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ABSTRACT:

Background: Medication compliance for patients with chronic diseases is still a hot issue to discuss. Low drug compliance contributes to treatment failure rates of up to 50%. Technologybased medicine reminder is starting to appear in the world community and is expected to be a solution to the problem of drug non-compliance. There is no comprehensive study related to the impact of this technology on patient drug compliance, so we need a special study to discuss this issue. Objective: The purpose of this study is to evaluate the effect of technology-based medicine reminders in improving patient drug compliance through systematic review and metaanalysis. Method: The collection of articles from a database related to technology-based medication reminders to increase compliance was carried out at 2010-2018 intervals. Google Scholar and two electronic databases, i.e., PUBMED and Science Direct, were used. After the articles were collected, the next step was the selection of eligible manuscripts, study quality assessment, data extraction, synthesis, and pooled analysis. Result: A total of 12 articles were analyzed and found that a technology-based medication reminder was able to influence patient medication compliance significantly. Pooled analysis result of risk ratio (RR) = 1.08 (CI95% 1.03-1.14) and mean difference (MD) = 0.70 (CI95% 0.65-0.75). Conclusion: Technology-based medication reminder is needed to deal with outpatients returning home with drugs to minimize therapeutic failure due to drug non-compliance.

Keywords: Chronic Disease, Compliance, Medicine Reminder, Outpatients, Technology

1. INTRODUCTION

Compliance with drug therapy in patients becomes an interesting issue to discuss in the world. Because by 30-50% of adult patients in the world who are undergoing treatment with outpatient medicine tend to have a low level of compliance. [1,2] Drug compliance is a patient's attitude in following the doctor's or pharmacist's recommendations regarding the use of the drug given to them. [2] Non-compliance of patients in drug therapy is one of the factors causing treatment failure, where the condition will indirectly have an impact on increasing treatment costs if left unchecked. [3]

The development of science and technology in the digital era is beneficial to people's lives. This rapid technological progress can help health workers in improving health services. [3–5] The problem of drug non-compliance in patients could be helped by technology, for example, technological assistance as a reminder to take medication. [6] Several studies have shown that the presence of medication reminder technology such as automatic SMS (short message service), application-based medicine reminder on smartphones, automated cellular phone calls, etc. has the potential to increase therapy compliance. [7–9] However, several studies also stated that the use of medication reminder technology is not very effective in improving patient compliance, and even tends to interfere with patient comfort in carrying out therapy. [10–12]

Until now, there has been no holistic analysis of the strengths and weaknesses of medication reminder tectory and how strong they can improve patient compliance with drug therapy. Therefore, a systematic review and meta-analysis are needed to investigate how much influence the medication reminder technology can have on improving compliance. The results of this study are expected to be able to contribute information to medical staff in determining strategies in enhancing patient medication compliance.

2. METHODS

This systematic review and meta-analysis investigated the effect of medication reminder technology on patients undergoing drug therapy on their compliance. The medication reminder technology referred to includes automatic SMS, automatic cellular calls, and application-based reminders on smartphones and other similar technologies.

a. Study identification

Google Scholar and two electronic databases, i.e., PUBMED (2010-2020) and Science Direct (2010-2020), were initially searched from September 2019 to April 2020. Search terms included 'Medication Reminder', 'Mediation SMS Reminder', 'Mediation Phone Call Reminder', 'Medication Application Reminder', 'Technology AND Compliance', and 'Medication Reminder AND Compliance'.

b. Eligibility criteria

The first step was the identification stage. The authors search for online related articles using predetermined keywords. The title and abstract of the original article were assessed by three independent reviewers. The second step was screening the abstracts of the materials obtained. This step was helped by using the ENDNOTE software that has been integrated with an electronic database. This process becomes convenient because the article selection process can be done online, referring to the keywords that have been inputted. Only abstracts that meet the specified eligibility criteria were downloaded to do the third stage, which is to determine the eligibility criteria. At the scene of determining eligibility criteria, the article will be assessed by reviewers regarding their eligibility with predetermined inclusion and

exclusion criteria. If there were differences in article eligibility opinions between reviewers, the problem was resolved through discussion until consensus was reached.

