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### The value of tailored communication in promoting medication intake behavior

Linn, A.J.

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## Chapter 3

# The effectiveness of interventions using electronic reminders to improve medication intake behavior<sup>2</sup> to chronic medication: a systematic review of the literature.

*Patient: "I cannot remember those things, and then, my mother asks what you told me, and I just don't remember...". Nurse: "Well, there is something like a SMS-alert that you can use so that you cannot forget" (male, 25 years old, Crohn's disease).*

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<sup>2</sup> For the purpose of this dissertation, the term adherence is changed into medication intake behavior

## Abstract

**Background:** Many patients experience difficulties in adhering to long-term treatment. Although patients' reasons for not being adherent are diverse, one of the most commonly reported barriers is forgetfulness. Reminding patients to take their medication may provide a solution. Electronic reminders (automatically sent reminders without personal contact between the healthcare provider and patient) are now increasingly being used in the effort to improve medication intake behavior.

**Objective:** To examine the effectiveness of interventions using electronic reminders in improving patients' medication intake behavior to chronic medication.

**Methods:** A comprehensive literature search was conducted in PubMed, Embase, PsycINFO, CINAHL and Cochrane Central Register of Controlled Trials. Electronic searches were supplemented by manual searching of reference lists and reviews. Two reviewers independently screened all citations. Full text was obtained from selected citations and screened for final inclusion. The methodological quality of studies was assessed.

**Results:** Thirteen studies met the inclusion criteria. Four studies evaluated short message service (SMS) reminders, seven audio-visual reminders from electronic reminder devices (ERD), and two pager messages. Best evidence synthesis revealed evidence for the effectiveness of electronic reminders, provided by eight (four high, four low quality) studies showing significant effects on patients' medication intake behavior, seven of which measured short-term effects (follow-up period <6 months). Improved medication intake behavior was found in all but one study using SMS reminders, four studies using ERD and one pager intervention. In addition, one high quality study using an ERD found subgroup effects.

**Conclusion:** This review provides evidence for the short-term effectiveness of electronic reminders, especially SMS reminders. However, long-term effects remain unclear.

## Introduction

Medication intake behavior is the extent to which a person's behavior taking medication and/or executing lifestyle changes corresponds with agreed recommendations from a healthcare provider (Sabaté, 2003). Many patients, especially those with chronic illnesses, experience difficulties in adhering to prescribed treatment. Average medication intake behavior rates to long-term treatment are low (DiMatteo, 2004; Sabaté, 2003). Poor medication intake behavior 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 (Roebuck, Liberman, Gemmill-Toyama, & Brennan, 2011; Simpson et al., 2006; Sokol, McGuigan, Verbrugge, & Epstein, 2005). Numerous interventions aimed at improving medication intake behavior have been conducted, but these were mostly complex and not very effective (Haynes et al., 2008). Complex interventions are often time consuming, labour intensive and costly, thus not feasible in busy clinical practice. According to experts in the field of medication intake behavior, simple interventions, i.e. interventions that are workable in daily practice and that are easy for both professional and patient, appear to be most promising in furthering patients' medication intake behavior (Van Dulmen et al., 2008). 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, i.e. patients who are willing to take their medication but forget it or are inaccurate with their timing (Wroe, 2002). Forgetfulness is commonly reported as a barrier to successful medication intake behavior in various patient populations (Bartlett, 2002; Bregnballe, Schiøtz, Boisen, Pressler, & Thastum, 2011; Lawson et al., 2011; Nair et al., 2011; Odegard & Gray, 2008; Olthoff, Hoevenaars, van den Borne, Webers, & Schouten, 2009; Roberts, 2000; Walker et al., 2006; Wu, Moser, Lennie, & Burkhart, 2008; Zelikovsky, Schast, Palmer, & Meyers, 2008). 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 (e.g., 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 medication intake behavior to long-term medications (Mahtani, Heneghan, Glasziou, & Perera, 2011; Zedler, Kakad, Colilla, Murrelle, & Shah, 2011). 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 medication intake behavior rates (Contreras et al., 2005; Waalen, Bruning, Peters, & Blau, 2009). 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 (Leventhal & Cameron, 1987). 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 intake behavior, there is a need to gain insight into the effects of this type of reminding. Previous reviews evaluating strategies for improving medication intake behavior among electronic reminders often focused on specific patient populations. For example, Gray and colleagues (2009) found that a reminder device might be beneficial to patients with glaucoma. Wise and Operario (2008) showed that half of the studies included in their review reported significantly improved medication intake behavior in HIV patients as a result of ERD. Misono and colleagues (2010) reviewed studies using healthcare information technology interventions to improve medication intake behavior to cardiovascular and diabetes medication, and showed that of these interventions, reminder systems provided the best evidence for increasing medication intake behavior. To our knowledge, no review has been conducted that systematically studied the effects of specifically electronic reminding (e.g., via SMS, ERD, pager/beeper systems) on patients' medication intake behavior 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' medication intake behavior 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; Higgins et al., 2008).

