Physical Medicine and Rehabilitation - International

Open Access

Austin Publishing Group

Research Article

Effects of an Ehealth Intervention, SHINE, on Therapy Adherence in Chronic Myeloid Leukemia Patients: A Pre-test/Post-test Intervention Study

JAJ (Koos) Ris BBA[1,2]*, Jeroen JWM Janssen[3] and Jacqueline G Hugtenburg[2]

[1]SHINE Health, Voorburg, The Netherlands

[2]Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Location VUMC, Amsterdam, The Netherlands

[3]Department of Hematology, Amsterdam UMC, Location VUMC, Amsterdam, The Netherlands

***Corresponding author:** JAJ (Koos) Ris, Department of Clinical Pharmacology and Pharmacy, Amsterdam UMC, Location VUMC, Amsterdam, The Netherlands

Received: May 14, 2022; **Accepted:** June 18, 2022; **Published:** June 25, 2022

Abstract

Background: Chronic myeloid leukemia (CML) is a malignant hematological disorder, which can be effectively treated with tyrosine kinase inhibitors. Non-adherence has been associated with disease progression. To remedy this, an innovative eHealth intervention, SHINE, has been developed: a personalized program built as smart phone application (app). By using the app, CML patients are supported in dealing with everyday life issues.

Aim: This study aimed to investigate the effects of the SHINE app on medication adherence and quality of life (QoL) of CML patients.

Ethics Approval: The studies involving human participants were reviewed and approved by Medisch Ethische Toetsingscommissie (METC) Amsterdam UMC on 21 September 2016, number 2016.405.

Methods: This pre-test/post-test intervention study included CML patients that used during a three-month pre-test period an electronic medicine box (MEMS) and otherwise received usual care. During the three months post-test period the SHINE app was also used. Functionalities of the app include: information presented as a chat, a medication overview, a reminder service. Adherence was measured with MEMS and MARS. Quality of life was measured with EORTC-QLQ-C30.

Results: 14 patients completed the trial out of 67 registered patients. Medication adherence increased after the SHINE app was introduced from 83.4%±18.8% before to 96.9%±4.2% (P< 0.009) measured with MEMS and from 38.5% to 84.6% (P < 0.031) measured with MARS. Quality of life was not influenced.

Conclusion: The SHINE app is a promising medication adherence support tool. Further research is needed to reduce attrition rates and to validate the effects of the intervention on long term medication adherence.

Impact of Findings on Practice:

- This study showed that the innovative electronic smartphone application SHINE in combination with an electronic medication box considerably increased medication adherence in CML patients
- Of the hundreds of apps aiming to improve medication adherence available, less than a dozen apps have a sound evidence base for efficacy. Adding one study, one app to this is significant.

Introduction

Chronic myeloid leukemia (CML)

CML is a malignant hematological disorder, characterized by a vast accumulation of leukemic white blood cells in blood, bone marrow and spleen. The disease is caused by a reciprocal translocation between the long arms of chromosome 9 and 22, resulting in an abnormally short chromosome 22, known as the Philadelphia chromosome. This translocation juxtaposes the BCR- and the ABL gene, leading to a fusion gene named BCR-ABL. The BCR-ABL fusion protein that is encoded by this abnormality leads to the clinical picture of CML. The disease is fatal if left untreated or when treated inadequately. Treatment with tyrosine kinase inhibitors (TKI) like imatinib, nilotinib or dasatinib however, results in deep molecular remissions in the majority of patients. These patients enjoy a near-normal life span [1].

Medication non-adherence in CML

Studies indicate that 25-35% of CML patients do not take their medication according to prescription [2]. Patients who take less than 90% of the prescribed dose of imatinib ("optimum adherence level") have a substantially higher risk of disease progression to more advanced phase and will almost never reach deep molecular remissions that make stopping feasible [3].

Citation: JAJ (Koos) Ris BBA, Jeroen JWM Janssen and Jacqueline G Hugtenburg. Effects of an Ehealth Intervention, SHINE, on Therapy Adherence in Chronic Myeloid Leukemia Patients: A Pre-test/Post-test Intervention Study. Phys Med Rehabil Int. 2022; 9(1): 1199.