The inclusion criteria in this study were RCT study, utilizing zechnology as a patient reminder to take medication, the outcome focuses on compliance, patients in the study were followed up, and patients in the study use outpatient medicines for a minimum of three days. If the article meets all the inclusion criteria, but in the review process, it is found that the compliance outcome is not clearly reported, then the article will be excluded.

c. Study Quality Assessment

Study quality seessment was carried out using Cochrane bias criteria. The criteria were consisting of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias found during the review process. The results of the study quality assessment were presented in a chart containing a compilation of bias percentages for all studies. [13]

d. Data extraction and synthesis

Data extraction was carried out by three independent reviewers, along with the author. Data were extracted into categories: author/year, setting (country), study design, target population, a form of intervention, follow-up duration, compliance measure, study result, and recommendation. All reviewers each extracted 12 selected articles, then the author compiles the data and complements the extracted data. Disagreement on the extracted data was resolved by discussion between the author and the reviewer through an open meeting discussion.

e. Statistical Analysis

Data analysis was performed for drug therapy compliance outcomes in patients who received technology-based medicine reminder interventions. Pooled analysis from Cochrane was used with the Risk Ratio (RR) and Mean Difference (MD) parameters. The risk ratio was used if the outcome in the article was the rate of compliance versus non-compliance in the intervention and usual care group. The natural difference was used if the outcome in the study was a difference between compliance in the intervention and usual care group. The confidence interval used was 95%. All analyzes were assisted with Review Manager tware version 5.3.

f. Role of the Funding Source

There was no specific funding for writing this article. We were not affiliated with any party, so the research and results report was purely independent without outside intervention.

3. RESULT

Study search results

The stages of tracing the study following the PRISMA guidelines are presented in Figure 1. In the period September 2019 to March 2020, 249 abstract articles were such sfully identified as candidates who will go through the review process. A total of 229 abstract articles were excluded because they did not fit the study criteria, medication reminder interventions were not based on technology, did not focus on compliance, and abstract articles took the form of duplication. Nineteen article titles were downloaded in full text to go through the eligibility criteria assessment. Seven articles did not clearly describe the measured outcome and follow up of patients less than three days, so as many as 12 articles received eligibility agreements for further analysis.

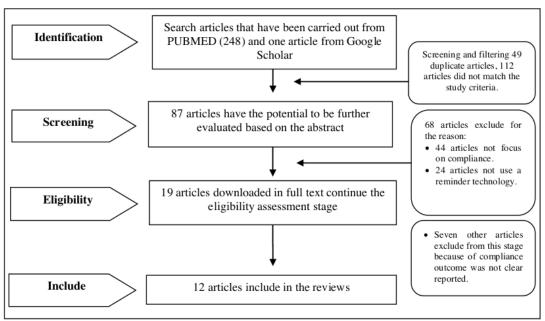


Figure 1. PRISMA diagram of the article selection process

Study Quality Assessment

Study quality assessments were carried out to provide an overview of the research bias in the articles used in the analysis. Bias criteria used the Cochrane study quality assessment. The smaller risk of bias in an article, the better the quality of the article. Twelve articles that have entered the eligibility criteria have passed the quality assessment stage with the results shown in Figure 2.

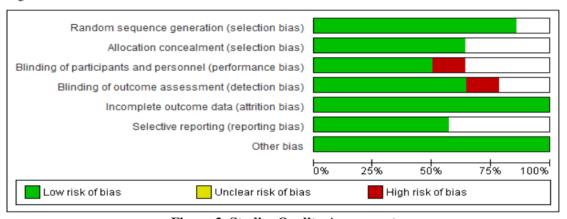


Figure 2. Studies Quality Assessment

Based on studies included in the quality assessment procedure, all the bias criteria at 10 igher / equal to 50%. The bias criteria that were difficult to fulfill in these studies were allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Five

studies have prepared a complete RCT design protocol separate from the main article. Such studies were expected because of the minimum bias that will occur.

