

Real Time Medication Monitoring with customized SMS reminders for people with refractory epilepsy

Will medication adherence levels improve when patients receive customized SMS reminders?

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Abstract— A high level of medication adherence is important for people with refractory epilepsy. For most people, however, it is difficult to have their medication intakes as prescribed every day. In this study we investigated if Real Time Medication Monitoring (RTMM) with customized SMS-reminding had an effect on the adherence level of people with epilepsy. We found a higher adherence level for people receiving these customized SMS reminders, compared to monitored patients not receiving reminders. Additionally, they also feel more adherent, their seizure frequency or severity decreases and they experience a better overall health.

Keywords: medication adherence; epilepsy; medication monitoring; medication reminders; SMS.

I. INTRODUCTION

Epilepsy is a disorder of recurrent unprovoked seizures. The prevalence of epilepsy in Europe is 0.007%, but in people with an intellectual disability the prevalence is about 30% [1]. Although it is a disturbance of brain function, epilepsy can be categorized as a chronic disease. Most people with epilepsy need to take daily medication over an extended period of time.

Although medication does not cure epilepsy, in about 70% of the people with epilepsy seizures disappear with medical treatment. For the remaining 30% seizures continue to exist. Continuing seizures are seen more often in persons with lower cognitive ability. The regularity of medication intake is important in epilepsy treatment since omission of one or more doses can provoke seizures [2]. The severity of these seizures, sometimes after a long period of seizure freeness, can be higher, sometimes resulting in a status epilepticus or even sudden unidentified death in epilepsy (SUDEP) [3]. For most people it is difficult to have their medication intakes as prescribed every day. In a Dutch questionnaire study into the medication use of people with epilepsy an adherence of 65% was found [4].

Especially persons with below-average cognitive ability and patients in puberty are groups who need extra support in medication adherence.

Several earlier studies evaluated SMS reminders showing positive results on adherence [5-10]. In these studies, however, SMS reminders were sent regardless of whether the patient had taken the medication or not. Such automated daily reminders may cause habituation resulting in a loss of effectiveness [8]. Hence, in our study we aim to avoid habituation by using a Real Time Medication Monitoring service with customized SMS-reminding: patients are only reminded when they have forgotten to take their medication.

To our knowledge our study is the first to evaluate a Real Time Medication Monitoring service with customized SMS-reminding to support people with refractory epilepsy in their medication use. The main aim of this study is to evaluate the effect of this service on the adherence to anti-epileptic medication in patients with refractory epilepsy. We focus on the aspect of adherence that refers to how well patients follow their prescribed regimen [11]. Furthermore we are interested in secondary effects of the improved medication adherence: do patients experience a change in seizure frequency or severity and in quality of life?

II. METHODS

A. The RTMM-service

The RTMM service is based on an electronic dispenser (see Figure 1). The dispenser sends a brief message to a central server each time it is opened. The message is sent wirelessly, through the GSM network via GPRS, to a central server. This message contains information about the date and time of the dispenser opening. The electronic dispenser works in nearly every country in the world at locations where mobile phones have network coverage.

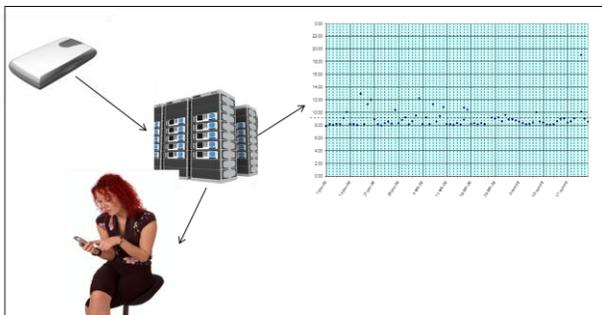


Figure 1. The RTMM service with customized SMS reminders

Patients were instructed when receiving the dispenser and chose one up to four time intervals within which they had to take their medication. This was according to their prescribed number of daily doses. The medication was placed in the dispenser by the patients themselves. An SMS reminder would be sent if they had not opened their medication dispenser within the agreed time interval. The content of the reminder was: "Have you taken your medication yet? Please take your medication as prescribed by your health care provider".

