

Postprint Version	1.0
Journal website	http://jamia.bmj.com/content/early/2012/04/12/amiajnl-2011-000748.full
Pubmed link	http://www.ncbi.nlm.nih.gov/pubmed/22534082
DOI	10.1136/amiajnl-2011-000748

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The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature.

MARCIA VERVLOET,¹ ANNEMIEK J LINN,² JULIA C M VAN WEERT,² DINNY H DE BAKKER,^{1,3} MARCEL L BOUVY,⁴ LISET VAN DIJK¹.

¹NIVEL, Netherlands Institute for Health Services Research, Utrecht, The Netherlands.

²Amsterdam School of Communication Research (ASCoR), University of Amsterdam, Amsterdam, The Netherlands.

³Tranzo, Scientific Centre for Care and Welfare, Tilburg University, Tilburg, The Netherlands.

⁴Utrecht Institute for Pharmaceutical Sciences (UIPS), Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht University, Utrecht, The Netherlands.

Adherence is the extent to which a person's behavior-taking medication and/or executing lifestyle changes-corresponds with agreed recommendations from a healthcare provider.¹ Many patients, especially those with chronic illnesses, experience difficulties in adhering to prescribed treatment. Average adherence rates to long-term treatment are low.^{1,2} Poor adherence compromises the effectiveness of medication treatment and results in suboptimal illness control. This can lead to increased use of healthcare services, reduction in patients' quality of life, and increased healthcare costs.³⁻⁵ Numerous interventions aimed at improving adherence have been conducted, but these were mostly complex and not very effective.⁶ Complex interventions are often time consuming, labor intensive and costly, thus not feasible in busy clinical practice. According to experts in the field of adherence, simple interventions, ie, interventions that are workable in daily practice and that are easy for both professional and patient, appear to be most promising in furthering patients' adherence.⁷ An example of a simple intervention is reminding patients of their medication intake. Reminders can especially provide a solution for patients who are unintentionally non-adherent, ie, patients who are willing to take their medication but forget it or are inaccurate with their timing.⁸ Forgetfulness is commonly reported as a barrier to adherence in various patient populations.⁹⁻¹⁸ Albeit the range of patients reporting this barrier varies from 22% to 73% across the studies, in all studies forgetting to take a dose was the most frequently cited reason for non-adherence.

Two reviews on the effectiveness of 'reminder packaging', which refers to any medication package (eg, a pill box, blister package, bottle) that physically incorporates a system for the day and/or time for medication to be taken, reported modest improvements in adherence to long-term medications.

^{19,20} However, patients are not actively reminded with this type of packaging. Studies evaluating the effect of personal-and thus active- reminders, such as telephone calls or emails from healthcare providers to patients, revealed positive effects on adherence rates.^{21,22} However, personal reminders can require an extensive time investment from healthcare providers. Electronic reminders, on the contrary, are automatically sent to patients at the appropriate time without interference of a healthcare provider. Examples are reminder messages automatically sent to a patient's mobile phone with a short message service (SMS), an electronic reminder device (ERD) that provides patients with an audio and/or visual reminder at predetermined times, or text messages sent to patients' pager to alert them of their medication.

This type of reminding does not require additional effort from professionals and may be easy to integrate in patients' daily life.

Interventions using reminders are primarily based on the principles of behavioral learning theory.²³ According to this theory, behavior depends on stimuli or cues, either internal (thoughts) or external

(environmental cues), suggesting that non-adherent behavior can be modified after sufficient repetition of external stimuli or cues such as reminders.

With the increasing use of electronic reminders aimed at improving medication adherence, there is a need to gain insight into the effects of this type of reminding. Previous reviews evaluating strategies for improving adherence among which electronic reminders often focused on specific patient populations. For example, Gray et al²⁴ found that a reminder device might be beneficial to patients with glaucoma. Wise and Operario²⁵ showed that half of the studies included in their review reported significantly improved adherence in HIV patients as a result of ERD. Misono et al²⁶ reviewed studies using healthcare information technology interventions to improve adherence to cardiovascular and diabetes medication, and showed that of these interventions, reminder systems provided the best evidence for increasing adherence.

To our knowledge, no review has been conducted that systematically studied the effects of specifically electronic reminding (eg, via SMS, ERD, pager/beeper systems) on patients' adherence to a range of long-term medication. Therefore, in this systematic review, we aim to synthesize and critically appraise the existing evidence on the effectiveness of electronic reminders in improving patients' adherence to chronic medication. In addition, we aim to investigate the characteristics of electronic reminders that are associated with their effectiveness.

METHODS.

This review was conducted according to the guidelines of the Cochrane Collaboration described in the Cochrane handbook for systematic reviews of interventions, version 5.1.0 (updated March 2011).²⁷

Inclusion criteria.