Studies characte 22 tics

All articles used in the systematic review and meta-analysis were RCTs from the year 2010-2018. Articles included in the study came from several countries such as Denmark^[14], USA ^[11,15,16], Netherland^[17], Texas^[18], Ghana^[8], Pakistan^[19], Africa^[12], Chile^[7], Uganda^[10], and Indonesia.^[9] Patients intervention settings were in the hospital and community. Patients who were intervened with medication reminder technology were patients diagnosed with asthma, infections (bacteria/viruses/parasite), diabetes mellitus, schizophrenia, post-stroke, neuropathy and hypertension. The total number of subjects analyzed being 2409 patients, all ages from 0 to > 65 years. The shortest duration of follow-up was seven days, and the longest was six months. The outcome measured in this study was medication compliance, either by using pill count techniques, questionnaires, direct observation, scoring, and so forth. A detailed description of the characteristics of the articles in this study can be seen in Table 1.

General Description of medication reminder to improve compliance

Medication compliance referred to in this study, is the condition of the patient to follow instructions or medical advice, especially in patients who get their medicine to home. Drug compliance in a definition that they understand the condition of the disease so that they will always be obedient to therapy (adherence) was not evaluated. This study was limited to the extent to which patients are able to follow instructions given by medical personnel about the drugs they bring home. The outcome observed in this meta-analysis is just where the effect of technology-based medication reminder interventions is compared with usual care on drug compliance according to the definition describe above.

Outcome Evaluation

a. Review of included studies

Seven from twelve studies illustrate that technology-based medication reminder interventions can improve compliance with drug therapy in outpatients. [7-9,14,18,16,19] From the results of this study there were several important findings: (1) this intervention is needed for patients who have a low level of compliance with drug therapy and chronic diseases; (2) need to develop the optimum technology-based reminder according to patient characteristics especially in geriatric because they need assistants to understand the technology.

While five other studies illustrate that these interventions do not help in increasing compliance to take medication for patients. [10–12,15,17] Medication reminder lacks an effect in increasing drug compliance in patients receiving short-term therapy (only up to 7 days), patients who have good knowledge of their illness (good adherence), and forms of technology-based drug reminder trigger patient discomfort due to the annoying reminder. Detailed substances related to these studies can be seen in Table 1.

To see how strong the effect of the technology-based medicine reminder intervention is, a pooled analysis was conducted for these studies. There was one study that cannot be analyzed because it does not display numerical data (both risk ratio [RR], mean difference [MD], and other numerical data) so that only 11 articles that go through a pooled analysis. The analysis was divided into two parameters consisting of risk ratio (RR) and mean difference (MD).