B. Illustration of data registered with RTMM

Figure 2 shows an example of data as collected by the RTMM service. The horizontal axis displays the days of the monitored month, the vertical axis displays the 24 hours of each day. Each opening of the medication dispenser is plotted by one dot in the diagram. The shaded segments represent the agreed time periods for medication intake. In this example the patient follows a medication regimen of four daily doses. The RTMM data reveals quite a regular pattern of medication use for this patient.

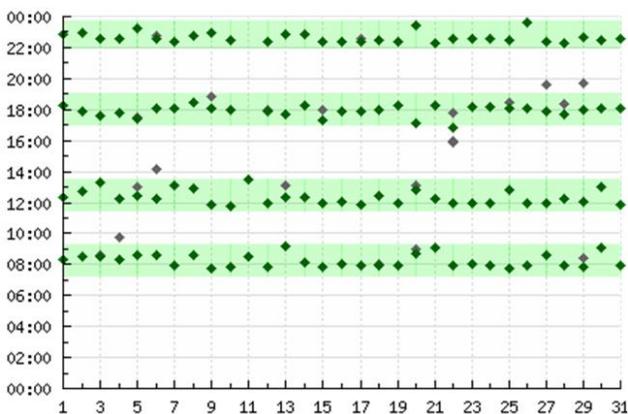


Figure 2. Example of medication intake data as registered with RTMM

C. Study design

The study described here is an observational cohort study of data collected during a period of at least two months during which participants (n=28) used RTMM with the intervention of SMS reminders.

The use of an electronic monitoring device may already contribute to a higher adherence because of patients'

awareness of being monitored [12]. To find the exclusive effect of the SMS-reminding function in this device, a subset of the included participants (n=18) were electronically monitored with RTMM without the SMS reminders, for at least 6 weeks (see Figure 3). This control period (t_0-t_1) was prior to the intervention period with the SMS reminder service (t_1-t_2).

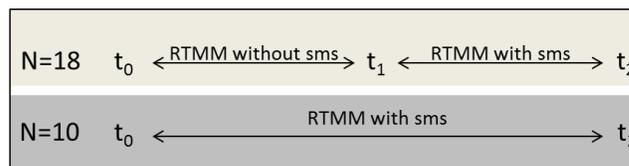


Figure 3. Included participants per type of intervention

D. Participants

Inclusion criteria for participants were: (1) having a clinically definite diagnosis of epilepsy; (2) having at least one epileptic seizure per week; (3) being able to present a precise documentation (diary) of all seizures during half a year prior to the start of the study; (4) aged 15 years or older; (5) independently taking and managing medication; (6) having access to and being able to use a computer and internet; (7) owning and being able to use a mobile phone. Besides these inclusion criteria there was one exclusion criterion: 'playing' with the device: opening and closing it for non-medication purposes for multiple times a day during a week. These criteria are elaborated upon in the research protocol [13].

Participants were recruited from the outpatient clinic of the tertiary epilepsy clinic in Zwolle. They responded to posters in the waiting rooms with a call for volunteers. Or they were asked by their neurologist, nurse practitioner or other paramedical co-worker of the clinic. The inclusion of the participants was performed by one of the investigators explaining the study and the participant's role. If the person with epilepsy agreed to participate and met the inclusion criteria an informed consent was signed by both the participant and investigator. Ultimately, 28 persons with epilepsy participated in the study.

E. Outcome measures

The first two outcome measures were calculated from data registered with the RTMM service during the intervention period.

- (1) *Correct intakes*: the proportion of doses taken within agreed and predefined standardized time intervals. This measure is to assess the precision with which the patients adhere to the prescribed regimen.
- (2) *Missed doses*: the proportion of doses not taken, calculated by dividing the total number of missed doses by the total number of prescribed doses during the intervention period. This measure is to assess whether the appropriate number of doses was taken each day.

