A Novel Text-Message Reminder System to Address Medication Non-Adherence

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ABSTRACT
There is a high rate of medication non-adherence, which can lead to disease progression, disability and mortality. This study tested a novel computer-based text message reminder system to improve adherence to medications. This system proved effective in improving adherence to a placebo in healthy volunteers, and to medications in cardiac patients over a two month period. It was especially effective in individuals at prospectively identified to be at high risk of non-adherence. This system represents a simple and scalable method to improve adherence to medications at a clinical or pharmaceutical level. Further research into the impact of repeated reminders is necessary to explore the impacts of text message reminders in other populations and in other lifestyle interventions.

BACKGROUND
Medication non-adherence or non-compliance is defined as erroneous methods of taking medication, whether at the incorrect quantity, or incorrect time as prescribed.1,3,4,5 This can limit the effectiveness of medications, lead to disease progression, and in some extreme cases, can lead to premature death.5,6 Studies suggest that non-adherence to medications is extremely prevalent in our society.1-6 Non-adherence to medication is categorized into two main groups: intentional and non-intentional.7 Intentional non-adherence can include deliberately choosing not to take medications due to personal preference, not understanding or believing in the importance of the medication or choosing not to take the medication due to perceived side effects.7 Non-intentional non-adherence occurs where the individual is not deliberately refusing to take medications, but may be making medication errors unintentionally due to factors like complexity of medication regimens, inability to acquire or administer the medication or forgetting to take the medication.7

Studies have identified forgetfulness as a leading cause of medication non-adherence.4,6,7 Although systems exist today to reduce non-adherence, few focus on reducing forgetfulness.3,4 Those systems that do address forgetfulness often are only able to address one part of forgetfulness; beepers remind patients to take medications but don’t inform them of what medications to take. Pill boxes help patients to take the correct medications, but don’t remind them to take them. In addition, because carrying these systems on one’s person is cumbersome, they are often left at home, reducing their effectiveness.3,4 Certain populations like the elderly, those with cognitive or neurological diseases like stroke, dementia and depression, as well as those with lower educational levels have been shown to be at greater risk for medication non-adherence.1,3,5,8 Available systems like pill boxes, blister packs and beepers have had limited success at reducing non-adherence (only 5-20% relative risk reduction).4-6 An effective solution to this clinical problem has yet to be determined4. A more effective, automated system of reminders could be used to help reduce
forgetfulness induced non-adherence to medication. This study tests the feasibility and the efficacy of a novel, computerized, automated text message (SMS) system to decrease non-adherence to placebos and medications.

METHODS:
Design:
This was a single center, pre- / post- intervention study of medication adherence using SMS reminders. There were three phases to this study.
Phase 1: Technology pilot
Phase 2: Pilot testing in volunteers
Phase 3: Real World Intervention

The study comprised of three phases with two initial pilot phases to ensure feasibility and technical reliability of the technology, and its ability to improve adherence to a placebo, and then a real world assessment involving volunteer Cardiac patients from a community cardiology clinic using their own medications on their own regimen.

Ethics:
A test protocol, & written informed consent form were reviewed by Dr. S. Sykes, University of Waterloo Human Research Ethics Board. We obtained written informed consent from all participants before any procedures were carried out.

Setting:
This study was carried out in the cities of Waterloo (pop. 100 000) and Cambridge (pop. 150 000), Ontario. Recruitment of four volunteers to test the reliability of the system took place in the city of Waterloo. Recruitment of 25 healthy volunteers for a pilot test also took place in Waterloo. 30 cardiac patients were recruited at Cambridge Cardiac Care (a community cardiology clinic serving Waterloo Region: pop. 550 000).

Population and Subject Selection:
In phases one and two, the populations studied were healthy volunteers. All participants were adults who had cell phones. In phase three, the population was volunteers from a Canadian cardiology community practice (Cambridge Cardiac Care Centre). Study population size was determined for phase three through power analysis of phase two data. We included all stable cardiac patients above 18 years of age, who were able to read and write English and competent to provide informed consent. Children, those without a cell phone, those unable to read and write in English, those unable to provide informed consent, those unable to comply with study protocol and incarcerated individuals were excluded from the study.