A study was included in this review if it met the following inclusion criteria: (1) the intervention was aimed at patients who were prescribed chronic medication; (2) the intervention involved an electronic reminder aimed at improving medication adherence; (3) the reminder was directed to the patient; (4) one of the outcome measures was medication adherence; (5) the study design was either a randomized controlled trial (RCT) or a controlled clinical trial (CCT); (6) the study was published in English. Studies using historical controls were excluded, as possible bias may be introduced due to factors (other than the intervention) that may have changed over time.

We defined an electronic reminder as an automatically sent reminder without personal contact between healthcare provider and patient. Consequently, telephone calls, emails or SMS personally sent by healthcare providers were excluded.

Search strategy.

We conducted a comprehensive literature search in PubMed, Embase, PsycINFO, CINAHL and the Cochrane Central Register of Controlled Trials. We used the following MeSH terms and keywords for searching PubMed: (medication adherence OR patient compliance OR medication therapy management) AND (cellular phone OR reminder systems OR text message OR electronic reminder) AND (intervention study OR randomized controlled trial OR controlled clinical trial). Advanced search, allowing for explosion search, mapping to preferred terminology, searching keywords or in all text was used in the other databases whenever possible. No restriction on publication date was applied. The electronic databases were last searched on 7 March 2011. Electronic searches were supplemented by manual searching of reference lists of relevant reviews ('snowball method').

Review procedures.

Reference Manager 11.0 was used to manage all citations.

Independently, three reviewers (MV as first reviewer and either AJL or LvD as second reviewer) screened all citations (title and abstract) identified by the electronic and manual searches. Full text was obtained for the potentially eligible studies and for those for which we had insufficient information. The interrater agreement between MV and AJL and MV and LvD was 92% and 97%, respectively. Full text articles were reviewed independently by AJL and MV for final inclusion in the review according to the inclusion criteria mentioned earlier. Reasons for exclusion of studies at this stage are given in supplementary appendix A (available online only). Disagreements between reviewers were resolved by discussion.

Data extraction.

MV extracted the following study characteristics (see table 1 and supplementary appendix B, available online only):

- < General information (first author, year of publication).
- < Study design.
- < Study population (sample size, age, gender, medication/disease).
- < Intervention (description of experiment and control condition, type of reminder).
- < Adherence measure (type of measurement, follow-up period)
- < Main study results.
- < Authors' conclusion.

Methodological quality.

The methodological quality of the studies was assessed independently by AJL and MV according to the criteria list from the Cochrane Collaboration Back Review Group.⁴¹ This list addresses 11 criteria for identifying potential sources of bias: 1. Selection bias (three criteria), referring to systematic differences between participants in the different groups: (a) proper generation of allocation sequence; (b) proper concealment of treatment allocation; and (c) comparability of groups at baseline.

2. Performance bias (four criteria), referring to systematic differences between the groups in the care provided to participants, apart from the intervention that is evaluated: (d) participants kept blind to treatment allocation; (e) care providers kept blind to treatment allocation; (g) co-interventions were avoided or were similar for all groups; (h) compliance was acceptable in all groups.

3. Attrition bias (two criteria), referring to systematic differences between the groups in participants who drop out and those who remain: (i) proper description of and acceptability of drop-out rate; (k) analysis according to intention-to-treat principle.

4. Detection bias (two criteria), referring to bias in how outcomes are ascertained, diagnosed or verified: (f) outcome assessor kept blind to participants' exposure to intervention; (j) timing of outcome assessment was similar in all groups.

Each criterion was scored with a 'yes', 'unclear' or 'no', where 'yes' indicates the criteria have been met and thus suggest a low risk of bias. The methodological quality of a study was considered high when six or more criteria were met. Disagreements between the reviewers were resolved by discussion.

[TABLE 1].

Data synthesis and sensitivity analysis.

It was not possible to perform a meta-analysis because of the heterogeneity of methods and interventions used. Therefore, a best evidence synthesis (BES) was conducted, based on the one proposed by van Tulder et al⁴¹ and adapted by Steultjens et al.⁴² This synthesis takes the design, methodological quality and outcomes of the studies into account and attributes various levels of evidence to the effectiveness of interventions. Box 1 presents the principles of BES. Sensitivity analysis was performed to identify how sensitive the results of BES are to changes in the way this synthesis was performed. For the sensitivity analysis, BES was repeated in two ways: low quality studies were excluded; studies were classified as high quality if they met four instead of six internal validity criteria.

Categorization of interventions and study outcomes

We categorized the type of electronic reminder in three categories: SMS reminder; audio/visual reminder from ERD; and reminder via pager systems. The effect of the intervention was also categorized in three categories: overall effect; subgroup effect; and no effect on adherence. Any effect, either overall or in subgroups, needed to be statistically significant ($p < 0.05$).

Furthermore, we investigated both short-term (follow-up period <6 months) and long-term (follow-up period <6 months) effects.

RESULTS.