### **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 intake behavior; (3) the reminder was directed to the patient; (4) one of the outcome measures was medication intake behavior; (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 3. Disagreements between reviewers were resolved by discussion.

## **Data extraction**

MV extracted the following study characteristics (see table 1 and supplementary Appendix 4):

1. General information (first author, year of publication)
2. Study design
3. Study population (sample size, age, gender, medication/disease)
4. Intervention (description of experiment and control condition, type of reminder)
5. Medication intake behavior measure (type of measurement, follow-up period)
6. Main study results
7. 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 (Van Tulder et al., 2003). 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.

## **Data syntheses 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 al (2003) and adapted by Steultjens and colleagues (2009). 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.

Textbox 1: Principles of Best Evidence Synthesis

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

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 CCTs (in the absence of high quality RCTs).

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 RCTs).

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 RCTs and CCTs **or** in case of no eligible studies.

### **Categorization of intervention 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 medication intake behavior. 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 3. Finally, a total of 13 studies met all inclusion criteria (see Figure 1).

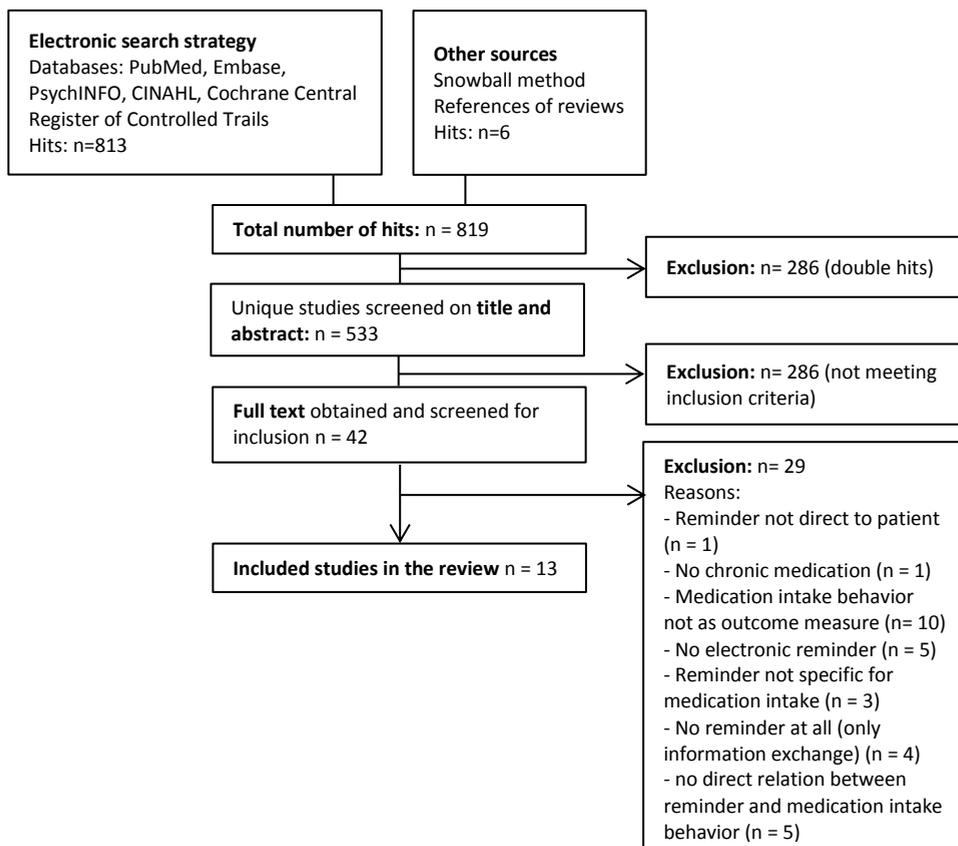


Figure 1. Flowchart of study inclusion.

### Description of the studies

Table 1 shows the main characteristics of the 13 included studies (for a more detailed description, see supplementary Appendix 4). The study population varied: patients on antiretroviral therapy (five studies; Andrade et al., 2005; Hardy et al., 2011; Pop-Eleches et al., 2011; Safren, Hendriksen, Desousa, Boswell, & Mayer, 2003; Simoni et al., 2009) patients with hypertension (three studies; Christensen et al., 2010; Costa et al., 2005; Santschi, Wuerzner, Schneider, Bugnon, & Burnier, 2007) patients with asthma (two studies; Charles et al., 2007; Strandbygaard, Thomsen, & Backer, 2010), patients with glaucoma (two studies; Ho, Camejo, Kahook, & Noecker, 2008; Laster, Martin, & Fleming, 1996), and women