The following outcome measures concern patients' experiences which were assessed with written questionnaires handed out to each patient both pre-test (t_0) and post-test (t_2). The following aspects were measured:

- (3) *Patients' judgment on their medication adherence.* Patients were asked to compare their adherence to medication use with and without the support of RTMM with SMS reminders.
- (4) *Seizure frequency.* Patients were asked for their seizure frequency in the prior six weeks based on their paper diaries. The paper diaries were also handed in and answers were checked by the investigators.
- (5) *Experienced effects on seizures after RTMM intervention.* Patients were asked to indicate if and how their seizures differed after the intervention period.
- (6) *Quality of live.* The health-related Quality-of-Live questionnaire, with 31-items (QOLIE-31) by Cramer et al. [14] was used to assess the quality of live. This validated questionnaire covers both general and epilepsy-specific domains. Cross-cultural translations were made for nine languages among which Dutch.
- (7) *Satisfaction with the RTMM service.* Patients were asked for their experience with the SMS reminder service on two aspects: convenience of total service, and ease of use of the medication dispenser.

III. RESULTS

A. Characteristics of Study Participants

In total 48 persons with epilepsy received the dispenser and the corresponding instructions. Eleven persons did not use it at all or only during a few days. Five persons used it only during 1-4 weeks and four only during the period without SMS reminders (control period). These 20 persons were classified as "drop outs". Their reasons for dropping out varied from the design of the dispenser to privacy concerns.

Ultimately, 28 persons with epilepsy participated in this study. The characteristics of both participants and drop outs are shown in Table I. There are no differences between both groups for gender, age, educational level, living situation, and seizure frequency. The groups differ in their daytime activities: participants had more regular daily activities, like work or school, than the drop outs (71.4% vs. 30%, $p=0.014$). Furthermore, the severity of epilepsy differed between both groups. In total 35% of the drop outs had severe tonic-clonic seizures compared to 14.2% of the participants ($p=0.041$).

TABLE I. CHARACTERISTICS PARTICIPANTS AND DROP OUTS

	Characteristics Participants and Drop Outs			
	Total	Participants	Drop Outs	p-Value
Number	48	28	20	
Male, n (%)	25 (52.1)	13 (46.4)	12 (60.0)	$p = 0.359$
Age, mean (min-max)	33.7 (15-62)	25.5 (15-61)	34.0 (15-62)	$p = 0.242$
Educational level medium or lower, n (%)	35 (72.9)	20 (71.4)	15 (75)	$p = 0.516$
Regular daily activities (occupation/school, n (%))	26 (54.2)	20 (71.4)	6 (30)	$p = 0.014$
Living alone, n (%)	9 (18.8)	4 (14.3)	5 (25)	$p = 0.549$
Seizure frequency per week				$p = 0.654$
1 seizure, n (%)	14 (29.2%)	8 (28.6%)	6 (30%)	
2-4 seizure, n (%)	16 (33.3%)	9 (32.1%)	7 (35%)	
4-6 seizures, n (%)	5 (10.4%)	2 (7.1%)	3 (15%)	
7 or more seizures, n (%)	13 (27.1%)	9 (32.1%)	4 (20%)	
Type of seizures				$p = 0.041$
Simple Partial	2 (4.2%)	2 (7.1%)	-	
Complex Partial	35 (72.9%)	22 (78.6%)	13 (65%)	
Tonic Clonic	11 (23.0%)	4 (14.2%)	7 (35%)	

As indicated, participants (n=18) were included in a control group using RTMM without SMS reminders in advance of using it with SMS reminders. Table II shows the number of included patients, the lengths of the study periods and the type of intervention (with/without SMS) they received during these study periods.

TABLE II. PARTICIPANTS PER TYPE OF INTERVENTION AND LENGTH OF STUDY PERIOD

Participants per type of intervention and length of study period			
	Study period	Median days (min-max)	Type of RTMM service
N=18	t_0-t_1	120 (30-120)	without SMS reminders
	t_1-t_2	225 (120-360)	with SMS reminders
N=10	t_0-t_2	360 (60-360)	with SMS reminders

B. Differences in Adherence

Table III shows the differences in adherence for the control group (N=18) between the RTMM service without SMS reminders and the same service with SMS reminders. While receiving SMS reminders participants had a significantly higher percentage of correct medication intakes ($p=0.003$). These participants also had an almost significant lower percentage of missed doses ($p=0.058$).

