Reminders and Negative Reinforcement in Intervention for Medication Adherence

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Abstract

Medication adherence is a critical factor to promote healthcare outcomes, especially for chronic medical conditions. Several mobile health (m-health) interventions have been proposed to increase medication adherence. This research provides design principles of multiple reminders in an intervention to keep medication's effectiveness and prevent patients from overdosing. Also, this research discusses multiple scenarios of implementation of negative reinforcement (NR) in the intervention design and evaluates the scenarios using analytical modeling. The results provide basic validation of NR in an intervention for medication adherence.

Keywords

Medication adherence, negative reinforcement, analytical modeling.

Introduction

Poor medication adherence among patients, especially patients with chronic disease, remains a major healthcare problem. This not only affects patient health adversely but also negatively impacts a patient's relationship with the healthcare provider. Additionally, it skews clinical therapy trials' results and increases health resource consumption dramatically. According to an estimate, poor adherence causes approximately 33% to 69% of medication-related hospitalizations and accounts for $100 billion annual healthcare costs (Osterberg and Blaschke 2005). The cause of poor medication adherence is broadly categorized as unintentional or intentional. Unintentional poor adherence involves intending to take medication as instructed but failing to do so for some reason, for example, forgetfulness. In contrast, intentional poor adherence involves making a reasoned decision not to take medication as instructed based on perceptions, feelings, or beliefs (Dayer et al. 2013).

To improve medication adherence among patients and simultaneously decrease related healthcare cost, researchers and healthcare professionals have proposed several interventions. However, the outcomes vary over a range. A Cochrane review, which focuses on adherence interventions utilizing randomized trials, showed that less than one half of them improve both clinical outcomes and long-term adherence and that the most effective interventions involved complex combinations of multiple strategies (Nieuwlaat et al. 2014). In recent years, mobile health (m-health) has become the appropriate platform to implement such complex interventions based on its supportive functionalities, inexpensiveness, and constant accessibility. Reminders are primarily used to mitigate unintentional poor adherence in m-health and has been found effective in research (Khatib et al. 2014). However, a simple and single reminder may lead to overdose due to the patient's catch-up behavior to take doses at an inappropriate time. On the other hand, reinforcement is utilized as a method to change intentional poor adherence behaviors (Dayer et al. 2013). Reinforcement is the action or process of strengthening a pattern of behavior. It can be broadly categorized as positive reinforcement (PR) and negative reinforcement (NR). Positive reinforcement is the action of adding a reward to increase certain response, and negative reinforcement is the action of taking away an element in the individual's environment when the undesired behavior happens. In clinical trials, several types of positive reinforcement have been tested for their effectiveness in modifying the patient's medication-taking behavior. The examined types include money, voucher, and lottery. Significant increases in MA were presented in several trials along with a lower possibility of re-hospitalization (Barnett et al. 2009; Messina et al. 2003; Moore et al. 2015; Sen et al. 2014). However, negative reinforcement (NR) as compared to positive reinforcement (PR) is much less studied.

A research in 2016 proposed a novel intervention including two reminders and both positive and negative reinforcement (Liu and Varshney 2016), yet the design lacks details and in-depth evaluation. In this paper, the principle and details of two reminders, as well as modeling and evaluation of NR will be discussed.

In the following sections, we will first overview the original intervention process followed by the detailed design of two reminders. Then, we provide scenarios and initial evaluation of negative reinforcement in the intervention. Finally, future research discussion and conclusions are presented.

Intervention Process

The previously designed intervention (Figure 1) starts with defining the scenario that a patient will go through by setting healthcare events, actions, reinforcements (positive and negative), and medication adherence rate (MAR) goal. The system will send two reminders with a time difference to the patient if a medication event is due. If the patient takes his/her medication, a corresponding positive reinforcement (i.e., financial reward) will be added to the reward record. If the patient does not take his/her medication, the system will calculate whether this medication dose is a critical one to maintain the MAR goal. If it is a critical dose, then the NR (e.g., blocking user's most used social media/entertainment App) will be implemented by the system immediately. Unlike NR, the accumulated reward will be granted to the patient at the end of each pre-set intervention period.