using oral contraceptives (one study; Hou, Hurwitz, Kavanagh, Fortin, & Goldberg, 2010). All studies involved adult patients, except for one study that also included adolescents aged 13 years or older (Charles et al., 2007). The duration of medication use varied across the studies and also within the studies. Seven studies included patients initiating or changing treatment (Andrade et al., 2005; Charles et al., 2007; Christensen et al., 2010; Ho et al., 2008; Hou et al., 2010; Pop-Eleches et al., 2011;

Simoni et al., 2009), four studies included patients currently using medication (Costa et al., 2005; Hardy et al., 2011; Laster et al., 1996; Safren, Hendriksen, Desousa, Boswell, & Mayer, 2003), and two studies included both new and current users (Santschi, Wuerzner, Schneider, Bugnon, & Burnier, 2007; Strandbygaard et al., 2010). Four interventions tested the effect of SMS reminders on patients' medication intake behavior (Hardy et al., 2011; Hou et al., 2010; Pop-Eleches et al., 2011; Strandbygaard et al., 2010) seven studies evaluated an ERD with audiovisual medication reminders (Andrade et al., 2005; Charles et al., 2007; Christensen et al., 2010; Costa et al., 2005; Ho et al., 2008; Laster et al., 1996; Santschi et al., 2007) and two studies concentrated on the effect of a pager reminder (Safren et al., 2003; Simoni et al., 2009). Almost half of the studies used multiple measures to assess medication intake behavior. Electronic monitoring (electronically registering the date and time of every medication intake) was used in 11 studies. Six studies exclusively used electronic monitoring (Charles et al., 2007; Ho et al., 2008; Pop-Eleches et al., 2011; Safren et al., 2003; Santschi et al., 2007; Strandbygaard et al., 2010), four combined electronic monitoring with self-report (Andrade et al., 2005; Christensen et al., 2010; Hou et al., 2010; Simoni et al., 2009) and one combined electronic monitoring with both pill count and self-report (Hardy et al., 2011). One study exclusively used pill count (Costa et al., 2005), one study assessed bottle weight (medication in soluble form) with self-report (Laster et al., 1996). Only three studies followed patients for a period of 6 months or longer (Christensen et al., 2010; Pop-Eleches et al., 2011; Simoni et al., 2009).

### **Methodological quality**

The methodological quality (risk of bias) of the thirteen included RCTs was assessed. Seven studies were classified as high quality studies, six studies were considered low quality (Table 2).