TABLE III. DIFFERENCES IN ADHERENCE DURING THE USE OF RTMM WITH AND WITHOUT SMS REMINDER SERVICE

Differences in adherence during the use of RTMM with and without SMS reminder service			
n=18	Without SMS (t ₁ -t ₁)	With SMS (t ₁ -t ₂)	Related-Samples Wilcoxon Signed Rank Test
% Correct intake median (min-max)	68.47 (31.11-102.50)	82.85 (30.83-98.89)	p=0.003
% Missed doses median (min-max)	17.92 (1.67-44.44)	7.11 (1.11-49.21)	p=0.058

In addition to the above control group, ten participants received SMS reminders from the start of their inclusion (t₀-t₂). In these ten participants the median percentage of correct intakes was 88.06% (34.58-97.92). The median percentage of missed doses was in these ten participants 9.17 (1.88-44.17). Both percentages did not differ significantly from the control group when receiving SMS reminders (t₁-t₂).

C. Experienced Adherence

In the post-test questionnaire a majority of the participants (57.1%) indicated they experienced an improved adherence due to the RTMM service with SMS reminders (Table IV).

TABLE IV. ADHERENCE AS EXPERIENCED BY PARTICIPANTS

Experienced Adherence	
Do you consider yourself more adherent with the use of RTMM?	N=28
Yes, n (%)	16 (57.1)
No, n (%)	6 (21.4)
No Answer, n (%)	6 (21.4)

D. Seizure Frequency

Both pre-test (t₀) and post-test (t₂) participants rated their seizure frequency based on their paper diaries. Results are presented in Figure 4.

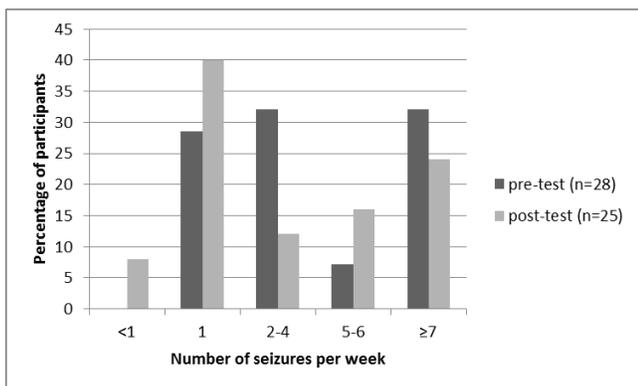


Figure 4. Number of seizures per week

Although these results were not statistically significant, a trend is visible: participants seem to have less seizures during the use of RTMM with SMS reminders than before this use.

E. Experienced effects on seizures

In the post-test questionnaire participants were asked about the effect of the RTMM service with SMS reminders on their seizures (Table V). A decrease of seizure frequency was mentioned by seven participants (25%). No change in seizure frequency but a decrease in seizure severity was mentioned by 16 participants (57.1%).

TABLE V. EFFECTS ON SEIZURES AS EXPERIENCED BY PATIENTS

Experienced effects on seizures	
Do you experience a decrease in seizures due to the use of the RTMM service?	N=28
Yes, n (%)	7 (25.0)
No, but less severe, n (%)	16 (57.1)
No, n (%)	2 (7.1)
No Answer, n (%)	3 (10.7)

F. Quality of Live

The Quality of Life in Epilepsy questionnaire (QOLIE-31) was distributed three times during the study (Table VI). A comparison for the control group between QOLIE(0) and QOLIE(1) indicated no significant differences in Total Score, nor in the six different dimensions (Seizure Worry, Emotional Well-being, Energy-fatigue, Cognitive functioning, Medication effects, Social functioning).

TABLE VI. DISTRIBUTION OF QOLIE-31 DURING THE STUDY

Distribution of QOLIE-31 during the study			
	t ₀ (pre-test)	t ₁	t ₂ (post-test)
Control group N=18	QOLIE(0) at start of RTMM without SMS	QOLIE(1) at start of RTMM with SMS	QOLIE(2)
N=10	QOLIE(0) at start of RTMM with SMS	-	QOLIE(2)

Comparing QOLIE(0) with QOLIE(2) for all 28 participants indicated no significant changes except for the scores on the Visual Analog Scale (VAS) about the overall health (Table VII). Participants experienced a higher overall health at the end of the study. This difference was significant.