A total of 813 hits, 527 of which were unique, resulted from the electronic database searches. Searching references from reviews provided six potentially relevant studies. After screening the title and abstract, 491 references were excluded because they did not

meet the inclusion criteria. Of the remaining 42 references, full text was obtained and assessed for inclusion in the review.

Details on excluded studies in this stage are given in supplementary appendix A (available online only). Finally, a total of 13 studies met all inclusion criteria (see figure 1).

[BOX 1].

Description of the studies.

Table 1 shows the main characteristics of the 13 included studies (for a more detailed description, see supplementary appendix B, available online only). The study population varied: patients on antiretroviral therapy (five studies),^{28 29 36 39 40} patients with hypertension (three studies),^{32 35 37} patients with asthma (two studies),^{31 34} patients with glaucoma (two studies)^{33 38} and women using oral contraceptives (one study).³⁰ All studies involved adult patients, except for one study that also included adolescents aged 13 years or older.³⁴ The duration of medication use varied across the studies and also within the studies.

Seven studies included patients initiating or changing treatment,^{29 30 32-34 36 39} four studies included patients currently using medication,^{28 37 38 40} and two studies included both new and current users.^{31 35} Four interventions tested the effect of SMS reminders on patients' adherence,²⁸⁻³¹ seven studies evaluated an ERD with audiovisual medication reminders,³²⁻³⁸ and two studies concentrated on the effect of a pager reminder.^{39 40} Almost half of the studies used multiple measures to assess adherence. Electronic monitoring (electronically registering the date and time of every medication intake) was used in 11 studies. Six studies exclusively used electronic monitoring,^{29 31 33-35 40} four combined electronic monitoring with self-report^{30 32 36 39} and one combined electronic monitoring with both pill count and self-report.²⁸ One study exclusively used pill count,³⁷ one study assessed bottle weight (medication in soluble form) with self-report.³⁸ Only three studies followed patients for a period of 6 months or longer.^{29 32 39}

Methodological quality

The methodological quality (risk of bias) of the 13 included RCT was assessed. Seven studies were classified as high quality studies, six studies had a low quality (table 2).

[FIGURE 1] [TABLE 2].

Effectiveness of interventions.

Tables 3 and 4 summarize the effects on adherence, methodological quality of the studies, and characteristics of the intervention (studied medication, type of electronic reminder, and type of adherence measurement), by length of follow-up period.

Eight (four high and four low quality) studies reported significant overall effects on patients' adherence as a result of an electronic reminder. Hardy et al²⁸ compared the adherence of HIV patients receiving SMS reminders with patients using a beeper as a reminder and found a significant difference in favor of SMS reminding. Strandbygaard et al³¹ revealed that adherence rates of asthma patients who received daily SMS reminders were higher than those of patients who were not reminded. The third study also focused on asthma patients and found that an ERD with an audiovisual reminder significantly improved adherence.

³⁴ Two other studies also used an ERD with audiovisual reminders, both in patients with glaucoma, and found higher adherence rates in patients receiving these reminders.^{33 38} Da Costa et al³⁷ reported significant differences in adherence between patients with hypertension who used a reminder alarm card that produced a beep at predetermined times, and patients who did not. Safren et al⁴⁰ revealed improvements in adherence in patients with HIV as a result of reminder messages sent to patients' pagers. The last study found that patients who were reminded once a week had higher adherence rates than patients reminded daily or patients not reminded at all.²⁹ One (high quality) study revealed significant effects in a subgroup of the intervention group; Andrade et al³⁶ found that an ERD with audiovisual reminders significantly improved adherence in memory-impaired patients (assessed with neuropsychological tests), but not in memory-intact patients. Finally, four (two high and two low quality) studies, two of which measured the impact of the reminder on multiple time points, showed no effects on adherence at any time point.^{30 32 35 39}

Relation between type of reminder and effects

Four studies used SMS reminders, three of which showed significant positive effects on adherence. Those studies used either personalized text messages that requested a reply from patients when taking the medication,²⁸ or standardized text messages without requiring acknowledgment.^{29 31} The study revealing no effect used standardized messages without requesting a reply.³⁰

[TABLE 3].

Four of the seven studies evaluating audio/visual reminders from ERD significantly improved patients' adherence. Three of them used an ERD that produced both an audible and visual reminder,^{33 34 38} the fourth used an ERD that only emitted an audible reminder.³⁷ The one study that found a subgroup effect evaluated an ERD with an audible reminder.³⁶ Two studies showed no effects, both of them used an ERD that accommodated blister packs.^{32 35} Two interventions used pagers, one of which revealed a significant effect.⁴⁰ This study delivered standardized text messages to patients' pagers at predetermined times and requested no reply.⁴⁰ The pager intervention revealing no effects delivered a minimum of three pager messages daily and a confirmation return page was requested for every message.³⁹

Relation between length of the follow-up period and effects

Ten studies had a follow-up period shorter than 6 months.