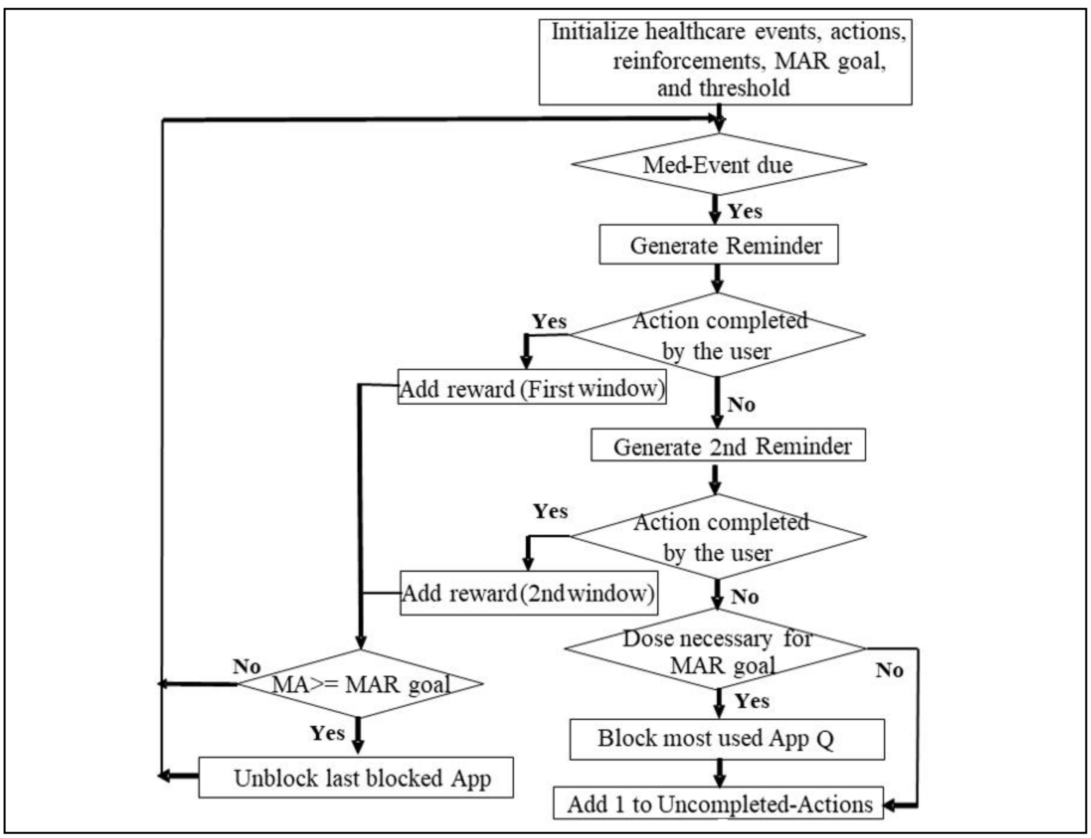

Figure 1: Intervention Process (Adapted from Liu and Varshney 2016)

The two reminders can reduce unintentionally-missed-doses. Additionally, these two reminders can assist in lowering the possibility of overdose due to the patient's catch-up behavior to take doses at an inappropriate time to make up for his/her skipped or delayed dose. Following is the detailed design of two reminders.

Detailed Reminders Design

Each reminder works in cooperate with a time-window which is specified by the healthcare professional. Time-window is an available time interval for a patient to take his/her medication dose. The two time-windows should be designed in such a way that the first time-window covers the period during which the taken dose will fulfill its full effect, and the second time-window specifies the last possible period for a taken dose to not interfere with the effect of next on-time-taken dose. At the beginning of the first time-window, the system will send the first reminder to the patient. If the patient takes medication during first time-window, no further reminder will be sent; if the patient doesn't take medication, another reminder will be sent at the beginning of the second time-window. The system will display a message after the second time-window, suggesting the patient should not take any medication until he/she receives the next reminder. In this way, the overdosing situation can be avoided.

The time interval between the beginning time of a dose's first time-window and the end time of the next dose's second time-window should not exceed the max-interdose-time for the medication to be effective. Thus,

$$T_{i+1,es} - T_{i,bf} \leq T_{max} \tag{1}$$

where T_{max} is the maximum interval time between two doses for them to remain medically effective and compliant, $T_{i,bf}$ is the beginning time of the first time-window of dose i, and $T_{i+1,es}$ is the ending time of the second time-window of dose i+1. Beside max-interdose-time, we also consider the min-interdose-time which prevents the patients from overdosing, that is to say

$$T_{i+1,bf} - T_{i,es} \geq T_{min} \tag{2}$$

where T_{min} is the minimum interval time between two doses for them to be compliant and safely consumed by the patient without causing any negative effects of overdosing, $T_{i,es}$ is the ending time of the second time-window of dose i, and $T_{i+1,bf}$ is the beginning of the first time-window of dose i+1. The illustration of time-windows, max-interdose-time and min-interdose-time is shown in Figure 2.