### **Effectiveness of interventions**

Tables 3 and 4 summarize the effects on medication intake behavior, methodological quality of the studies, and characteristics of the intervention (studied medication, type of electronic reminder, and type of medication intake behavior measurement), by length of follow-up period. Eight (four high and four low quality) studies reported significant overall effects on patients' medication intake behavior as a result of an electronic reminder. Hardy and colleagues (2011) compared the medication intake behavior 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 and colleagues (2010) revealed that medication intake behavior 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 medication intake behavior (Charles et al., 2007).

Table 2.

*Methodological quality of included RCTs*

<b>Study</b>	<b>Validity criteria met<sup>a</sup></b>	<b>Methodological quality<sup>b</sup></b>
Hardy 2011	a, b, c, g, h, i, j	High
Pop-Eleches 2011	a, c, g, h, i, j, k	High
Hou 2010	a, b, c, f, g, h, i, j, k	High
Strandbygaard 2010	a, c, g, h, i, j	High
Simoni 2009	a, b, c, g, h, i, j, k	High
Charles 2007	a, b, c, g, h, i, j	High
Andrade 2005	c, g, h, i, j, k	High
Christensen 2010	c, g, h, j	Low
Ho 2008	g, h, j	Low
Santschi 2007	a, g, h, i	Low
Da Costa 2005	c, g, h, j	Low
Safren 2003	c, g, h, j, k	Low
Laster 1996	g, h, i, j	Low

<sup>a</sup> 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.

<sup>b</sup> high quality: 6 or more criteria met; low quality: 5 or less criteria met

Two other studies also used an ERD with audiovisual reminders, both in patients with glaucoma, and found higher medication intake behavior rates in patients receiving these reminders (Ho et al., 2008; Laster et al., 1996). Da Costa and colleagues (2005) reported significant differences in medication intake behavior between patients with hypertension who used a reminder alarm card that produced a beep at predetermined times, and patients who did not. Safren and colleagues (2003) revealed improvements in medication intake behavior 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 medication intake behavior rates than patients reminded daily or patients not reminded at all (Pop-Eleches et al., 2011). One (high quality) study revealed significant effects in a subgroup of the intervention group; Andrade and colleagues (2005) found that an ERD with audiovisual reminders significantly improved medication intake behavior 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 medication intake behavior at any time point (Christensen et al., 2010; Hou et al., 2010; Santschi et al., 2007; Simoni et al., 2009).

Table 1.

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

<b>Author, year of publication, study design</b>	<b>Study population</b>	<b>Type of reminder</b>	<b>Description of intervention</b>	<b>Type of medication intake behavior measure</b>	<b>Timing of medication intake behavior measurement</b>	<b>Main findings</b>
Hardy 2011 RCT parallel	Adult patients with HIV (n=19)	SMS (versus beeper)	Daily personalized (by adding info on topic chosen by patient, e.g. news, weather, sports) text messages sent for each dose scheduled by caregiver. 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 medication intake behavior at week 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 2011 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% medication intake behavior by 13–16%. No differences were found between long and short reminders. Daily reminders did not improve medication intake behavior.
Hou 2010 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.

Author, year of publication, study design	Study population	Type of reminder	Description of intervention	Type of medication intake behavior measure	Timing of medication intake behavior measurement	Main findings
Strandbygaard 2010 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 2010 RCT cross-over	Adult patients with hypertension (n=398)	ERD 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 cross-over).	Use of the HHDC device with reminders did not lead to significant improvement in medication intake behavior.
Ho 2008 RCT parallel	Adult patients with glaucoma (n=42)	ERD with audiovisual reminder	Use of TDA which has a LCD screen that displays a flashing eye drop symbol on the front 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 reminders and patients using TDA without reminders.