Within this group, all but two studies revealed significant overall effects^{28 31 33 34 36-38 40} or a subgroup effect.³⁶ The follow-up period varied from 3 weeks to 3 months. In contrast, only one of three studies following patients for over 6 months reported significant effects. That study followed patients for 48 weeks.²⁹ The two studies reporting no effects followed patients for 9³⁹ and 12 months.³²

Relation between type of adherence measurement and effects.

Eleven studies used electronic monitoring as a method to measure adherence. Six of them reported significant overall effects,^{28 29 31 33 34 40} one found a subgroup effect.³⁶ In addition to electronic monitoring, five studies used self-report to measure adherence. Two of those studies showed inconclusive results between the two methods: significant effects were only found when adherence was measured with electronic monitoring, not with self-report.^{28 36} One study also used pill count as a third method for measuring adherence, but again effects were only found with electronic monitoring.²⁸ One study exclusively using pill count³⁷ as well as a study using 'pill count' (or weight of medication solution) combined with self-report³⁸ showed significant effects on adherence.

Other characteristics.

The number of patients participating in the studies was often limited: six studies included fewer than 30 patients in each arm.

Despite this limited sample size, four of them revealed significant effects^{28 31 33 38} and one a subgroup effect³⁶ on adherence.

In addition, four studies included between 30 and 50 patients in each arm, three of which showed significant effects.^{34 37 40} Of the three studies that included more than 50 patients in each arm, one study reported significant effects.²⁹

BES and sensitivity analysis.

Seven of the 13 included RCT were classified as high quality studies. Four of them reported significant overall effects, three of which were effects measured short term (<6 months follow-up).

In addition, four low quality studies found significant effects, all short term. Only one high quality study found significant effects measured long term (6 months or longer follow-up).

Using the principles of BES (see box 1), these results indicate that there is evidence of the short-term effectiveness of electronic reminders in improving patients' adherence to medication.

Regarding the type of electronic reminder, there is evidence resulting from three high quality studies of the effectiveness of SMS reminders in improving adherence.^{28 31} Moderate evidence was found for audiovisual reminders from ERD as a strategy to improve adherence, as one high quality and three low quality studies found significant effects.^{33 34 37 38} There is insufficient evidence for the effect of pager reminders in particular, as the low quality study reported significant effects.⁴⁰ As sensitivity analysis, BES was first repeated using seven high quality RCT (thus disregarding six low quality RCT). Evidence

[TABLE 4].

for the short-term effectiveness as well as evidence for the effectiveness of SMS reminders in particular remained. However, limited evidence is now found for the effectiveness of ERD with audiovisual reminders. Second, BES was repeated using four instead of six (out of 11) validity criteria for classifying RCT as high quality studies. Again, evidence for the short-term effectiveness as well as evidence for SMS reminders remained. In addition, evidence was also provided for audiovisual reminders from ERD.

DISCUSSION.

This review provides evidence for the short-term effectiveness of electronic reminders in improving adherence in patients using chronic medication. Significant improvements in adherence were found in all but two studies following patients for a period of less than 6 months (four high and four low quality studies).

Only one (with a high quality) of three studies with long-term follow-up reported significant effects on patients' adherence.

The electronic reminders evaluated in those studies included SMS reminders, audio/visual reminders from ERD and reminders delivered to pagers. Stratified by the type of electronic reminder, our review shows that SMS reminders in particular but also ERD can be effective strategies for improving patients' adherence in the short run.

Most studies included in this review followed patients for a period of less than 6 months. It is, however, important to investigate whether the effects of electronic reminding remain for a longer time period. Patients who are adherent at first can become non-adherent over time.⁴³ Furthermore, all 13 studies included in this review automatically sent electronic reminders regardless of whether or not patients took their medication.

This may negatively influence the long-term effects of electronic reminders, as these automated reminders can become a routine resulting in habituation. This may be the reason that Pop- Eleches et al²⁹ found that SMS reminders sent once a week significantly improved the adherence of HIV patients whereas daily reminders did not. Further research is needed to investigate the influence of the frequency with which reminders are sent in improving of adherence. Moreover, real time adherence monitoring is now upcoming,^{44 45} offering the possibility to intervene only when patients miss a dose, thus avoiding the reminders becoming routine. The effectiveness of this nonautomated type of electronic reminding on adherence is currently being investigated.⁴⁶ With technology evolving rapidly, the use of older technologies such as pager systems is likely to decrease and new technologies may arise, such as applications for smart phones.