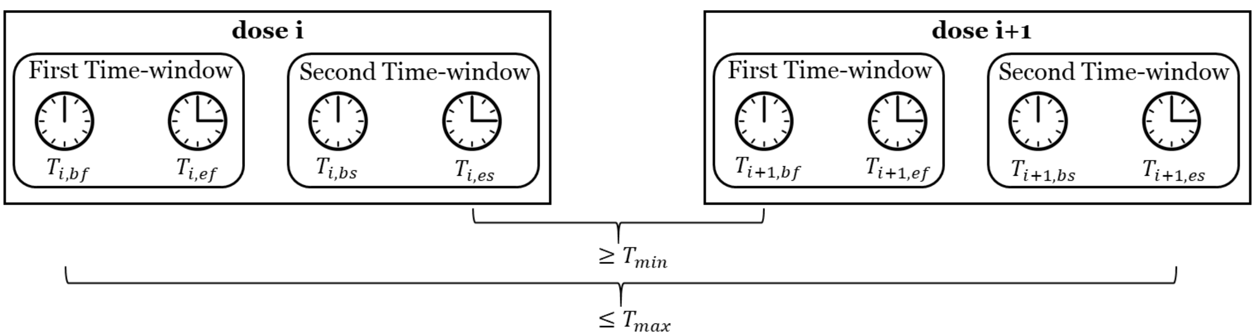

Figure 2. Illustration of Time-windows Design

Initial Evaluation of Negative Reinforcement

In the original design, NR would only be implemented when the system calculates the patient's MAR drops below the expected MAR because he/she skipped the most recent dose. However, in real life, the patient would miss several consecutive doses without decreasing MAR to lower than MAR goal. For example, if the patient's MAR goal is 80%, he/she could miss the last three consecutive doses without receiving NR within a total of fifteen doses as long as he/she takes all other twelve doses. We should also prevent this consecutive-missed-doses case by utilizing NR. Thus, we extend the design of negative reinforcement implementation to cover two conditions: first, the patient's MAR drops below expected MAR for medication to be effective in treatment; second, the patient has missed a certain number of doses consecutively. The maximum number of possible consecutive-missed-doses should be decided by a healthcare professional.

We use analytical modeling to model these two conditions and provide the evaluation based on our model.

Modeling

We assume the two conditions are independent of each other. To model the occurrence probability of the first condition, we realize it is the opposite situation of the patient always taking at least $\lceil R_{ex}N_P \rceil$ doses within a total of N_P doses, R_{ex} is the expected MAR. Based on Liu and Varshney (2017), The probability that a patient has MAR equal or higher than expected MAR with reminders and positive reinforcement is

$$P_{withR} = \sum_{N_{st}=1}^{N_P} \left(\frac{\prod_{i=0}^{N_P} i * P_{st}^{N_{st}}(1-P_{st})^{N_P-N_{st}}}{\prod_{i=1}^{N_{st}} i * \prod_{i=1}^{N_P-N_{st}} i} \right) * \sum_{N_{nd}=max(\lceil R_{ex}N_P \rceil - N_{st},1)}^{N_P-N_{st}} \left(\frac{\prod_{i=1}^{N_P-N_{st}} i * P_{nd}^{N_{nd}}(1-P_{nd})^{N_P-N_{st}-N_{nd}}}{\prod_{i=1}^{N_{nd}} i * \prod_{i=1}^{N_P-N_{st}-N_{nd}} i} \right) \quad (3)$$

where P_{st} is the probability that the patient takes the dose during the first time-window, and P_{nd} is the probability that the patient takes the dose during the second time window. N_{st} is the number of doses the patient takes during the first time-windows over the observed period, and N_{nd} is the number of doses the patient takes during the second time-windows over the observed period. We have the probability of implementing NR under the first condition as

$$P_{NR1} = 1 - P_{withR} \quad (4)$$

Following Feller's (Feller 1968) study about consecutive missing trials, the probability of the patient receives NR under the second condition can be expressed as:

$$P_{NR2} \sim 1 - \frac{1-P_R x}{(N_m+1-N_m x)q} * \frac{1}{x^{N_P+1}} \quad (5)$$

where N_m is the number of consecutive-missed-doses, P_R is the overall probability that a patient takes one dose through two time-windows,

$$P_R = P_{st} + (1-P_{st}) * P_{nd} \quad (6)$$

and $q = 1 - P_R$, x is the root near 1 of

$$1 - x + qP_R{}^{N_m}x^{N_m+1} = 0 \quad (7)$$

Evaluation and Results

We apply a real-life condition considering a prescription for one month (30 days) with three doses/day to evaluate the two conditions of NR implementation.