Medication non-adherence is a widespread problem [4], with on average 50% of patients not adhering to their therapy, which leads to poorer treatment outcome and higher health care costs [5-11].

More than 200 variables have been identified influencing medication adherence. Reasons for poor adherence may be patient-related, such as hindering beliefs [12] and personality traits [13]; they may be external [14], such as work-related demands; they may concern the relationship with the health care professional [15]; as well as related to the the regimen prescribed.

Medication non-adherence can be intentional or unintentional [16]. Unintentionally failing to adhere is not the result of a cognitive decision, but of forgetfulness or physical barriers [17]. Intentionally failing to adhere is, if only temporarily, an active, cognitive and explicit decision [18]. For instance, patients report having trouble adhering to their prescription during social activities [19].

Both from the perspective of the patient as well as from a societal perspective, adherence enhancement is urgently needed. However, improving health behavior - including the intake of medicines - is difficult to achieve, both for patients and for health care professionals. Currently, health care professionals try to improve medication adherence among CML patients by improving knowledge through patient education, thereby attempting to convince them that using medication according to the prescription is necessary for their health. They subsequently hope this is enough to improve medication adherence. In reality, the results of this approach are very disappointing [20,21]. Patients are left to solve this by themselves, and solutions for this problem are urgently needed.

To help overcome this problem and with the aim of (1) providing patients with support and (2) providing health care professionals with an effective and efficient tool to support patients, an innovative eHealth intervention called SHINE (not an acronym) was developed. SHINE is a personalized program built as a smartphone application ("app").

The app was described to patients ("positioned") as a support tool to deal with everyday issues in the life of a CML patient. The app was connected with an electronic pillbox in order to record medication intake.

The aim of this study was to investigate the effects of the SHINE app on medication adherence of CML patients to their treatment with TKIs and on their overall quality of life.

Methods and Materials

Study Design

A six months pretest-posttest intervention study was performed including patients with CML treated with a TKI in the period September 2018 to July 2019. Over a three-month pretest period patients used an electronic medicine box to monitor medication intake, but received usual care. Subsequently, in a three months posttest phase patients used the SHINE Smartphone application in combination with the electronic medicine box.

Both at the end of the pre-test and the post-test period patients were asked to complete a questionnaire including the Medication Adherence Report Scale (MARS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C 30 (EORTC-QLQ-C30) supplemented with the CML-specific EORTC QLQ-CML24, and several questions on side effects.

The study was approved by the medical ethics committee of the Amsterdam UMC, location VUmc.

The SHINE Intervention

The SHINE intervention is a personalized e-health program aiming to make life for people with CML and using TKI's easier. It consists of two separate, but connected components: an electronic medicine box (MEMS) and a smartphone app.

The electronic medicine box, battery powered, is connected with the SHINE app through Bluetooth technology. The medicine box records the opening and closing of the lid, which is considered to be equivalent with the intake of a TKI.

Participants could choose between a smaller pill box (15mm x 66mm x 35mm) able to contain three TKI pills and a larger version with a four compartments (22mm x 100mm x 76mm) able to contain a week's supply of CML medication. Both versions had identical functionality: recording of the medicine intake and connection to the smartphone app.

Through the Bluetooth connection of the he electronic medicine box medicine intake data are transferred to the app. The app contains a multitude of functionalities, amongst which:

- A medication intake overview utilizing the data transferred from the electronic medicine box.
- A chat bot delivering information, tips and tricks on a variety of issues related to life with CML.
- An FAQ section with the information of the prescribed TKI's standard patient package inserts reshuffled and presented in a novel way. Allowing patients in this way easier access to the information.
- "Smart" reminders, notifications only reminding patients to take their medicines in case they had not done so.
- Other functionalities included options to log side effects and blood values.
- The program was designed to positively approach dealing with all kinds of issues of life with CML. The development process entailed literature research, 10 semi-structured telephone interviews and a questionnaire (n=164), after which the app was created. This process is not the subject of this article.