Currently, SMS reminding is increasingly being implemented in interventions aimed at improving adherence as mobile penetration is high. The effectiveness is influenced by patients' willingness to receive SMS reminders. Two of the included studies reported patient experiences with SMS reminding.^{30 31} Both studies reported a positive evaluation of this type of electronic reminding, although in one of the studies the majority of patients indicated that the predetermined time at which the reminder was sent daily was unsuitable.³¹ In addition, three included studies evaluating ERD reported that these devices were well accepted by patients,^{35 36 38} which is in line with other research.^{47 48} Our review showed that SMS reminders are effective in increasing adherence. There are, however, differences in the SMS reminders sent. One study used personalized text messages that requested a reply,²⁸ the other two studies yielding significant effects sent standardized text messages without requiring acknowledgment.^{29 31} Earlier research showed that a tailored message is usually more effective than a standard text.⁴⁹ This cannot be confirmed by our findings. However, more studies are needed to investigate the influence of the content of reminder messages on adherence behavior.

Reminders can especially be used to modify the behavior of unintentionally non-adherent patients, ie, patients who are willing to take their medication but forget it or are inaccurate.⁸ Nonetheless, none of the included studies focused specifically on this patient group, implying that the intervention was possibly not suited for some of the patients; those who deliberately miss or alter their doses and make a rational decision to do so by weighing pros and cons of the medication. Interventions using reminders may be more effective when they are solely focused on patients who are unintentionally non-adherent. On the other hand, using text messages, for example, to stimulate patients who doubt the effectiveness of medication by stressing the importance of the intake in the message may provide a solution for intentionally non-adherent patients.⁵⁰ Reminders can be beneficial for improving adherence in patients of all ages. Elderly patients may be at risk of forgetting to take their medication because of memory problems. Adolescents, on the other hand, may be at risk for forgetting their dose because of their busy (social) lives. Zelikovsky et al¹⁸ reported that being out with friends and participating in activities were reasons for forgetting among adolescent renal transplant candidates.

Furthermore, as adolescents extensively use mobile phones, SMS reminders might be particularly useful for reminding them. Miloh et al,⁵¹ for example, showed improved adherence rates as a result of text

messaging in pediatric liver transplant recipients. None of the studies included in our review, though, specifically targeted the pediatric population. Future studies involving the pediatric population are recommended.

Electronic monitoring is currently seen as the most reliable and objective method in measuring adherence, while self-report is considered less reliable as this measure tends to overestimate adherence.^{52 53} Most studies included in the review used electronic monitoring for adherence measurement, sometimes combined with self-report. In two studies, in which adherence was measured with both electronic monitoring and self-report, effects were only found when adherence was measured with electronic monitoring, while no effects were found for self-report.

A possible explanation may be that with self-report patients report a high adherence rate from the beginning, leaving no or insufficient room for improvement. These findings emphasize the importance of incorporating objective methods for adherence measurement into studies whenever possible.⁶

Limitations.

Limitations of the included studies.

The methodological quality of the studies varied. In studies identified as low quality, mostly the risk of selection and attrition bias is present. By using a BES, this methodological quality was taken into account in attributing levels of evidence to effects found in studies.

The electronic database searches provided five studies in which a more complex intervention was used, with an electronic reminder as one of the aspects of the intervention.⁵⁴⁻⁵⁸ Those studies only reported the total effect of the complex intervention on patients' medication adherence, no direct relation between the reminder and adherence was reported. Therefore, those studies could not contribute to this review, thus we decided to exclude those studies.

The primary aim of electronic reminders is to improve patients' medication adherence. Therefore, we focused not on clinical outcomes, but on adherence as (one of the) main outcome measures. In adherence research, a patient is often classified as adherent when an adherence rate of over 80% is reached.⁵⁹ This cut-off point indicates the minimum level of adherence needed for therapeutic effect. In the HIV population, the cut-off point is 90%. Although often used, these cut-off points are arbitrary. Only two studies in our review used a cutoff point for adherence. Pop-Eleches et al²⁹ used a binary indicator of whether HIV patients achieved more than 90% adherence as a primary outcome. Charles et al³⁴ used cut-off points of over 50%, over 80% and over 90% adherence for asthma patients. Both studies, however, did not link their findings to clinical outcomes nor reported on the clinical significance of the effects found. Trials aiming to evaluate the effects on patients' medication adherence usually have insufficient power to detect significant differences in clinical outcome measures. Of the nine studies that showed an effect on adherence, three studies also reported clinical outcomes,^{31 36 37} of which one found a significant improvement in the intervention group.³⁶ Although adherence appears to be an intermediate outcome, there is evidence of the association between increased adherence rates and positive health outcomes.^{4 60}

Limitations of the review.

A methodological limitation of our review may be that we used a 'top-down' approach in our search strategy, which means that we relied on existing databases and their search terms for identifying relevant studies. This may lead to missing relevant studies due to miscoding of search terms. A 'bottom-up' strategy, relying on searching existing databases in the broadest way possible, is significantly more time and labor-intensive but has the advantage of being comprehensible. To reduce this potential problem, we used the snowball method to identify studies that we possibly missed with our top-down strategy in addition to the electronic database searches.

CLINICAL IMPLICATIONS.

After providing patients with the electronic reminders, no additional effort is needed from healthcare providers, making this an intervention easy to implement in daily practice.