If the system implements NR when the patient's MAR drops below expected MAR, the implementation probability is shown in Figure 3. With the different level of expected MAR varying from 0.8 to 0.95, the patient needs to always keep a high P_R, the overall probability of taking a dose through two time-windows with rewards attached, to avoid receiving NR. For example, if the expected MAR is 0.8, the patient should have at least P_R = 0.8 to reduce his/her probability of being disconnected with the favorite mobile App to less than 45%.

If the system implements NR when the patient misses several consecutive doses, the implementation probability is shown in Figure 4. With different tolerance of consecutive-missed-doses, the probability of the patient receiving NR has significant variation. For example, comparing a tolerance of two consecutive-missed-doses with a tolerance of four consecutive-missed-doses, the patient would have a much lower P_R, 0.37, in four-consecutive-missed cases to avoid being disconnected from the favorite App, than the needed P_R, 0.7, in the two-consecutive-missed cases.

From both NR implementation conditions, we observe that if the patient needs to avoid them, he/she should have a very high level of overall probability to take each medication dose, especially when the expected MAR is high, or the tolerance number of consecutive-missed-doses is small.

Conclusion and Future Research

In this emergent research, detailed design principles, analytical modeling, and evaluations based on a novel intervention utilizing two reminders and both positive and negative reinforcements are presented. We extend the original design and provide more applicable details to enrich the intervention aiming to improve medication adherence. Our initial analytical modeling and evaluation of negative reinforcement provide basic validation of its effectiveness in the intervention.

More models and validations should be conducted to complete this research. Broader scale evaluation on how the intervention could help patients' hospitalization savings, how the interplay of positive and negative reinforcements will increase the patient's medication adherence, and the validation of intervention based on different patient scenario types are in process.

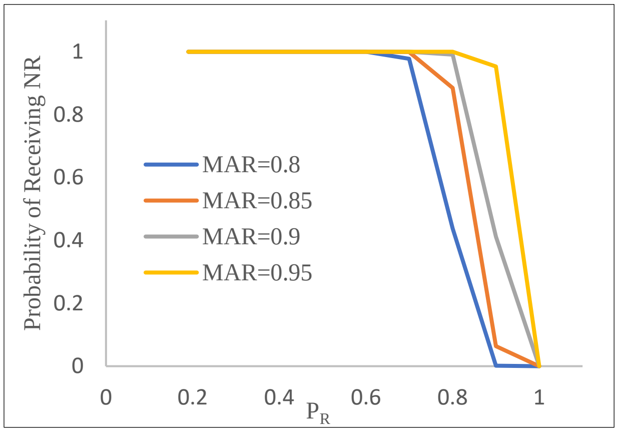

Figure 3. The Probability of Receiving NR due to MAR Lower than Expected

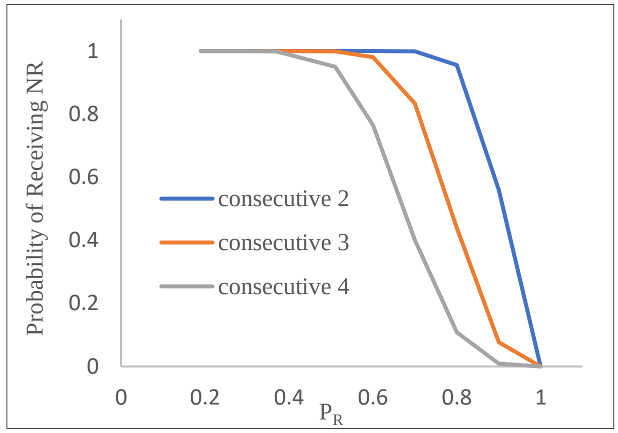

Figure 4. The Probability of Receiving NR due to Consecutive-Missed-Doses

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