Author, year of publication, study design	Study population	Type of reminder	Description of intervention	Type of medication intake behavior measure	Timing of medication intake behavior measurement	Main findings
Charles 2007 RCT parallel	Adult and adolescent patients with asthma (n=90)	ERD with audiovisual reminder	Use of SmartInhaler which emitted a beep at predetermined times (selected by patient) once every 30 sec 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 reminders significantly improved medication intake behavior from 74% to 93%. Around 1 in 4 patients using the device with reminders had <50% medication intake behavior, compared with 1 in 20 patients using it without reminders.
Santschi 2007 RCT cross-over	Adult patients with hypertension (n=24)	ERD 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 month 2 and 4 (after cross-over).	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 to MEMS.
Andrade 2005 RCT parallel	Adult patients with HIV (n=58)	ERD 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	Week 4, 8, 12, 16, 20 and 24.	No differences in medication intake behavior between patients who used DMAS and patients who did not. Stratified to memory impairment: significantly higher medication intake behavior in memory-impaired patients using DMAS than memory-intact patients using DMAS.

Author, year of publication, study design	Study population	Type of reminder	Description of intervention	Type of medication intake behavior measure	Timing of medication intake behavior measurement	Main findings
Da Costa 2005 RCT parallel	Adult patients with hypertension (n=71)	ERD 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 20s for 3h, then stop and re-initiate 8h later, beeping every 20s for 1h.	Pill count	Baseline and month 1, 2 and 3.	Medication intake behavior of patients using the reminder alarm card was higher at all timepoints than that of patients not using this card, reaching statistical significance at the third month (mean medication intake behavior difference 10%).
Laster 1996 RCT cross-over	Adult patients with glaucoma (n=13)	ERD 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 vial 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 day 30 and 60.	Patients using TimeCap with reminders administered significantly more eye drops (about one additional dose of pilocarpine per day) than patients who did not use TimeCap.

Author, year of publication, study design	Study population	Type of reminder	Description of intervention	Type of medication intake behavior measure	Timing of medication intake behavior measurement	Main findings
Simoni 2009 RCT parallel	Adult patients with HIV (n=224)	Two-way pager system	Three interventions: 1) peer support: 6 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, 3 other messages were sent: a) educational; b) entertainment; c) medication intake behavior assessments. Minimum of 3 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 month 3, 6 and 9.	Pager support did not have a significant effect on medication intake behavior at 3, 6, or 9 months either measured with self-report or EM.
Safren 2003 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 (e.g. "Take 2 Combivir with water" every day at 9:00, "Take the 2 blue pills now") to patients' pagers at designated times. Study staff could incorporate other reminders (e.g. timing of meals, appointments). No response required.	Electronic monitoring	Baseline and week 2 and 12.	Patients using the pager system revealed greater improvements in medication intake behavior at week 2 and 12 than patients who are only monitored. But at both assessment points, medication intake behavior was less than optimal (<70%).

*CAS, composite medication intake behavior score; DMAS, disease management assistance system; ERD, electronic reminder device; HAART, highly active antiretroviral therapy; HHDC, helping hand data capture; IDAS II, intelligent drug administration system; RCT, randomized controlled trial; SMS, shortmessage service; TDA, travatan dosing aid.*

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 <sup>a</sup> on medication intake behavior measured with:		
				EM <sup>b</sup>	self-report	pill count
Hou	contraception	SMS	high	–	–	
Hardy	HIV	SMS	high	++	–	–
Strandbygaard	asthma	SMS	high	++		
Charles	asthma	ERD	high	++		
Andrade	HIV	ERD	high	+	–	
Ho	glaucoma	ERD	low	++		
Santschi	hypertension	ERD	low	–		
Da Costa	hypertension	ERD	low			++
Laster	glaucoma	ERD	low		++	++ <sup>c</sup>
Safren	HIV	pager	low	++		

<sup>a</sup> ++ = overall effect; + = subgroup effect; – = no effect.<sup>b</sup> EM = electronic monitoring<sup>c</sup> amount of eye drops left estimated by bottle weight

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 <sup>a</sup> on medication intake behavior measured with:	
				EM <sup>b</sup>	self-report
Pop-Eleches	HIV	SMS	high	++	
Simoni	HIV	pager	high	–	–
Christensen	hypertension	ERD	low	–	–