Furthermore, electronic reminders and especially SMS reminders appear to be easily integrated into patients' lives. As such, this seems to be a simple intervention for both patient and professional for enhancing medication adherence. However, the healthcare system needs to be ready to include the use of electronic reminders in usual care for patients using chronic medication.

IMPLICATIONS FOR FURTHER RESEARCH.

Future studies should aim specifically at patients who are unintentionally non-adherent in examining the effects of electronic reminders on adherence. In addition, further research is needed to identify for which patient groups electronic reminding is most beneficial, for example, studies involving the pediatric population and studies involving patients with other types of chronic illnesses. Moreover, the included studies mostly found short-term improvements. Future studies should investigate the long-term effects of electronic reminders and search for additional features of electronic reminding to improve adherence in the long-term. One example may be not to send patients reminders daily at predetermined times, but to intervene only when necessary, by sending patients reminders only when they forget to take their medication.⁴⁶ Another example may be to tailor the content of the reminder message to the needs of the patients based on their illness and treatment beliefs.⁵⁰

CONCLUSIONS.

This review shows that electronic reminders lead to short-term improvements of patients' adherence to chronic medication, while the long-term effects remain unclear. The increasing opportunities of new technologies make it possible to tailor reminding both in timing (only when needed) and in content (tailored messages). In this way, long-term improvements in medication adherence may be achieved.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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BOX AND TABLES

Table 1 Main characteristics of included studies (ranked according to type of reminder and year of publication)

Author, study design	Study population	Type of reminder	Description of intervention	Type of adherence measure	Timing of adherence measurement	Main findings
Hardy <i>et al.</i> , ²⁸ RCT parallel	Adult patients with HIV (n=19)	SMS (vs beeper)	Daily personalized (by adding info on topic chosen by patient, eg. news, weather, sports) text messages sent for each dose scheduled by care giver. Response with text message required. If no response given, the phone would beep every 15 min.	Self-report, pill count, electronic monitoring, CAS	Baseline, week 3 and week 6	Significant difference in adherence at weeks 3 and 6 were found in favor of the SMS, when measured with electronic monitoring and CAS. No differences were found with self-report nor pill count.
Pop-Eleches <i>et al.</i> , ²⁹ RCT parallel	Adult patients with HIV (n=428)	SMS	Four interventions: (1) daily short reminder; (2) daily long reminder; (3) weekly short reminder; (4) weekly long reminder. Short message: 'This is your reminder', long message providing additional support: 'This is your reminder. Be strong and courageous, we care about you'. Message was sent at 12:00. No response required.	Electronic monitoring	Every 12-week period in 48 weeks	Weekly reminders significantly increased percentage of participants achieving 90% adherence by 13–16%. No differences were found between long and short reminders. Daily reminders did not improve adherence.
Hou <i>et al.</i> , ³⁰ RCT parallel	Women on oral contraceptives (n=73)	SMS	Daily text message 'Please remember to take your birth control pill' sent at a designated time chosen by patient. No response required.	Self-report and electronic monitoring	Every month for 3 months	No difference in mean number of missed pills per cycle with either self-report or electronic monitoring between women who received SMS reminders and women who did not.
Strandbygaard <i>et al.</i> , ³¹ RCT parallel	Adult patients with asthma (n=26)	SMS	Daily text message 'Remember to take your asthma medication morning and evening. From the Respiratory Unit' sent at 10:00. No response required.	Electronic monitoring	Week 4 and week 12	Patients who received a daily SMS reminder remembered to take, on average, significantly more doses (about 18%).
Christensen <i>et al.</i> , ³² RCT crossover	Adult patients with hypertension (n=398)	Electronic reminder device with audiovisual reminder	Use of HHDC device operated with tablet blister packs, which gives an audiovisual reminder when it is time to take the medication.	Self-report and electronic monitoring	At month 6 and month 12 (after crossover)	Use of the HHDC device with audiovisual reminders did not lead to significant improvement in adherence.
Ho <i>et al.</i> , ³³ RCT parallel	Adult patients with glaucoma (n=42)	Electronic reminder device with audiovisual reminder	Use of TDA, which has a LCD screen that displays a flashing eye drop symbol on the front as and emits a beep when patients are supposed to give themselves a dose of medication.	Electronic monitoring	At 3–5 weeks	Significant differences in mean adherence and rate of missed doses between patients using TDA with audiovisual reminders and patients using TDA without reminders.
Charles <i>et al.</i> , ³⁴ RCT parallel	Adult and adolescent patients with asthma (n=80)	Electronic reminder device with audiovisual reminder	Use of SmartInhaler, which emitted a beep at predetermined times (selected by patient) once every 30 s for 60 min and stopped if device was actuated or after 60 min. Device had a light which was green before actuation, changing to red once the dose was taken.	Electronic monitoring	Baseline and week 6, 12, 18 and 24	Use of SmartInhaler with audiovisual reminders significantly improved adherence from 74% to 93%. Approx. 1 in 4 patients using the device with reminders had <50% adherence, compared with 1 in 20 patients using the device without reminders.
Santschi <i>et al.</i> , ³⁵ RCT crossover	Adult patients with hypertension (n=24)	Electronic reminder device with audiovisual reminder (versus MEMS caps)	Use of IDAS II that accommodates blister packs. Visual reminder (indicating time elapsed since last dose) and audible reminder, which sounds at chosen time for 1 min or until device is opened, and can be deactivated upon request.	Electronic monitoring	Baseline and months 2 and 4 (after crossover)	Median taking adherence was high and did not differ between patients using IDAS II and patients using MEMS caps. Regularity of drug intake timing was significantly higher with IDAS II compared with MEMS.
Andrade <i>et al.</i> , ³⁶ RCT parallel	Adult patients with HIV (n=58)	Electronic reminder device with audible reminder	Use of DMAS device programmed with reminder messages and dosing times for each medication in the HAART regimen.	Self-report and electronic monitoring	Weeks 4, 8, 12, 16, 20 and 24	No differences in adherence between patients who used DMAS and patients who did not. Stratified to memory impairment: adherence was significantly higher in memory-impaired patients using DMAS than memory-intact patients using DMAS.
Da Costa <i>et al.</i> , ³⁷ RCT parallel	Adult patients with hypertension (n=71)	Electronic reminder device with audible reminder	Use of alarm card set up to beep every day at fixed time, preselected by pharmacist and/or patient. If alarm was ignored, it would beep every 20 s for 3 h, then stop and re-initiate 8 h later, beeping every 20 s for 1 h.	Pill count	Baseline and months 1, 2 and 3	Adherence of patients using the reminder alarm card was higher at all time points than that of patients not using this card, reaching statistical significance at the third month (mean adherence difference 10%).
Laster <i>et al.</i> , ³⁸ RCT crossover	Adult patients with glaucoma (n=13)	Electronic reminder device with audiovisual reminder	Use of TimeCap, a medication alarm device serving as cap on medication bottle. It has a digital display that shows time and day of week when the phial was last opened and an alarm that beeps when a dose is due. If the beep is ignored, the digital face flashes to provide a visual reminder that a dose has been missed.	Self-report and amount of solution used estimated by weighing of bottle	At days 30 and 60	Patient using TimeCap with audiovisual reminders administered significantly more eye drops (about one additional dose of pilocarpine per day) than patients who did not use TimeCap.