Patient Recruitment

Patients with CML older than 18 years treated with TKI were selected using the pharmacy information system of the outpatient pharmacy of the Amsterdam UMC, location VUmc. Patients were asked to participate in the study by means of a letter. Patients were also notified to the study by the hematologists of the Amsterdam UMC, location VUmc during consultations and through a news post on the website of the patient advocacy group Hematon. In the letter, during the consultations and on the Hematon website patients were given information on the study and asked to participate in it. Those wishing to participate could register for the study by following a link

to a VUmc registration website where they could register for the study. Upon registration patients were asked to submit their email address, give informed consent, provide information about their smartphone and mobile operating system, and were asked which TKI they had been prescribed. They could also choose between the two sizes of available medicine boxes.

CML patients with incompatible smartphones or those who had discontinued TKI treatment were excluded. All others who submitted all information were included.

Participating patients were sent a welcome letter by mail. This letter also contained the chosen electronic medicine box; instructions how to download the app; log in with a unique, personal activation code; and a manual on connecting the electronic medicine box to the smartphone and app. Support by email and by telephone was available.

Measurements

Adherence was measured using the electronic medicine box, a Medication Event Monitoring System (MEMS) device. Adherence was also measured by means of the questionnaire Medication Adherence Report Scale (MARS-5) [22]. Quality of life was measured with the EORTC-QLQ-C30 [23] aswell aswith EORTC QLQ-CML24 [24], illness perceptions with the Brief IPQ [25] and beliefs about medicines with the BMQ specific [26]. In addition, questions about side effects were asked.

Data Analysis

Medication adherence was calculated as the number of tablets taken divided by the number of prescribed tablets and expressed as a percentage.

An adherence rate of 90% or higher in CML is correlated with a very low chance of disease progression and a much higher chance of attaining deep molecular remission. In the present study "optimal adherence" was introduced, defined as taking at least 90% of the prescribed TKI dose.

A paired sample t-test was used to assess the difference over time in medication adherence as measured with MEMS, expressed as the percentage of prescribed tablets that were consumed. The difference in medication adherence assessed with the MARS questionnaire between the pre- and post-testperiod was analyzed using a McNemar test. Only patients with a MARS-score of 25 were considered to be medication adherent. The change in quality of life score was analyzed with a Wilcoxon signed rank test. Continuous data were checked on normality using QQ-plots. Results were considered to be statistically significant when a p-value was below 0.05. All data was analyzed using SPSS IBM statistics (version 26).

Results

Participation

147 patients started the registration for the study. Of these patients, 67 completed the registration and started the pre-test period. Table 1 shows the demographic characteristics of the participating patients and their treatment characteristics. Of the 67 patients who started the pre/test period 12 did not initiate to use the electronic medicine box nor did they download the app. Due to connection problems, the medication adherence data of 28 patients were not properly collected.

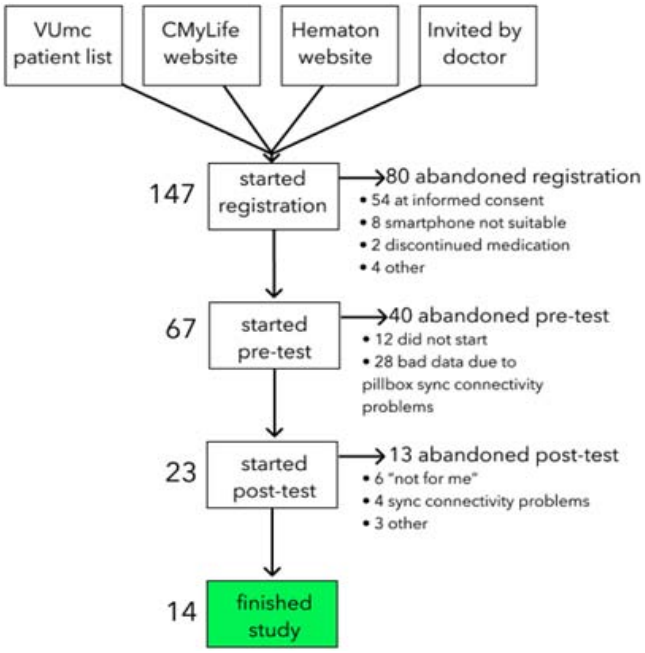

Figure 1: Participation and attrition.