<sup>a</sup> ++ = overall effect; + = subgroup effect; – = no effect.<sup>b</sup> EM = electronic monitoring

### Relation between type of reminder and effects

Four studies used SMS reminders, three of which showed significant positive effects on medication intake behavior. Those studies used either personalized text messages that requested a reply from patients when taking the medication (Hardy et al., 2011), or standardized text messages without requiring acknowledgment (Pop-Eleches et al., 2011; Strandbygaard et al., 2010). The study revealing no effect used standardized messages without requesting a reply (Hou et al., 2010). Four of the seven studies evaluating audio/visual reminders from ERD significantly improved patients' medication intake behavior. Three of them used an ERD that produced both an audible and visual reminder (Charles et al., 2007; Ho et al., 2008; Laster et al., 1996), the fourth used an ERD that only emitted an audible reminder (Costa et al., 2005). The one study that found a subgroup effect evaluated an ERD with an audible reminder (Andrade et al., 2005). Two studies showed no effects, both of them used an ERD that accommodated blister packs (Christensen et al., 2010; Laster et al., 1996). Two interventions used pagers, one of which revealed a significant effect (Safren et al., 2003). This study delivered standardized text messages to patients' pagers at predetermined times and requested no reply (Safren et al.,

2003). The pager intervention revealing no effects delivered a minimum of three pager messages daily and a confirmation return page was requested for every message (Simoni et al., 2009).

### **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 (Andrade et al., 2005; Charles et al., 2007; Costa et al., 2005; Hardy et al., 2011; Ho et al., 2008; Laster et al., 1996; Safren et al., 2003; Strandbygaard et al., 2010) or a subgroup effect (Andrade et al., 2005). 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 (Pop-Eleches et al., 2011). The two studies reporting no effects followed patients for 9 (Simoni et al., 2009) and 12 months (Christensen et al., 2010).

### **Relation between type of medication intake behavior measurement and effects**

Eleven studies used electronic monitoring as a method to measure medication intake behavior. Six of them reported significant overall effects, (Charles et al., 2007; Hardy et al., 2011; Ho et al., 2008; Pop-Eleches et al., 2011; Safren et al., 2003; Strandbygaard et al., 2010) one found a subgroup effect (Andrade et al., 2005). In addition to electronic monitoring, five studies used self-report to measure medication intake behavior. Two of those studies showed inconclusive results between the two methods: significant effects were only found when medication intake behavior was measured with electronic monitoring, not with self-report (Andrade et al., 2005; Hardy et al., 2011). One study also used pill count as a third method for measuring medication intake behavior, but again effects were only found with electronic monitoring (Hardy et al., 2011). One study exclusively using pill count (Costa et al., 2005) as well as a study using 'pill count' (or weight of medication solution) combined with self-report (Laster et al., 1996) showed significant effects on medication intake behavior.

### **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 (Hardy et al., 2011; Ho et al., 2008; Laster et al., 1996; Strandbygaard et al., 2010) and one a subgroup effect (Andrade et al., 2005) on medication intake behavior. In addition, four studies included between 30 and 50 patients in each arm, three of which showed significant effects (Charles et al., 2007; Costa et al., 2005; Safren et al., 2003). Of the three studies that included more than 50 patients in each arm, one study reported significant effects (Pop-Eleches et al., 2011).

### **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' medication intake behavior 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 medication intake behavior (Hardy et al., 2011; Strandbygaard et al., 2010). Moderate evidence was found for audiovisual reminders from ERD as a strategy to improve medication intake behavior, as one high quality and three low quality studies found significant effects (Charles et al., 2007; Costa et al., 2005; Ho et al., 2008; Laster et al., 1996). There is insufficient evidence for the effect of pager reminders in particular, as the low quality study reported significant effects (Safren et al., 2003). As sensitivity analysis, BES was first repeated using seven high quality RCT (thus disregarding six low quality RCT). Evidence 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 medication intake behavior in patients using chronic medication. Significant improvements in medication intake behavior 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' medication intake behavior. 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' medication intake behavior 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 (Vrijens, Vincze, Kristanto, Urquhart, & Burnier, 2008).