Phase One: Intervention and Technology Pilot:
In phase one, we created a computer program to send text messages to cell phones using Microsoft Visual Basic 2008 Express Edition. The automated text message reminder system checks the time every minute, until it reaches a specific time when a patient is supposed to take a medication. The system sends an email to a web portal, which converts the email to a text message and sends it to the patient’s cell phone. Text messages were sent four times daily to 4 volunteers with different cell phones and different cell phone providers over two months, to validate the stability and reliability of this system.

PHASE TWO: PILOT TEST:
Twenty-five healthy volunteers were recruited to test this model. Demographic information was obtained on all volunteers: age, gender, education level, cell phone number, and cell phone provider. The test procedure involved self-reported removal of a placebo (a raisin) from vials. Individuals had to remove and discard a raisin at 7:30 am, 12 pm, 6:00 pm, and 9:00 pm. Volunteers were randomized, using a web based random number generator (http://www.randomnumbergenerator.com), to receive text message reminders in either week one or week two. For one week, individuals removed the placebo raisins without any reminders. For a second week, they received reminder text messages & had to record whether they received the text message & whether they removed the raisin. Volunteers recorded removal of raisins & receipt of text messages in specially prepared and supplied logbooks. Half of the subjects began receiving text message reminders for the first week, and received no text message for the second week, while the other half of subjects did not receive text message reminders in the first week, and received text message reminders in the second
week. Adherence was determined by measuring the number of total prescribed doses of raisins, and the number of doses of raisins actually removed as recorded in log books. Total overall accuracy of self-reported placebo removal was determined through a “pill count” of returned vials of raisins. Individuals had been randomized to receive text messages either in week one or week two to mitigate a potential trainer effect bias, which is a bias introduced by being exposed to a specific task and becoming familiar with the task such that it influences the result of a subsequent intervention being investigated.

PHASE THREE: REAL WORLD VALIDATION

Thirty random volunteers from a local cardiology practice were recruited. A nurse at this facility was contacted, and patients were recruited under her supervision. Written informed consent was obtained. Demographic information was obtained on all volunteers. Volunteer were asked to take their own medications at their own prescribed regimen for one month and record their adherence in a specially designed logbook. For a second month, they received reminder text messages & had to record their adherence according to their own prescribed regimen. The percent adherence was determined by dividing the medications taken by the medication prescribed. Half of the subjects were randomized to receive text message reminders for the first month, and received no text message for the second month, while the other half of subjects were randomized not to receive text message reminders in the first month, and to receive text message reminders in the second month to eliminate any potential trainer effect.

DATA ANALYSIS

We performed three main types of analysis: absolute risk reduction, relative risk reduction, and subgroup analysis. Adherence was determined from patient medication logs by calculating the number of total prescribed doses, and measuring the number of doses actually taken as recorded in log books. Absolute risk reduction was determined by dividing absolute risk reduction by the control incidence rate (non-adherence in the individuals not receiving reminders). Certain groups, chosen prospectively according to literature review, were identified as having a greater risk of medication regimen non-adherence (elderly, less than grade 12 education, patients with depression, and dementia). Adherence, and risk reduction for these groups was compared to that of the total study population.

Statistical Analysis:

We used GraphPad Instat 3.10 to perform statistical analysis. We used paired Students T-test for comparisons of two variables because the same subjects were used for each period of time and served as their own controls. We used ANOVA with Bonferroni correction test (for multiple comparisons) for comparisons with two or more variables. A p-value of 0.05 was considered statistically significant.