Tabel 1. Data Extraction

No.	Author / Year	Setting (country)	Study	Target population	Form of intervention	Follow up duration	Compliance measure	Result	Recommendation
	Stranbygaard U. et al. 2010	Copenhagen, Denmark.	RCT, n=26; CG=14; IG=12.	Adults age range 18-45 years with asthma.	SMS reminder daily every 10 am VS usual care (no SMS).	3 month	Compliance by pill count.	CG 4 weeks to CG 12 weeks decrease 14.2% from 84.2% to 70.1% (10/14); IG 4 weeks to CG 12 weeks increase 3.6% from 77.9% to 81.5% Difference between 2 group (4-12 weeks) 17.8%, p= 0.019 sig.	SMS reminder found useful to improve compliance treatment in asthma. It needs to apply this method across a larger spectrum of chronic diseases.
2	Suffoletto B. et al. 2012	Pennsylvania, USA.	RCT, n=144; CG=72; IG=72.	Adults age ≥ 18 years, who got oral antibiotics.	SMS reminder once daily VS usual care.	7 days each subject	Compliance by pill count.	CG= 45% (32/72); IG= 57% (41/72). p = 0.16 NS.	Medicine reminder is not needed for short- term use of drugs.
8	Vervloet M. et al. 2012	Netherland.	RCT, n=104; CG=48; IG=56.	Adults age with type 2 diabetes mellitus (age mean 55 years).	SMS reminder once daily VS usual care.	6 month	Compliance by no days without dosing (NDWD) and no missed doses (NMD).	CG DWD = 86.2% (41/48), IG NDWD = 88.1% (49/56), p= 0.283 NS. CG MD =80.8% (39/48), IG NMD= 85.5% (48/56), p= 0.065 NS.	Concentrate on patients with suboptimal levels of compliance
4	Velligan D. et al. 2013	San Antonio, Texas.	RCT, n= 91; TAU=45; MM=46.	Adults age 18- 60 years with schizophrenia.	Med e-Monitor (M.M): e- prescribing, medicine, and phone reminder compare to TAU (Treatment As Usual).	3 month	Compliance by pill count.	Compliance CG (TAU) = 73% (33/45); IG (MM) = 90% (41/46) p < 0.05 Sig.	The use of electronic devices helps improve compliance significantly.
S	Mbuagbaw et al, 2012	Canada, USA.	RCT, n=200, CG=99; IG=101.	Adults age >21 years with HIV positive.	SMS reminder VS Usual Care.	6 month	Compliance by self report no missed doses (NMD).	No Missed Dose: CG= 79% (78/99); IG= 79.2% (80/101), RR= 1.01 (CI95% 0.87-1.16) NS.	The standardized motivational mobile phone text message did not significantly improve compliance. Other types of term studies are recommended.
9	Raifman. et al. 2014	Tamale, Ghana.	RCT, n= 1140; CG=554; I.G.: Short	All population (0 - >60 year), outpatients antimalarial	Short SMS reminder, Long SMS reminder, Usual care	Not clear reported (minimum after 66-	Compliance by pill count.	CG= 61.5% (341/554); Short SMS= 66.4% (151/227); Long SMS = 64.1% (198/309). OR CG	Mobile phone text messages significantly improve compliance. Short SMS more

			SMS=277; I.G.: Long	treatment.	(without SMS reminder).	hour initial		vs Short SMS = 1.45 (CI95% 1.03-2.04) sig.	effective than long SMS.
			SMS=309.			visit).		OR CG vs Long SMS = 0.77 (CI95% 0.5-1.2) sig.	
	Kamal et al. 2015	Paki stan.	RCT, n =162; CG=79; IG=83.	Adults age >18 years with a post-stroke attack.	SMS reminder one daily VS usual care (non- SMS).	2 month	Compliance by MMAS questionnaire score.		Medicine reminders can improve compliance. It needs to develop an SMS reminder for another stroke outcome.
∞	Jhonsen et al. 2015	USA.	RCT, n =65, CG=29; IG=36.	Childrens age 12-17 years with asthma.	Text message program called MMH VS usual care.	7 Days	Compliance by an adolescent on controller score.	CG baseline (score) 5.17 to 3.83 (decrease 1.345 \pm 2.22). IG baseline 4.35 to 4.86 (increase 0.611 \pm 2.06). Difference between group, p= 0.011 sig.	MMH program can imp 9 e compliance, and further research is needed to identify and address barriers to adoption.
6	Steury. 2016	Zambia, Africa.	RCT, n=96; CG=46; IG=46.	Adults age range 36-50 years who got antimalarial antibiotics.	SMS reminder once daily VS usual care	They are Varies. Until the final dose of the drug was given.	Compliance by pill count.	CG= 68% (33/48); IG= 64.6% (31/48). p > 0.05 NS.	Need development a specific technology of mobile phone to improve drug compliance on patients with low levels of compliance
10	Varleta P. et al. 2017	Santiago, Chile.	RCT, n=291; CG=140; IG=151.	Adults age 30- 80 years with 1- 6 previous hypertensions	SMS reminder VS non-SMS (usual care)	6 month	Compliance by pill count.	CG = 51.4% (71/140); IG= 62.3% (94/151). RR = 1.3 (CI95% 1.0-1.6) sig.	SMS reminder must be given to patients with low compliance
Ξ	Himelhoch et al 2017	Uganda.	RCT, n=28, CG=9; IG=19.	Adults age 18- 64 years with HIV positive.	Heart2HAART program and smartphone (I.G.) VS smartphone alone (C.G.).	3 month	Compliance by pill count.	Participants showed excellent compliance to their medication regimen. There is no difference between IG. and CG. (p> 0.05).	Heart2HAART needs to be developed. All smartphones have an advantage in improving compliance.
12	Sutema et al. 2018	Bali, Indonesia.	RCT, n=62; CG=31; IG=31.	Geriatrics (>60 years) with diabetic neuropathic pain.	Medicine reminder application (IOS/ Android) in smartphone VS usual care.	1 month	Compliance by pill count.	Compliance CG= 41.94% (13/31); IG= 100% (31/31). p< 0.05 Sig. RR = 2.38 (CI95% 1.58-3.61)	Medicine reminders on a smartphone can improve compliance in geriatric patients. Geriatrics need assistance in applying smartphones.