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 and colleagues (2011) found that SMS reminders sent once a week significantly improved the medication intake behavior 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 medication intake behavior. Moreover, real time medication intake behavior monitoring is now upcoming (Haberer et al., 2010; Haberer et al., 2012), offering the possibility to intervene only when patients miss a dose, thus avoiding the reminders becoming routine. The effectiveness of this non-automated type of electronic reminding on medication intake behavior is currently being investigated (Vervloet et al., 2011).

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 medication intake behavior 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 (Hou et al., 2010; Strandbygaard et al., 2010). 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 (Strandbygaard et al., 2010). In addition, three included studies evaluating ERD reported that these devices were well accepted by patients (Andrade et al., 2005; Laster et al., 1996; Santschi et al., 2007), which is in line with other research (Christensen et al., 2009; Sahm, MacCurtain, Hayden, Roche, & Richards, 2009).

Our review showed that SMS reminders are effective in increasing medication intake behavior. There are, however, differences in the SMS reminders sent. One study used personalized text messages that requested a reply (Hardy et al., 2011), the other two studies yielding significant effects sent standardized text messages without requiring acknowledgment (Pop-Eleches et al., 2011; Strandbygaard et al., 2010). Earlier research showed that a tailored message is usually more effective than a standard text (Kreuter & Wray, 2003). 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, i.e., patients who are willing to take their medication but forget it or are inaccurate (Wroe, 2002). 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 (Petrie et al., 2012).

Reminders can be beneficial for improving medication intake behavior 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 and colleagues (2008) 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 and colleagues (2009), for example, showed improved medication intake behavior 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 medication intake behavior, while self-report is considered less reliable as this measure tends to overestimate medication intake behavior (Farmer, 1999; Osterberg & Blaschke, 2005). Most studies included in the review used electronic monitoring for medication intake behavior measurement, sometimes combined with self-report. In two studies, in which medication intake behavior was measured with both electronic monitoring and self-report, effects were only found when medication intake behavior 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 medication intake behavior rate from the beginning, leaving no or insufficient room for improvement. These findings emphasize the importance of incorporating objective methods for medication intake behavior measurement into studies whenever possible (Haynes et al., 2008).

### **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 (Düsing, Handrock, Klebs, Tousset, & Vrijens, 2009; Fairley et al., 2003; Franklin, Waller, Pagliari, & Greene, 2006; Ostrop & Gill, 2000; Simoni et al., 2011). Those studies only reported the total effect of the complex intervention on patients' medication intake behavior, no direct relation between the reminder and medication intake behavior

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 intake behavior. Therefore, we focused not on clinical outcomes, but on medication intake behavior as (one of the) main outcome measures. In medication intake behavior research, a patient is often classified as adherent when an medication intake behavior rate of over 80% is reached (Karve et al., 2009). This cut-off point indicates the minimum level of medication intake behavior 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 cut-off point for medication intake behavior. Pop-Eleches and colleagues (2011) used a binary indicator of whether HIV patients achieved more than 90% medication intake behavior as a primary outcome. Charles and colleagues (2007) used cut-off points of over 50%, over 80% and over 90% medication intake behavior 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 intake behavior usually have insufficient power to detect significant differences in clinical outcome measures. Of the nine studies that showed an effect on medication intake behavior, three studies also reported clinical outcomes (Andrade et al., 2005; Costa et al., 2005; Strandbygaard et al., 2010), of which one found a significant improvement in the intervention group (Andrade et al., 2005). Although medication intake behavior appears to be an intermediate outcome, there is evidence of the association between increased medication intake behavior rates and positive health outcomes (Rozenfeld, Hunt, Plauschinat, & Wong, 2008; Simpson et al., 2006).

### **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 intake behavior. 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 medication intake behavior. 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 medication intake behavior 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 (Vervloet et al., 2011). 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 (Petrie et al., 2012).

### **Conclusions**

This review shows that electronic reminders lead to short-term improvements of patients' medication intake behavior 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 intake behavior may be achieved.