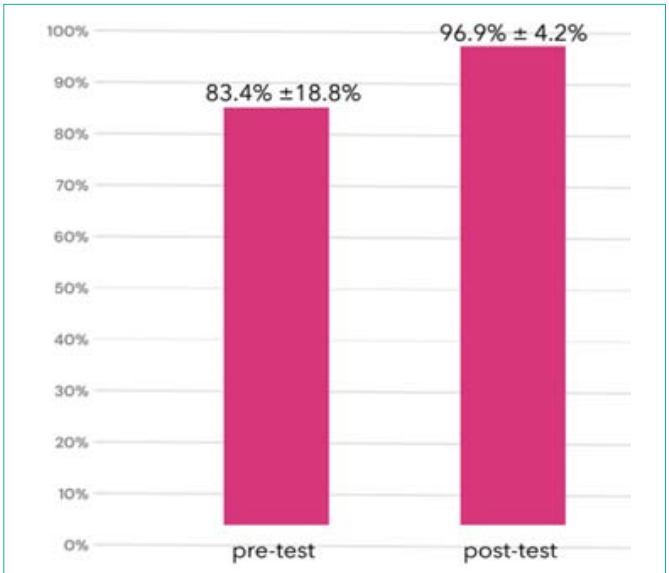

Figure 2: Medication Adherence (MEMS) (percentage of medication taken, p=0.009)

The remaining 23 entered the post-test phase of the study. Of these, 14 patients completed the study. Figure 1 describes participation and attrition.

Some patients experienced difficulty in connecting the app and the medicine box. Others indicated the features of the medicine boxes were inconvenient for them.

Medication adherence

Mean medication adherence as measured by the MEMS was 83.4% before and 96.9% after the SHINE app was introduced, using the paired Samples t-test, as shown in Table 2.

Table 1: Patient characteristics (n=14).

Patient demographics (number of patients)	
Age category	
< 60 years	8
≥ 60 years	6
Male gender	9
Higher education	6
Household, Single	1
Employed	9
Treatment characteristics (number of patients)	
Medication prescribed	
Imatinib	7
Nilotinib	3
Dasatinib	4
Current medication is first line prescription, number of patients	9
History of TKI use	
< 1 year	0
1-2 years	6
2-4 years	8

Table 2: Medication adherence (n=14).

Measurement method	PRE-test	POST-test	p-value
	Median IQR	Median IQR	
MEMS	83.4% (SD±18.8)	96.6% (SD±4.1)	0.009
MARS	38.5%	84.6%	0.031

Table 3: Feedback on features.

Feature	Average score	SD
App		
Useful information	77	22
Clear logs	79	20
Convenient smart reminder	71	32
Pleasant chats	75	29
Medicine box		
Too big	56	31
Convenient	77	37
Overall study		
Enjoyable	84	17

During the pre-test period, 38.5% (n=5) of the patients were adherent to their medication therapy according to the MARS questionnaire. This increased to 84.6% (n=11) during the post-test period (p=0.031, OR = 1.33 [95% CI 0.89-1.99], n=13) using the McNemar test, also shown in Table 2.

Optimal medication adherence (adherence of over 90%) as measured by MEMS rose considerably, from 50 to 93%, as shown in Figure 2.

Quality of Life

Mean Quality of Life as measured in the QoL Questionnaire was 5.0 after the pretest (4.8; 6.0), rising to 6.0 (5.0; 6.0) after the SHINE intervention, showing a P of 0.366 using the Wilcoxon Signed Rank test.

App experience

On average, participants rated the use of the app and the medicine box as enjoyable, as detailed in Table 3.

Discussion

Statement of Key Findings

This study shows that the innovative electronic smartphone application SHINE in combination with an electronic medication box considerably increases medication adherence in CML patients. These results are in line with other studies showing that advanced eHealth apps can improve adherence [27-29]. Of the hundreds of apps aiming to improve medication adherence available, less than a dozen have a sound evidence base for efficacy [30,31]. Adding one study, one app to this is significant.