b. Risk ratio (RR) of patient compliance with and without medicine reminder technology Based on 11 articles included in the analysis, 9 of them provided RR outcomes, and 2 of them had two compliance outcon so there were 11 data pooled in the analysis. A total of 2762 subjects were analyzed into the intervention group (1109) and the usual care group (1653).

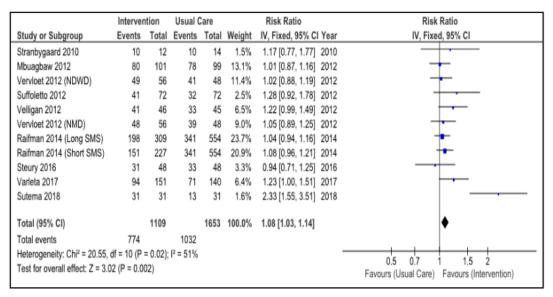


Figure 3. Pooled Analysis of Medication Compliance Risk Ratio in Patients at Intervention versus Usual Care Group

An intervention group is a group of patients who get drug information when dispensing by pharmacists and get a technology-based medicine reminder every day while the usual care group is a group that only gets drug information when pharmacists were dispensing drugs. Both groups were followed up within a certain time limit with the observed outcome was compliance with taking the medication. The outcome was determined using the pill count technique and no days without missing dose (direct observation or self-report).

The pooled analysis in Figure 3 shows the RR value of 1.08 with a 95% fidence interval 1.03-1.14. This data illustrates that the ratio of patient drug compliance in the intervention group was one time greater than that of the usu7 care group. The data in this analysis indicate that the risk of patients forgetting to use drugs in the intervention group is lower compared to the usual care group.

c. Mean difference reduction of patient compliance with and without medicine reminder technology

the analysis of the mean difference (MD) 2 studies provide data on the difference in improvement in medication compliance between the intervention group and the control group that we pooled using MD parameters. A total of 22 patients were evaluated for compliance with their medication, which was divided into 119 patients in the intervention group and 108 patients in the control group as shown in Figure 4. Similar results with the RR parameter (Figure 3) were obtained for the MD parameter (Figure 4) where the MD value of the pooled analysis result was obtained 0.70 with a 95% confidence interval 0.65-0.75.

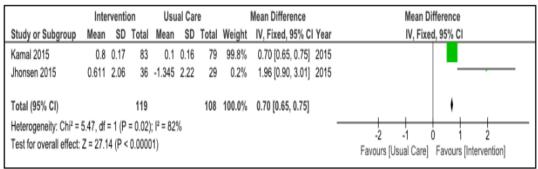


Figure 4. Pooled Analysis of Medication Compliance Mean Difference in Patients at Intervention versus Usual Care Group

This value illustrates that patients in the intervention group experienced an increase in medication compliance by 0.7 times greater than the usual care group significantly. This finding wad important because it provides information that interventions with a technology-based medication reminder can improve patient compliance with drugs in carrying out outpatient therapy. The results of all analyses in this research can provide recommendations for medical personnel, especially pharmacists who handle outpatients to provide interventions in the form of technology-based medicine reminders to patients during communication, information, education, and dispensing activities.