Continued

Table 1 Continued

Author, study design	Study population	Type of reminder	Description of intervention	Type of adherence measure	Timing of adherence measurement	Main findings
Simoni <i>et al.</i> ³⁹ RCT parallel	Adult patients with HIV (n=224)	Two-way pager system	Three interventions: (1) peer support: six peer meetings and weekly phone calls from peers to participants. (2) use of two-way pager system: study coordinator customized message schedule to patients' daily regimen. In addition to dose reminders, three other messages were sent: educational; entertainment; adherence assessments. Minimum of three pager messages sent daily for 2 months. Pages gradually tapered in third month. Confirmation page was requested. (3) peer support and pager combined.	Self-report and electronic monitoring	At months 3, 6 and 9	Pager support did not have a significant effect on adherence at 3, 6, or 9 months either measured with self-report or electronic monitoring.
Safren <i>et al.</i> ⁴⁰ RCT parallel	Adult patients with HIV (n=70)	One-way pager system	Study staff used website to input patients' schedule of daily pages, which is linked to paging service delivering messages (eg, 'Take 2 Combivir with water' every day at 09:00, 'Take the 2 blue pills now') to patients' pagers at designated times. Study staff could incorporate other reminders (eg, timing of meals, appointments). No response required.	Electronic monitoring	Baseline and weeks 2 and 12	Patients using the pager system revealed greater improvements in adherence at weeks 2 and 12 than patients who are only monitored. But at both assessment points, adherence was less than optimal (<70%).

CAS, composite adherence score; DMAS, disease management assistance system; HAART, highly active antiretroviral therapy; HHDC, helping hand data capture; IDAS II, intelligent drug administration system; RCT, randomized controlled trial; SMS, short message service; TDA, travatan dosing aid.

Box 1 Principles of BES

Evidence
 Provided by consistent significant findings in outcome measures in at least two high quality RCT.

Moderate evidence
 Provided by consistent significant findings in outcome measures in at least one high quality RCT and at least one low quality RCT or high quality CCT.

Limited evidence
 Provided by significant findings in outcome measures in at least one high quality RCT or provided by consistent significant findings in outcome measures in at least two high quality CCT (in the absence of high quality RCT).

Indicative findings
 Provided by significant findings in outcome measures in at least one high quality CCT or low quality RCT (in the absence of high quality RCT).