As most patients' adherence improved quickly, the smart reminder or the medication intake overview appeared to work for them. "Context-aware" reminders, such as SHINE's smart reminder, outperform regular reminders [32]. Adherence improvement for others took longer, suggesting that the information provided in the chatbot was useful. However, as a detailed process evaluation was not executed, it is unclear which element of the SHINE app or which deployed behavior change strategies mediated the observed improvement in medication adherence.

To our knowledge, there is little evidence available which strategies - if any - applied in apps improves medication adherence [33].

Strategies commonly deployed to improve medication adherence are reminders, education and behavior strategies [30].

As the SHINE app deploys all three of these strategies, the combination of these strategies likely led to the improved medication adherence.

In next studies it should be investigated from which elements of the app contributed most to the improved adherence.

Effective eHealth interventions can complement – support – currently use "offline" interventions to improve medication adherence, such as education [34], motivational interviewing [35] and pharmacist-led multidisciplinary interventions [36], as they can be helpful to reduce labor and thus costs.

The use of the SHINE app also resulted in a small increase in quality of life. Patients reported their physical and emotional functioning improved and to feel more in control over their disease, while the perceived influence of the disease on daily life decreased. The app provides detailed information about side effects and ways how to manage them. This may have resulted in an improvement in physical quality of life. On the other hand, social functioning decreased. This might be explained by the greater focus on the disease during the study, which may be stressful for patients, thereby affecting social functioning.

Dropout from the study was considerable. There are a number

of possible reasons for the high attrition. Firstly, the inclusion procedures may have been too complicated for several patients, as reflected by the large numbers of patients who did not complete the registration with the study. Secondly, participating in both the pre-test and the post-test requires the patients being dedicated to the study for a considerable time-period; and thirdly, also the use of both the MEMs device and the app seemed too much work for many patients. Fourthly, although testing an innovative app such as the SHINE app seems attractive to many CML patients, complying with the requirements of the study procedures, such as six months use of an electronic medicine box or other requirements of our study proved less attractive. Fifthly, apps and electronic medicine boxes are not useful for everyone, not everyone is "smartphone literate". While some participants were very quick to resolve connection problems, others simply could not overcome them, even with support by telephone.

Attrition rates reported in other studies vary widely, from none to over 75% [37,38]. Little research is available on factors behind attrition [39]. Patient reported reasons for attrition include technical problems, time constraints, feeling fine and failing to meet patients' needs [40]. More generally, evaluation by patients of the intervention – its relevance – will influence their resolve (motivation) to continue its use. The need for an intervention may increase with the intensity of the disease and/or treatment. The perceived usefulness of the intervention's function, such as communication with the HCP or remembering to take medicines, varies between functions and between patients. Poorly designed interventions (with a lower ease of use, usability, attractiveness, ease of understanding [41] will hamper participation. Apps connecting to devices (such as blood pressure monitors, electronic scales or electronic pill boxes) potentially increasing attrition due to technical difficulties. Similarly, study design influences attrition: longer studies, more frequent intervention use required the absence of active live support, all potentially negatively influence attrition.

Measures to effectively reduce attrition will depend on the observed reasons for it and may include the use of empathy and social dialogue [42] as well as reminders [43].

Study Limitations

The low number of patients that completed the study is a major limitation. However, half of these patients were non-adherent, and despite the high attrition rate we were able to demonstrate positive effects of the app on medication adherence. A strength of the study is that medication adherence was measured with both an objective and a subjective measure. This provides more detailed insight into the effects of the SHINE app on medication adherence. While the study had a duration of six months with the intervention lasting three months, the study provides no insight in the effects of the SHINE intervention on the longer term. A longer test period would entail a serious extra effort in creating additional content and functionality, as the intervention needs to stay attractive over a longer period of time in order to keep attrition rates as low as possible.

Conclusions

Interpretations

The positive effect of the SHINE app on medication adherence is promising. Healthcare providers may advise their patients to use apps like the SHINE app to CML patients, in addition to their regular educational efforts of promoting adherence, in particular with non-adherent patients.

Further Research

As treatment of CML with TKI medication is mostly life long, the effects of the SHINE intervention in the longer terms needs to be investigated. Ways to improve attrition rates also need to be investigated.

These types of eHealth applications may also be useful in other areas of medicine, such as diabetes care and hypertension where low adherence rates are common.

Declarations

Funding

The development of the SHINE app and the purchase of the electronic medicine boxes was partly funded by an innovation fund ("Doorbraakfonds") by health care insurer CZ.

Example statements:

Disclosure

J.J.W.M. Janssen has received research funding from Novartis and BMS; has received speaker honoraria from Abbvie, Pfizer and Incyte; has served on advisory boards of Novartis, Abbvie and Pfizer. He is the President of the apps for CARE AND SCIENCE FOUNDATION which develops the Hematology App and which is supported by unrestricted grants from Abbvie, Astellas, Pfizer, Takeda, Roche, Novartis, Jazz, BMS, Olympus, Amgen, Daiichi-Sankyo and Servier.

J.A.J.Ris is the developer of the SHINE app.

Author contributions

JH developed the study protocol. JR drafted the manuscript, coordinated data collection, analyzed and interpreted the data, and reported the study results. JH and JJ interpreted the data and revised the manuscript. All authors read and approved the final manuscript.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Consent to Participate

The patients/participants provided their written informed consent to participate in this study.

Consent to Publish

The patients/participants provided their written informed consent to publish the data they provided in this study.

References

1. Kantarjian HM, Deisseroth A, Kurzrock R, Estrov Z, Talpaz M. Chronic myelogenous leukemia: a concise update. Blood. 1993; 82(3): 691-703. doi:10.1182/BLOOD.V82.3.691.BLOODJOURNAL823691.

2. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. Leukemia research. 2011; 35(5): 626-630. doi:10.1016/j.leukres.2010.10.017.

3. Marin D, Bazeos A, Mahon F, Eliasson L, Milojkovic D, Bua M, et al. Adherence

is the critical factor for achieving molecular responses in patients with chronic myeloid leukemia who achieve complete cytogenetic responses on imatinib. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010; 28(14): 2381-2388. doi:10.1200/JCO.2009.26.3087.

4. Burkhart PV, Sabaté E. Adherence to long-term therapies: evidence for action. Journal of nursing scholarship : an official publication of Sigma Theta Tau International Honor Society of Nursing. 2003; 35(3): 207-207. doi:10.1111/j.1547-5069.2003.tb00001.x.

5. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost. Medical Care. 2005; 43(6): 521-530. doi:10.1097/01.mlr.0000163641.86870.af.

6. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health affairs. 2011; 30(1): 91-99. doi:10.1377/hlthaff.2009.1087.

7. Dragomir A, Côté R, Roy L, Blais L, Lalonde L, Bérard A, et al. Impact of Adherence to Antihypertensive Agents on Clinical Outcomes and Hospitalization Costs. Medical Care. 2010; 48(5): 418-425. doi:10.1097/MLR.0b013e3181d567bd.

8. Faught RE, Weiner JR, Guérin A, Cunnington MC, Duh MS. Impact of nonadherence to antiepileptic drugs on health care utilization and costs: Findings from the RANSOM study. Epilepsia. 2009; 50(3): 501-509. doi:10.1111/j.1528-1167.2008.01794.x.

9. Esposito D, Bagchi AD, Verdier JM, Bencio DS, Kim MS. Medicaid beneficiaries with congestive heart failure: association of medication adherence with healthcare use and costs. The American journal of managed care. 2009; 15(7): 437-45.

10. Halpern R, Becker L, Iqbal SU, Kazis LE, Macarios D, Badamgarav E. The association of adherence to osteoporosis therapies with fracture, all-cause medical costs, and all-cause hospitalizations: a retrospective claims analysis of female health plan enrollees with osteoporosis. Journal of managed care pharmacy : JMCP. 2011; 17(1): 25-39. doi:10.18553/JMCP.2011.17.1.25.

11. Timmers L, Boons C, Hugtenburg J. Therapietrouw van groot belang bij orale oncolytica. Pharmaceutischweekblad. 2014; 149(45): 18-19.

12. Leventhal H, Meyer D, Nerenz D. The common sense model of illness danger. In: Rachman S. editor. Medical Psychology, ed. New York, NY: Pergamon; 1980. pp. 7–30.

13. Costa Jr. PR, Mccrae RR. Domains and facets : hierarchical personality assessment using the revised NEO Personality Inventory. J. Pers. Assess. 2010; 64(1): 21-50. doi: 10.1207/s15327752jpa6401_2.

14. Fishbein M, Yzer MC. Using theory to design effective health behavior interventions. Commun. Theory. 2003; 13(2): 164–183. doi: 10.1111/j.1468-2885.2003.tb00287.x.

15. Nunes V, Neilson J, O'Flynn N, et al. Clinical Guidelines and Evidence Review for Medicines Adherence: involving patients in decisions about prescribed medicines and supporting adherence. London, UK: National Collaborating Centre for Primary Care and Royal College of General Practitioners; 2009.

16. Vrijens B, Geest SD, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. British journal of clinical pharmacology. 2012; 73(5): 691-705. doi:10.1111/j.1365-2125.2012.04167.x.

17. Iihara N, Nishio T, Okura M, Anzai H, Kagawa M, Houchi H, et al. Comparing patient dissatisfaction and rational judgment in intentional medication non□adherence versus unintentional non□adherence. Journal of Clinical Pharmacy and Therapeutics. 2014; 39(1): 45-52. doi:10.1111/jcpt.12100.

18. Wroe A, Thomas M. Intentional and unintentional nonadherence in patients prescribed HAART treatment regimens. Psychology, Health & Medicine. 2003; 8(4) :453-463. doi:10.1080/1354850310001604595.

19. Boons CCLM, Harbers L, Timmers L, Jong JD, Swart EL, Hendrikse NH, et al. Needs for information and reasons for (non)adherence in chronic myeloid leukaemia: Be aware of social activities disturbing daily routines. European Journal of Haematology. 2018; 101(5): 643-653. doi:10.1111/ejh.13155.

20. World Health Organisation. Adherence to long-term therapies. World Health Organization, Geneva. 2003. ISBN 92 4 154599 2.

21. Breekveldt-Postma NS, Gerrits CMJM, Lammers JWJ, Raaijmakers JAM, Herings RMC. Persistence with inhaled corticosteroid therapy in daily practice. Respiratory medicine. 2004; 98(8): 752-759. doi:10.1016/J.RMED.2004.01.014.

22. Horne R, Weinman J. Self-regulation and self-management in asthma: Exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. Psychology & Health, 2002; 17(1): 17–32. doi: 10.1080/08870440290001502.

23. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute. 1993; 85(5): 365-376. doi:10.1093/JNCI/85.5.365.

24. Efficace F, Baccarani M, Breccia M, Saussele S, Abel G, Caocci G, et al. International development of an EORTC questionnaire for assessing health-related quality of life in chronic myeloid leukemia patients: the EORTC QLQ-CML24. Quality of Life Research. 2013;23(3):825-836. doi:10.1007/s11136-013-0523-5

25. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. Journal of psychosomatic research. 2006; 60(6): 631-637. doi:10.1016/J.JPSYCHORES.2005.10.020.

26. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology & Health, 1999; 14(1): 1–24. doi: 10.1080/08870449908407311.

27. Peng Y, Wang H, Fang Q, Xie L, Shu L, Sun W, et al. Effectiveness of Mobile Applications on Medication Adherence in Adults with Chronic Diseases: A Systematic Review and Meta-Analysis. Journal of managed care & specialty pharmacy. 2020; 26(4): 550-561. doi:10.18553/jmcp.2020.26.4.550.

28. Al-Arkee S, Mason J, Lane DA, Fabritz L, Chua W, Haque MS, et al. Mobile Apps to Improve Medication Adherence in Cardiovascular Disease: Systematic Review and Meta-analysis. Journal of Medical Internet Research. 2021; 23(5): e24190. doi:10.2196/24190.

29. Pérez-Jover V, Sala-González M, Guilabert M, Mira JJ. Mobile Apps for Increasing Treatment Adherence: Systematic Review. Journal of Medical Internet Research. 2019; 21(6): e12505. doi:10.2196/12505.

30. Ahmed I, Ahmad NS, Ali S, Ali S, George A, Danish HS, et al. Medication Adherence Apps: Review and Content Analysis. JMIR mHealth and uHealth. 2018; 6(3): e62. doi:10.2196/mhealth.6432.

31. Li A, Olmo MGD, Fong M, Sim K, Lymer SJ, Cunich M, et al. Effect of a smartphone application (Perx) on medication adherence and clinical outcomes: a 12-month randomised controlled trial. BMJ Open. 2021; 11(8): e047041. doi:10.1136/bmjopen-2020-047041.

32. Varshney U, Singh N. An analytical model to evaluate reminders for medication adherence. International journal of medical informatics. 2020;136:104091. doi:10.1016/j.ijmedinf.2020.104091

33. Armitage LC, Kassavou A, Sutton S. Do mobile device apps designed to support medication adherence demonstrate efficacy? A systematic review of randomised controlled trials, with meta-analysis. BMJ Open. 2020; 10(1): e032045. doi:10.1136/bmjopen-2019-032045.

34. Conn VS, Ruppar TM, Chase JD, Enriquez M, Cooper PS. Interventions to Improve Medication Adherence in Hypertensive Patients: Systematic Review and Meta-analysis. Current Hypertension Reports. 2015;17(12):1-15. doi:10.1007/s11906-015-0606-5.

35. Zomahoun HTV, Guénette L, Grégoire J, Lauzier S, Lawani AM, Ferdynus C, et al. Effectiveness of motivational interviewing interventions on medication adherence in adults with chronic diseases: a systematic review and meta-analysis. International journal of epidemiology. 2017; 46(2) :dyw273. doi:10.1093/ije/dyw273.

36. Davis EM, Packard KA, Jackevicius CA. The pharmacist role in predicting and improving medication adherence in heart failure patients. Journal of managed care & specialty pharmacy. 2014; 20(7): 741-755. doi:10.18553/

JMCP.2014.20.7.741.

37. Escobar-Viera C, Zhou Z, Morano JP, Lucero R, Lieb S, McIntosh S, et al. The Florida Mobile Health Adherence Project for People Living With HIV (FL-mAPP): Longitudinal Assessment of Feasibility, Acceptability, and Clinical Outcomes. JMIR mHealth and uHealth. 2020; 8(1): e14557. doi:10.2196/14557.

38. Eysenbach G. The Law of Attrition. Journal of Medical Internet Research. 2005; 7(1): e11. doi:10.2196/JMIR.7.1.E11.

39. Meyerowitz-Katz G, Ravi S, Arnolda L, Feng X, Maberly G, Astell-Burt T. Rates of Attrition and Dropout in App-Based Interventions for Chronic Disease: Systematic Review and Meta-Analysis. Journal of Medical Internet Research. 2020; 22(9): e20283. doi:10.2196/20283.

40. Habibović M, Cuijpers P, Alings M, Voort PVD, Theuns D, Bouwels L, et al. Attrition and Adherence in a Web-Based Distress Management Program for Implantable Cardioverter Defibrillator Patients (WEBCARE): Randomized Controlled Trial. Journal of Medical Internet Research. 2014; 16(2): e52. doi:10.2196/jmir.2809.

41. Aapro M, Bossi P, Dasari A, et al. Digital health for optimal supportive care in oncology: benefits, limits, and future perspectives, Support Care Cancer. 2020; 28(10): 4589–4612. doi: 10.1007/s00520-020-05539-1.

42. Bickmore T, Gruber A, Picard R. Establishing the computer-patient working alliance in automated health behavior change interventions. Patient education and counseling. 2005; 59(1): 21-30. doi:10.1016/J.PEC.2004.09.008.

43. Clarke G, Eubanks D, Reid E, Kelleher C, O'Connor E, DeBar LL, et al. Overcoming Depression on the Internet (ODIN) (2): A Randomized Trial of a Self-Help Depression Skills Program With Reminders. Journal of Medical Internet Research. 2005; 7(2): e16. doi:10.2196/JMIR.7.2.E16.