required to determine the efficacy of different approaches over time and to explore topics such as patient acceptance, clinical outcomes, cost-effectiveness and theory supporting medication adherence behaviour.

The next decade of research with mobile phones will likely evolve into applying more smartphone apps in place of TM interventions. The efficacy of mobile phone apps vs. TM has yet to be explored in research. As the number of smartphone users continues to grow with 58% of Americans owning a smartphone in 2014 (Pew Research Center 2014), interventions that apply apps as opposed to TM will inform us about the full potential of mHealth to support medication adherence and disease management. The features that are available from smartphones will likely engage users by allowing more interaction and increased variability.

Mobile health will continue to enhance clinical practice and allow for easily accessible and remote solutions,

especially for patients with chronic diseases requiring life-long medication adherence for optimal outcomes. The real possibilities of mHealth in promoting medication adherence await further research and will continue to take shape as the results of pilot studies and rigorous intervention trials continue to inform us in this promising field.

Author contributions

The authors have confirmed that all authors meet the ICMJE criteria for authorship credit (www.icmje.org/ethical_1author.html), as follows:

- substantial contributions to conception and design of, or acquisition of data or analysis and interpretation of data,
- drafting the article or revising it critically for important intellectual content and
- final approval of the version to be published.

Supporting Information Online

Additional Supporting Information may be found in the online version of this article:

Table S1. Risk of bias assessment.

Table S2. Criteria met for risk of bias assessment.

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