4. DISCUSSION

The development of science and technology brought very rapid changes to information systems. Currently, the information system used is more focused on computer-based information systems, including smartphone devices in it. [3,20,21] With the hope of using information technology or computer-based information systems, it can produce more accurate and quality information. Increasing community dependence on information systems, hardware, databases, and telecommunications), can be a good opportunity to improve the quality of life, especially in the health sector. [22,23]

The main thing that determines the success of patient therapy is the accuracy of diagnosis and drug therapy that has been planned by health workers. Medication compliance is one important factor that can support the success of the therapy. [21,22,24] Because if only the diagnosis and drug treatment are right, without the support of good compliance, the failure of therapy will occur, and this condition will be exacerbated by the difficulty of health workers to detect the failure factor of the therapy. Thus, the more compliance the patient will be treated, the potential for therapy failure will be further reduced. [21,22]

Overall studies analyzed, in essence, illustrate that technology-based medication reminder interventions have the potential to improve outpatient drug compliance. Studies assessing that medication reminder does not produce good outcomes were generally caused by techniques in the use of this technology that need to be developed, patient follow-up time was considered too short, and the number of subjects analyzed was too small. [7,9-12,15-17]

One study that observed the compliance of patients who received oral antibiotics at a one-week follow-up produced an insignificant outcome. This condition was thought to be due to patients awareness within one week of observation were still high for the infectious disease they suffered, plus signs and symptoms of pain felt by the patient still makes patients alert not

to leave the medicine. [23–25] Unlike the case with patients with chronic diseases without signs and symptoms, like diabetes, hypertension, dyslipidemia, and other chronic diseases that are silent killers. Patients who do not understand this chronic disease will tend to forget and leave the medication without a medication reminder system. Characteristics of these patients will only return to using drugs when bad complications come to them. [21–23]

Several studies with other meaningless outcomes provide an explanation that they need to redevelop an effective and efficient reminder method. [10,12,14-16,19] They do not state that reminder drugs are not important, but rather tend to change the method for the better. Frequency of reminder that is too often also causes the patient to be disturbed and resistant to the reminder given. [14-16,19]

The results of this study will be the basis for consideration of health workers who work in health care facilities to overcome non-compliance with drug therapy for patients currently undergoing therapy, especially outpatient. The recommendations made by researchers include: a technology-based reminder is recommended to be used for patients. This recommendation is given specifically to pharmacists when counseling, dispensing, or communicating, informing, educating in health facilities such as community pharmacies, clinical practice, or hospital pharmacy department. The use of technology-based medicine reminder is prioritized for patients undergoing long-term (chronic) therapy with a duration of drug use longer or equal to one-month such as hypertension, diabetes, tuberculosis infection, HIV infection, asthma, cardiovascular disease, schizophrenia and geriatric. [21–25]

This research certainly has some limitations. The limited access of researchers to paid databases as well as access to articles that researchers consider good but not open access is a limitation of researchers 19 this study. Even with all the limitations, it is possible to provide a picture to practitioners in the health care system to consider the use of smart medicine reminders in the world of health in the future.

5. CONCLUSION

Technology-based medicine reminders can improve patient compliance with drugs. Therefore health workers such as doctors, pharmacists, nurses, and other health workers are highly recommended to provide these services, especially in patients who bring drugs home for therapy for more than one month.

18BREVIATIONS USED

IG= intervention group; CG= Control Group; RCT= Randomize Control Trial; DWD= Days without Dosing; NMD= No Missed Dose; NDWD= No Days Without Dosing; SMS= Short Messages Service; OR= Odd Ratio; RR= Risk Ratio; MD= Mean Difference; TAU= Treatment as Usual; M.M = Medication e-Monitor; n = subjects; MMAS= Morisky Medication Adherence Scale; MMH= My Medi Health (medicine reminder program); 95%CI= 95% Confidence Interval; NS= Not Significant; sig.= Significant; vs = versus.

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