RESULTS:

DISCUSSION:

Based on the work of Choudhry et al. in 2011, absolute increases in adherence of over 5% can be considered a clinically significant improvement. In a population of stable cardiac patients, this study demonstrated on average 11% absolute improvement in medication adherence, suggesting this system may have a meaningful clinical impact. This is in accordance with the work of Friedman et al. 1996, which demonstrated

Phase One:

In the first phase of our study, our feasibility pilot, our four healthy volunteers received and logged 100% of text messages sent. We verified each text message reminder logged by the volunteers with an email audit trail. All messages were sent in a timely and accurate fashion.
**Table 1: Phase Two - Pilot Test**

<table>
<thead>
<tr>
<th>Healthy Volunteers</th>
<th>Without Reminders</th>
<th>With Reminders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total missed doses</td>
<td>155</td>
<td>67</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Average # of missed doses per person</td>
<td>9.7</td>
<td>4.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percentage of the times doses were taken</td>
<td>65.4</td>
<td>85.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td># of people who improved with reminders</td>
<td>N/A</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>% of people who improved with reminders</td>
<td>N/A</td>
<td>87.5%</td>
<td>N/A</td>
</tr>
<tr>
<td>% Absolute improvement in adherence</td>
<td>N/A</td>
<td>19.6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>% Relative improvement in adherence (Relative Risk Reduction for non-adherence)</td>
<td>N/A</td>
<td>64.8%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**Phase Two:**

Table 1 shows the results from the cohort study in Phase Two. A high rate of medication non-adherence to placebo regimen was noted in healthy volunteers (35%). Improvements in adherence with this text message reminder system were consistent, with an average absolute improvement of 20%, with a relative risk reduction for non-adherence of 65%. Text message reminders were reliably sent from an automated computer program and were effective at improving adherence in all groups studied. Adherence was determined using self-recorded log books. This is the method routinely used in medication adherence research. Total overall accuracy of self-reported placebo removal was determined through a “pill count” of returned vials of raisins and matched nearly identically (97% concordance) in all individuals and groups, validating log books as an effective tool for adherence analysis in other parts of this study. Whether volunteers received text message reminders in the first half or second half of the study did not affect adherence rates, suggesting no significant trainer effect in this study.

**Table 2: Phase Three - Real World Validation**

<table>
<thead>
<tr>
<th>Stable Cardiac Patients</th>
<th>Without Reminders</th>
<th>With Reminders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of correctly taken doses per month</td>
<td>1705</td>
<td>1897</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average number of prescribed doses weekly</td>
<td>67.2</td>
<td>67.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Average number of doses taken for the week per person</td>
<td>56.8</td>
<td>63.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% taken correctly</td>
<td>83.0</td>
<td>93.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Improved Subjects</td>
<td>N/A</td>
<td>100</td>
<td>N/A</td>
</tr>
<tr>
<td>% Absolute improvement in adherence</td>
<td>N/A</td>
<td>10.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>% Relative improvement in adherence (Relative Risk Reduction for non-adherence)</td>
<td>N/A</td>
<td>63.9%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

the ability of communication technology to be used as a motivator for improving adherence to medications. This study is the first, however, to test the use of text messages as a mode of reminder for reducing forgetfulness.

Subgroups identified in other studies to be at higher risk of non-adherence to medications, such as in MacLaughlin et al. (2005), were demonstrated to be less adherent to medications in this study. These groups were demonstrated to improve more with this system, perhaps as a result of their increased risk of forgetfulness. Numerous studies such as Wroe et al. (2002) have also shown lower adherence rates in less educated individuals. This study also demonstrated increased rates of improvement in these individuals as well. In all groups analyzed, individuals with lower baseline adherence rates appeared to benefit most from this system.

Additionally, while this system is designed to address only forgetfulness as a cause of non-adherence,
Phase Three:

Table 2 shows the results from the cohort study in Phase Three. A high rate of medication non-adherence was noted in cardiac patients (17%). This system of text message reminders consistently improved adherence to medications, with all subjects improving. The average absolute improvement was 11%, with a relative risk reduction for non-adherence of 64%. Certain groups of cardiac patients appeared to have lower baseline adherence. The elderly, stroke, dementia, and depression patients, as well as those with less education, showed lower rates of adherence to medications (Table 3). Consistent with other studies, the vast majority of subjects, 71%, reported that forgetfulness was a main contributor to their missed medications (Figure 2). Text message reminders were reliably sent from an automated computer program and were effective at improving adherence in all groups studied. Whether individuals received text message in the first half of the study or in the second half of the study did not impact the adherence rates significantly in any groups (p>0.05). As a result, no trainer effect was noted in cardiac patients.