No/insufficient evidence
 If the number of studies that show evidence is less than 50% of the total number of studies found within the same category of methodological quality and study design or if the results of eligible studies do not meet the criteria for one of the above stated levels of evidence or in case of conflicting (significantly positive and significantly negative) results among RCT and CCT or in the case of no eligible studies.

FIGURE 1 FLOWCHART OF STUDY INCLUSION.

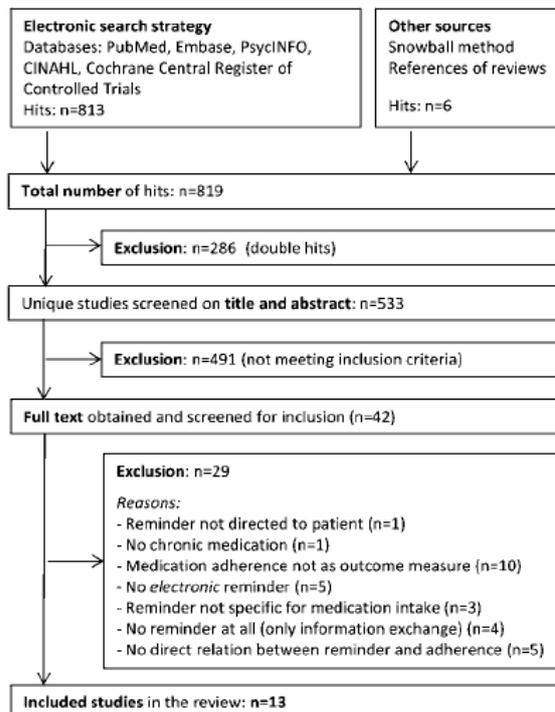


Table 2 Methodological quality of included RCT

Study	Validity criteria met*	Methodological quality†
Hardy <i>et al</i> ²⁸	a, b, c, g, h, i, j	High
Pop-Eleches <i>et al</i> ²⁹	a, c, g, h, i, j, k	High
Hou <i>et al</i> ³⁰	a, b, c, f, g, h, i, j, k	High
Strandbygaard <i>et al</i> ³¹	a, c, g, h, i, j	High
Simoni <i>et al</i> ³⁹	a, b, c, g, h, i, j, k	High
Charles <i>et al</i> ³⁴	a, b, c, g, h, i, j	High
Andrade <i>et al</i> ³⁶	c, g, h, i, j, k	High
Christensen <i>et al</i> ³²	c, g, h, j	Low
Ho <i>et al</i> ³³	g, h, j	Low
Santschi <i>et al</i> ³⁵	a, g, h, i	Low
Da Costa <i>et al</i> ³⁷	c, g, h, j	Low
Safren <i>et al</i> ⁴⁰	c, g, h, j, k	Low
Laster <i>et al</i> ³⁸	g, h, i, j	Low

*Selection bias: criteria a, b, c; performance bias: criteria d, e, g and h; attrition bias: criteria i and k; detection bias: criteria f and j.

†High quality: six or more criteria met; low quality: five or fewer criteria met.
RCT, randomised controlled trial.

Table 3 Characteristics and effectiveness of interventions with a short-term follow-up period (<6 months)

Study	Medication for	Type of reminder	Study quality	Short-term effect* on adherence measured with:		
				Electronic monitoring	Self-report	Pill count
Hou <i>et al</i> ³⁰	Contraception	SMS	High	-	-	-
Hardy <i>et al</i> ²⁸	HIV	SMS	High	++	-	-
Strandbygaard <i>et al</i> ³¹	Asthma	SMS	High	++	-	-
Charles <i>et al</i> ³⁴	Asthma	ERD	High	++	-	-
Andrade <i>et al</i> ³⁶	HIV	ERD	High	+	-	-
Ho <i>et al</i> ³³	Glaucoma	ERD	Low	++	-	-
Santschi <i>et al</i> ³⁵	Hypertension	ERD	Low	-	-	++
Da Costa <i>et al</i> ³⁷	Hypertension	ERD	Low	-	-	+++
Laster <i>et al</i> ³⁸	Glaucoma	ERD	Low	-	++	+++
Safren <i>et al</i> ⁴⁰	HIV	pager	Low	++	-	-

* +++ = Overall effect; + = subgroup effect; - = no effect.

† Amount of eye drops left estimated by bottle weight.

ERD, electronic reminder device; SMS, short message service.

Table 4 Characteristics and effectiveness of interventions with a long-term follow-up period (≥6 months)

Study	Medication for	Type of reminder	Study quality	Long-term effect* on adherence measured with:	
				Electronic monitoring	Self-report
Pop-Eleches <i>et al</i> ²⁹	HIV	SMS	High	++	-
Simoni <i>et al</i> ³³	HIV	Pager	High	-	-
Christensen <i>et al</i> ³²	Hypertension	ERD	Low	-	-

* +++ = Overall effect; + = subgroup effect; - = no effect.

ERD, electronic reminder device; SMS, short message service.