TABLE VII. OVERALL HEALTH AS EXPERIENCED BY PARTICIPANTS

	Experienced Overall Health		
	t_0 (pre-test) (n=28)	t_2 (post-test) (n=28)	p-Value
Mean health score on a Visual Analogue Scale from 0-100 points	59.8	65.7	$p = 0,049$

G. Satisfaction with the RTMM service

At the end of the study participants filled out a questionnaire about their experiences in this study and their satisfaction with the RTMM service (Table VIII). The questions about the use of the dispenser showed in general results fitting to moderate satisfaction. Most people thought the device helped them in medication use resulting in a better compliance. They were satisfied with the reminders by SMS. Half of the participants were satisfied with the design of the medication box.

TABLE VIII. SATISFACTION WITH THE RTMM SERVICE

Satisfaction with the RTMM service	
N=28	
Did you experience the SMS reminder service as pleasant?	
Yes, n (%)	18 (64.3)
Neutral, n (%)	4 (14.3)
No, n (%)	2 (7.2)
No Answer, n (%)	4 (14.3)
Did you experience the medication box as easy to use?	
Yes, n (%)	13 (46.4)
Neutral, n (%)	5 (17.9)
No, n (%)	7 (25.0)
No Answer, n (%)	3 (10.7)

IV. CONCLUSION AND FUTURE WORK

People with refractory epilepsy using Real Time Medication Monitoring (RTMM) with customized SMS-reminding to support their medication use, have a higher adherence level than patients who do not receive SMS-reminding. Additionally, they also feel more adherent, their seizure frequency or severity decreases and they experience a better overall health. Overall, patients' experiences with the RTMM system are positive.

Since other patient groups have adherence difficulties as well, the RTMM service with customized SMS-reminding may provide opportunities for increasing adherence for other chronic diseases.

A. Discussion

Our findings are in line with the results from the single previous study we found evaluating the effect of RTMM with customized SMS reminders on adherence [15]. Similar to our results, Vervloet et al. found increased adherence levels for participants receiving SMS reminders compared to participants who were only monitored with RTMM. Vervloet's study concerned type 2 diabetes patients. What we added to this study was not only the effect on adherence for a different group of patients, but also the effect on the health of these patients, be it subjective. Where Vervloet did not collect clinical data (i.e. blood glucose levels) or subjective data on health conditions, we collected data on the experienced epileptic seizures and quality of life.

Participants in our study experience less seizures or less severe seizures and an increase in overall health. The latter is likely to stem from the decreased number or severity of seizures, but may also (partly) be the effect of a feeling of reassurance participants get from the SMS reminders: they do not have to worry to forget a dose since they will receive a reminder by SMS. We did not investigate whether this reassurance was one of the effects of the RTMM service with customized SMS reminders.

A common critique of RTMM is that opening the medication dispenser is not a confirmation of the actual ingestion of the medication. However, the validity of electronic monitoring devices is confirmed by studies comparing drug assays with medication intake behaviour measured through electronic dispensers [16-18].

B. Limitations

This study was performed in a small sample of people with refractory epilepsy, in an epilepsy clinic. This limitation influences the statistical significance of results and it prevented us from analysing results of subgroups within the total group of participants.

A second limitation of the study concerns the chosen inclusion criterion of having at least one seizure per week. This resulted in participants with high seizure frequencies. We selected this group expecting they would benefit most from RTMM with customized SMS reminders. Future research should also include participants with lower seizure frequencies.

C. Future Work

Due to the positive results of the above study the RTMM service with customized SMS-reminding is now structurally embedded in the involved epilepsy clinic. It is offered to a broader group of persons with epilepsy than based on the above inclusion criteria. Young people, mentally disabled people and persons with lower seizure frequencies are using the service and will be monitored. This offers the authors the opportunity to build on the above study with new data concerning longer term effects of a larger sample of participants from different subgroups.

The authors strongly recommend for future studies to investigate the differences in adherence effects between customized and non-customized SMS reminders. The latter have become available by freely downloadable apps running on smartphones. As indicated in the Introduction, daily sent reminders may cause habituation leading to lower effectiveness. Future studies should include a control group monitored by RTMM but receiving non-customized SMS reminders.

Future research is also recommended to further investigate the impact of RTMM and SMS reminders on seizure frequency and severity. The authors aim at studying this impact by requesting participants to keep a digital diary on computer or mobile. Hence, the relation between adherence and frequency and severity of seizures can be automatically deduced. These studies should concern long term intervention periods and also include patients with lower seizure frequencies.

A final recommendation for future research concerns the use of the adherence data by involved specialists and nurse practitioners. To what extent and how do involved medical professionals use this data logged by the RTMM service and how does it influence their (medication) treatment of people with refractory epilepsy?

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REFERENCES

- [1] *Richtlijnen voor de diagnose en behandeling van epilepsie*, in *Nederlandse Vereniging voor Neurologie* 2006.
- [2] Cramer, J.A., M. Glassman, and V. Rienzi, *The relationship between poor medication compliance and seizures*. *Epilepsy & Behavior*, 2002. **3**: p. 338-342.
- [3] Brodie, M.J. and G.L. Holmes, *Should all patients be told about sudden unexpected death in epilepsy (SUDEP)? Pros and Cons*. *Epilepsia*, 2008. **49**(9): p. 99-101.
- [4] Kunwar, R., *Therapietrouw onder de leden van de EVN*, 2010, Epilepsie Vereniging Nederland: Ede.
- [5] Hardy, H., et al., *Randomized controlled trial of a personalized cellular phone reminder system to enhance adherence to antiretroviral therapy*. *AIDS Patient Care STDS*, 2011.
- [6] Strandbygaard, U., S.F. Thomsen, and V. Backer, *A daily SMS reminder increases adherence to asthma treatment: a three-month follow-up study*. *Respir. Med.*, 2010. **104**: p. 166-171.
- [7] Lester, R.T., et al., *Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial*. *Lancet*, 2010. **376**(1838-1845).
- [8] Pop-Eleches, C., et al., *Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders*. *AIDS*, 2011. **25**(6): p. 825-834.
- [9] Miloh, T., et al., *Improved adherence and outcomes for pediatric liver transplant recipients by using text messaging*. *Pediatrics*, 2009. **124**: p. e844-e850.
- [10] Vervloet, M., et al., *The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature*. *J Am Med Inform Assoc*, 2012.
- [11] Urquhart, J. and B. Vrijens, *New findings about patient adherence to prescribed drug dosing regimens: an introduction to pharmionics*. *Eur. J. Hosp. Pharm*, 2005. **11**: p. 103-106.
- [12] Wetzels, G.E., et al., *Electronic monitoring of adherence as a tool to improve blood pressure control. A randomized controlled trial*. *Am. J. Hypertens*, 2007. **20**: p. 119-125.
- [13] Gutter, T., *Research Protocol RealTime Medication Monitoring in Epilepsy*, 2010, The Epilepsy Institutes of the Netherlands Foundation.
- [14] Cramer, J.A., et al., *Development and Cross-Cultural Translations of a 3 1 -Item Quality of Life in Epilepsy Inventory*. *Epilepsia*, 1998. **39**(1): p. 81-88.
- [15] Vervloet, M., et al., *SMS reminders improve adherence to oral medication in type 2 diabetes patients who are real time electronically monitored*. *Int. J. Med. Inform.*, 2012. **81**(9): p. 594-604.
- [16] Vrijens, B., et al., *Successful projection of the time course of drug concentration in plasma during a 1-year period from electronically compiled dosing-time data used as input to individually parameterized pharmacokinetic models*. *J. Clin. Pharmacol.*, 2005. **45**: p. 461-467.
- [17] Girard, P., et al., *Do we need full compliance data for population pharmacokinetic analysis?* *J. Pharmacokinet. Biopharm.*, 1996. **24**: p. 265-282.
- [18] Vrijens, B. and E. Goetghebeur, *The impact of compliance in pharmacokinetic studies*. *Stat. Methods Med. Res.*, 1999. **8**: p. 247-262.