Table 3: Phase Three - Subgroup Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Without Reminders</th>
<th>With Reminders</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects</td>
<td>83.0%</td>
<td>93.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>68.2%</td>
<td>88.6%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Dementia</td>
<td>79.9%</td>
<td>94.2%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Depression</td>
<td>73.8%</td>
<td>91.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elderly &gt;65</td>
<td>84.0%</td>
<td>96.1%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Extreme Elderly &gt;80</td>
<td>65.4%</td>
<td>89.5%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>&lt;12 Grade Education</td>
<td>75.0%</td>
<td>93.8%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Grade 12 Education</td>
<td>84.3%</td>
<td>94.2%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Post Secondary</td>
<td>85.2%</td>
<td>94.8%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Stratification by Education:

Figure 1 illustrates the improvements of patients stratified by education level. Previous studies have noted that less education is a predictor for non-adherence to medications. It was noted in this study, individuals with fewer years of education (having attained 12 or less years or education) had lower baseline adherence but also appeared to improve adherence more through this text message reminder system (an 18% improvement vs. 11% in the total study population).

Reasons for Non-adherence:

Figure 2 shows the participants’ self-perceived reasons for non-adherence to their own medications. Forgetfulness represented 71% of the reasons identified by the participants for non-adherence. Cost, side effects and routine were also reasons that participants felt caused them to be non-adherent to their medications.
it seems to have a marked effect on reducing non-adherence with 100% of stable patients demonstrating some degree of improvement in adherence with a relative risk reduction for non-adherence of 64% for the whole study population. This suggests that forgetfulness may be an important mechanism leading to medication non-adherence and strategies, such as this system, that effectively address forgetfulness, may improve adherence to medications.

LIMITATIONS:
Not all individuals have cell phones. A preliminary test of this program, however, demonstrates that it is able to deliver a recorded voice message over landline phones which may reduce this limitation. This study was conducted with a small group of volunteers. This study was short in duration, measuring adherence over a few weeks only. A longer study assessing the impact of this system in cardiac patients has been undertaken. This was a self-reported adherence study, although past research has shown this to be an effective way to determine adherence. This study only addresses one reason for medication non-adherence: forgetfulness.

CONCLUSIONS:
This novel text message reminder system demonstrated reliability, accurately sending text messages to numerous cell phones with different cell phone providers without fail. The system proved effective in improving adherence to a placebo in healthy volunteers, and to medications in cardiac patients, over a two month period. In all groups studied, this system proved effective at reducing the number of missed doses, and seemed to be most effective in those groups with lower baseline adherence.

In the future, a similar automated text message reminder system could be used to reduce medication non-adherence. The system could be offered by hospitals or clinics as a way of reducing non-adherence to medications. The applicability of the system could also be tested in numerous other fields to test its effectiveness at reducing non-adherence to lifestyle changes, and exercise regimens. Strategies, such as this text message reminder system, that effectively address forgetfulness, may be expected to significantly impact non-adherence and perhaps over time, contribute to a reduction in morbidity and mortality through greater adherence to appropriate medications.

Key Word: Medication Adherence, education Non-compliance, E-solution, SMS Reminder, Forgetfulness

ACKNOWLEDGMENTS:
I would like to thank teachers, Mr. O. Visser (KW-Bilingual School), Mr. M. Menhennet and Mr. C. Fusco (Waterloo Collegiate Institute), for their assistance and guidance. I would like to thank Dr. Alter, Cardiologist, and Associate professor in the Department of Medicine at the University of Toronto for his useful discussions and for his assistance in manuscript preparation. I would like to thank Dr. N. Choudhry, Associate Professor, Harvard Medical School, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women’s Hospital for his valuable discussions, and assistance with analysis manuscript preparation. I would like to thank Dr. S. Shankar, statistician at the University of Waterloo for her valuable aid in statistical analysis. I would like to thank Dr. Susan Sykes, University of Waterloo Human Research Ethics Board for reviewing the protocol, the informed consent form and for valuable discussions. I would like to thank Mr. Rob Morris for his assistance in computer programming. I would like to thank Ms. Kelly Cronin, Cardiac nurse for aid with data collection. Most importantly, I would like to thank the 59 volunteers who participated in this study.

REFERENCES:


