

A systematic review on experimental studies about patient adherence to treatment

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Abstract

Better understanding patients' adherence to treatment is a prerequisite to maximize the benefit of healthcare care provision for patients, reduce treatment costs, and is a key factor in a variety of subsequent health outcomes. We aim to understand the state of the art of scientific evidence about which factors influence patients' adherence to treatment. A systematic literature review was conducted using PRISMA guidelines in five separate electronic databases of scientific publications: PubMed, PsycINFO (ProQuest), Cochrane library (Ovid), Google Scholar, and Web of Science. The search focused on literature reporting the significance of factors in adherence to treatment between 2011-2021, including only experimental studies (e.g., randomized controlled trials [RCT], clinical trials, etc.). We included 47 experimental studies. The results of the systematic review (SR) are grouped according to predetermined categories of the World Health Organization (WHO): Socioeconomic, Treatment, Condition, Personal, and Healthcare-related factors. This review gives an actual overview of evidence-based studies on adherence and analysed the significance of factors defined by the WHO classification. By showing the strength of certain factors in several independent studies and concomitantly uncovering gaps in research, these insights could serve as a basis for the design of future adherence studies and models.

Introduction

Patients' adherence to treatment is important to maximize the benefit of healthcare provided to patients and is a key factor in a variety of subsequent health outcomes. We understand adherence to treatment as the process in which the patient engages in a health, technology or medication treatment that was agreed upon together with a healthcare professional. Adherence includes meeting the following conditions that are relevant to the treatment: (1) Taking prescribed medication correctly at the minimum clinical threshold agreed upon, including initiation, dosage, and persistence; (2) Carrying out recommended health behaviours, such as attending follow-up appointments, and/or implementing lifestyle changes (e.g., avoiding certain foods or engaging in specific exercise), at the minimum clinical threshold agreed upon.

Currently, lack of adherence is associated with personal suffering, poorer health outcomes, and a significant

burden on healthcare costs/budgets (Cutler et al., 2018). Overall, up to 125,000 premature deaths per year in the US (Martin et al., 2014) and 200,000 in the EU (OECD & European Union, 2018) can be related to non-adherence. On average, 25 percent of patients do not engage in recommendations for prevention and disease management activities, including medication intake, technical treatment modalities (e.g., positive airway pressure [PAP]), appointment scheduling, screening, exercise, and dietary changes (DiMatteo, 2004; Dobler, 2021). More general estimates show that almost 50 percent of patients do not adhere to treatment recommendations (Anglada-Martinez et al., 2015). When preventive or treatment regimens are complex and/or require lifestyle changes and modification of existing habits, non-adherence can be as high as 70 percent (Chesney et al., 2000; Dobler, 2021). Treatment non-adherence has been identified as a major barrier to the effective (self-)management of chronic conditions, leading to poorer health outcomes among patients, higher hospitalization rates, and increased mortality. Therefore, non-adherence eventually causes an additional financial burden on healthcare systems and the overall social costs (Cutler et al., 2018; Kim et al. 2019).

Given the proportion of the patient population that does not adhere to treatments, efforts to improve treatment adherence represent a great opportunity to enjoy the full benefit of treatment and enhance health outcomes while ensuring quality, efficiency, and sustainability of the healthcare system. Action to better understand the complexity of factors that influence patients' capacities and the reasons driving behaviour change towards treatment adherence is urgently needed to address the situation, focusing on "*real individuals*" instead of the "*ideal individuals*" (Bavel et al., 2020). Therefore, for effective care provision, it is necessary to activate the patient and the patient's community of support to better understand the complexity of factors and improve adherence to treatment. The main aim of this systematic review (SR) is to understand the state of the art of scientific evidence about the relationship and impact of different types of interventions developed to increase adherence to treatment.

Methods

The information sources consulted for this SR were the following electronic databases of scientific publications: PubMed, PsycINFO (ProQuest), Cochrane library (Ovid), Google Scholar, and Web of Science.

Search strategy

Table 1 below represents the basic search string developed for this SR. The full list of search strings that were used to inspect and search each of the databases mentioned above is available in Supplementary Material; Table S1. The search strings were developed through several discussions among all the authors and were pretested several times in the different databases in order to make sure valid and reliable outcomes were obtained.

–Table 1 should come around here –

Eligibility criteria

The focus of the SR was to analyse the literature reporting on the effect of factors in adherence to treatment. The initial review included both experimental and non-experimental studies, and the results of both searches were analysed independently. The SR reported here focused only on the experimental studies, excluding the non-experimental ones that will be analysed and reported in a separate article. Studies published within the last ten years (2011-2022) were considered. All eligible studies had to be written in English. The population of interest in the studies under review was restricted to adult human patients who had been or were planning to be under treatment for a certain chronic or acute physical condition. Consequently, treatment was defined as not only medication taking, but also engaging in other health behaviours, such as attending follow-up appointments, implementing lifestyle changes (e.g., avoiding certain foods, engaging in specific exercise), and using medical devices. Finally, eligible publications had to report the effect of one or more factors on treatment adherence to be included in this review. The inclusion and exclusion criteria for the studies eligible for this review are summarized in Table 2.

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Selection of studies for inclusion

Data management

Data were managed using Microsoft Excel and plain text files stored in Microsoft SharePoint for easy access. The search hits (including publication title, authors, abstract and DOI) were downloaded in .csv, .txt or .xlsx format, depending on the database options. A file containing all hits for each search was stored in Microsoft's SharePoint. Search hits from different databases were merged and duplications were removed, non-experimental records were excluded, resulting in one file prepared for the screening of the search hits for experimental studies only (n=12113).

Selection process

The outcome of the study was screened and selected using an open-source machine learning (ML)-aided pipeline applying active learning: ASReview, Active learning for Systematic Reviews (Van de Schoot et al., 2021). ASReview is a tool that increases the efficiency of screening titles and abstracts by determining prioritization with active learning. The ASReview tool is extensively tested and validated and has shown to achieve better performance in SR's than manually evaluation titles and abstracts (Van de Schoot et al., 2021). The tool was initially trained for the current study with 10 relevant and 10 irrelevant publications selected by two independent researchers (ARU & KvH). After feeding the tool with the training publications, the tool returned the set of hits ordered according to relevance priority. These results were checked by the same two independent researchers. In case of several irrelevant results among the top priority hits, the tool was further trained by manually screening at least 1% of the total number of publications in the whole set. Publications selected for further full-text review (n=99) were those prioritized by ASReview. For each assigned publication, authors checked each criterion and assessed the inclusion of only those publications that met all criteria. Each publication was reviewed by a second independent author following concordant and stratified criteria. The full list of studies included for full-text review as well as the inclusion and exclusion criteria can be consulted in Supplementary Material; Table S2. For the selected publications (n=47), authors annotated some additional publication details (e.g., country of the study, participants included, disease area, factors affecting adherence considered, study design, type of experimental design, etc.). The total number of records after each screening round was documented using the PRISMA flow diagram template (see Figure 1 below).

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Subsequently, the data related to the effect of interventions to increase adherence were extracted from each study. These effects were grouped according to the following dimensions: Socioeconomic, Treatment, Condition, Personal, and Healthcare-related factors, which were based on WHO's 5 dimensions of treatment adherence (Sabaté, 2003). For each adherence factor, both the inclusion and exclusion in each of the reviewed studies were reported, as well as evidence of a significant association of that specific factor with treatment adherence. Variables related to the characteristics of the study, study sample, and study intervention were also extracted.

Results

The included studies are grouped according to the following categories: Socioeconomic, Treatment, Condition, Personal, and Healthcare-related factors, based on the WHO dimensions of patients' adherence to treatment.

Socioeconomic factors

Socioeconomic factors can be divided into those factors related to social or environmental variables, economic factors, and those related to the lifestyle of patients. Among the studies analysed, we identified four studies that showed a significant effect of social or environmental factors (i.e., social interaction and support networks) on treatment adherence (Siregar & Andayani, 2020; Zullig et al., 2015; Reddy et al., 2017; Park et al., 2015). Concerning the set of economic factors, several studies reported a significant association between adherence to treatment and financial status (Wooldrich et al., 2015; Crowley et al., 2012; McAlister et al.,

2019; Shankari, 2020), education and literacy (Siregar and Andayani, 2020; Crowley et al., 2012; Al-Haj Mohd et al., 2016), employment (Sieben et al., 2021; Zullig et al., 2015; Crowley et al., 2012), and living condition of patients (Meggetto et al., 2017; Tola et al., 2016; Wooldrich et al., 2015). This SR also identified scientific evidence on the effect of patients' lifestyle on treatment adherence. The lifestyle factors with a reported significant effect are substance use and abuse (Meggetto et al., 2017; Sieben et al., 2021; Llorca et al., 2021) and physical activity (Nascimento et al., 2016; Shankari, 2020). Among the studies reviewed, no reference was made to the study of the effect of the social situation of the patient in adherence to treatment. For full reference to the data extracted, see Table 3 and Supplementary Material; Table S3.

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Factors related to the Healthcare System

The healthcare system-related factors were divided into two sets of factors: those concerning the relationship between the patient and the healthcare professional (HCP), and those directly related to the healthcare system. In this SR, ample evidence showed that provision of patient education, training, and follow-up of the patient by the HCP significantly increased adherence (Tola et al., 2016; Bonetti et al., 2018; Hohmann et al., 2014; Hovland et al., 2020; Kamal et al., 2015; Ababneh et al., 2019; Wan, 2016; Asgari et al., 2021; Alfian et al., 2020; Jahn et al., 2014; Wang et al., 2020). Moreover, the patients' trust in their HCP (McAlister, 2019) and HCPs' time available for consultation (Colvin et al., 2018) were also found to have a significant effect on patients' adherence to treatment. When considering only the healthcare system-related factors, it was found that both the provision of feedback and training to the HCP and the support of the community influence patients' adherence to treatment (Grigoryan et al., 2012; Mitchell et al., 2015). Among the studies reviewed, no reference was made to the study of the effect of the "quality and cost of health services", "Provider continuity", "Regulation process", or "Drug supply" in adherence to treatment. For a complete reference to the data extracted, see Table 4 and Supplementary Material; Table S3.

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Disease-related factors

The third dimension of adherence considered in this SR concerned disease-related factors. Two studies found evidence for the effect of progress, duration, and severity of the disease, and its symptomatology as an influencer of adherence (Nieuwkerk et al., 2012; Al-Haj Mohd et al., 2016). Furthermore, several studies identified the existence of comorbidities as a factor significantly affecting adherence to treatment (Grigoryan et al., 2012; Park et al., 2015; Shankari, 2020). In addition, the level of disability caused by the condition at the physical, psychological, social, and vocational levels has also been found to play a significant role in the level of patients' adherence to treatment, according to three articles (Crowley et al., 2012; Nascimento et al., 2016; Laba et al., 2018). For full reference to the data extracted, see Table 5 and Supplementary Material; Table S3.

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Treatment-related factors

Several adherence factors associated with patients' treatment have also been identified as modifiers of adherence. These treatment-related factors can be further categorized as factors related to the treatment regimen, the effects of the treatment, and the treatment properties. Regarding the treatment regimen, ten articles in this SR reported scientific evidence that complexity and duration of the treatment have a causal effect on patients' adherence levels (Flicoteaux et al., 2017; Gillespie et al., 2014; Kuypers et al., 2013; Suffoletto et al., 2012; Wooldrich et al., 2015; Sieben et al., 2021; Matsumura et al., 2013; Llorca et al., 2021; Calvo-Arbeloa, 2019; Kamal et al., 2015). Similarly, another study identified how the treatment properties, specifically the formulation and physical properties of the medication, had a significant effect on the patients' adherence levels (Hohmann, 2014). Focusing on the treatment effects, only one article found evidence that the appearance

of beneficial effects or side effects and experience of failures in previous treatments to influence adherence (Shankari et al., 2020; Meggetto et al., 2017). Among the studies reviewed, no reference was made to the study of the effect of the “Interference in the routine of the patient” or “Cost of treatment” in adherence to treatment. For full reference to the data extracted, see Table 6 and Supplementary Material; Table S3.

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Patient-related factors

The final dimension in the WHO framework is patient-related factors, which was further divided into three sets of factors: unalterable characteristics, cognitive and psychological factors, and behavioural factors. Regarding the first factor, ample studies in this SR identified demographics to play a significant role in adherence to treatment (Suffoletto, 2012; Crowley et al., 2014; Sieben et al., 2021; Mohan et al., 2014; Crowley, 2012; Grigoryan et al., 2012; Al-Haj Mohd et al., 2016; Matsumura et al., 2013; Llorca et al., 2021; Shankari et al., 2020; Laba et al., 2018; Calvo-Arbeloa, 2019), while only one study showed this significance for experience with treatment and treatment setting (Beckers, 2013). Also, the physical characteristics of the patients were found to be predictors for adherence to treatment in this SR (Meggetto et al., 2017; Crowley, 2012). Among the cognitive and psychological factors that were studied, health literacy (Crowley, 2012), perceptions, beliefs, and concerns of the patients regarding their condition (Crowley et al., 2014; Nieuwkerk et al., 2012; Crowley, 2012), patients’ knowledge about their treatment (Beckers, 2014; Al-Haj Mohd et al., 2016; Shankari et al., 2020), and patients’ knowledge about their disease (Beckers, 2013; Siregar & Anadayani, 2020; Nieuwkerk et al., 2012; Llorca et al., 2021) were reported as predictors for adherence to treatment. Finally, some behavioral factors were found to have an effect on adherence, such as the lifestyle of the patient (Gillespie et al., 2014; Mugo et al., 2014; Llorca et al., 2021; Shankari et al., 2020) and the planning abilities and self-efficacy, which were found in three studies (Kuypers et al., 2013; Crowley et al., 2014; Llorca et al., 2021). The table below shows the results of the quantification of the factors affecting adherence based on the SR of experimental studies. For full reference to the data extracted, see Table 7 and Supplementary Material; Table S3.

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Inclusion of covariates

In total, 7 of the 47 studies analysed for this SR reported having controlled the effect of any covariate. From those studies, the table below presents which factors these studies analysed as covariates. As Table 6 shows, demographic factors are the most used as covariates in the reviewed studies. These are followed by factors related to the characteristics of the treatment or disease, or the economic situation of the patient. Other factors are rarely analysed as covariates in the reviewed studies.

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Discussion

In this study we describe the state of the art of the existing scientific experimental evidence on the factors and determinants that influence patients’ adherence to treatment. As can be seen in the results section and the Supplementary Material, many studies have examined the effects of several factors and determinants on adherence to treatment. In particular regarding socioeconomic factors, most studies have considered determinants from the patients’ background or environment including their financial status, education, employment status, and living condition. Besides that significant associations have been found, these factors and determinants are difficult to modify or influence. Other factors studied relate to the existence of social support networks, which have been found to significantly affect adherence to treatment by several studies (Siregar and Andayani, 2020; Zullig et al., 2015; Reddy et al., 2017). Easily modifiable patient lifestyle factors have also been identified to have a significant contribution to adherence levels (Meggetto et al., 2017; Sieben et al., 2021; Llorca et al., 2021; Nascimento et al., 2016; Shankari et al., 2020). Multiple studies have explored the effect of those factors on adherence related to the patient-HCP relationship and to the different figures and institutions involved in healthcare. From these, the most relevant factor associated with adherence to

treatment is the provision of education and follow-up to patients. In fact, several studies have identified its effect on the level of adherence to treatment (Tola et al., 2016; Bonetti et al., 2018; Hohmann et al., 2014; Hovland et al., 2020; Kamal et al., 2015; Ababneh et al., 2019; Wan et al., 2016; Asgari et al., 2021; Alfian et al., 2020; Jahn et al., 2014; Wang et al., 2020), although some studies did not find any significant relation. This evidence is highly relevant as it can guide future interventions and guidelines that can help improve patients' adherence to treatment.

The characteristics of the treatment-related factors, the duration and its symptomatology have also been identified as having a strong influence on the patients' adherence levels. Furthermore, not only the condition but also the treatment characteristics have been identified as strong influencers, with complexity and duration of the treatment being the major factors (Flicoteaux et al., 2017; Gillespie et al., 2014; Kuypers et al., 2013; Suffoletto et al., 2012; Wooldrich et al., 2015; Sieben et al., 2021; Kamal et al., 2015). The relevance of identifying treatment complexity as an adherence determinant may help HCPs when deciding on the treatment options available for a specific patient and the associated risk of non-adherence to such treatment.

Finally, there are some factors that are related to the physical and behavioral characteristics of the patients and their environment. Factors like age, gender and ethnicity that are unalterable for the treatment purpose have been identified by many studies as being associated with treatment adherence. However, not all studies agree on the direction of the effect of these factors, which indicates that the effects of these factors can be highly dependent on the study setting (e.g., type of disease, type of treatment, intervention, participants included). Other factors identified as modifiers of the adherence levels were factors related to the patients' health literacy and pre-existing beliefs and concerns about the condition and the treatment (outcomes) (Crowley et al., 2014; Nieuwkerk et al., 2012; Crowley et al., 2012; Beckers et al., 2012; Al-Haj Mohd et al., 2016; Shankari et al., 2020; Siregar and Andayani, 2020; Llorca et al., 2021). Other relevant factors are those related to the patients' lifestyle, their self-efficacy and planning abilities (Gillespie et al., 2014; Mugo et al., 2014; Wan, 2016; Llorca et al., 2021; Shankari et al., 2020; Kuypers et al., 2013; Crowley et al. 2014). The identification of these factors related to the competences of the patients, their behaviors, and psychosocial factors is highly relevant to better understand a patient's behavior towards recommended treatments and to better design approaches to improve the patient's adherence levels.

It should be noted, however, that this study has some limitations. First, the eligibility criteria limited the search to those studies published in the last decade in English. Still, most studies nowadays are published in English, and we see the studies do not show a bias towards studies based on English-speaking regions. Second, our SR has shown that regarding adherence to treatment, most studies focus on adherence to medication and do not include additional treatment options, such as lifestyle changes, which are necessary in most cases. Subsequently, we also see that most of the studies rely only on self-reported data (N=31), a small number of studies used pill counts (N=7) or devices on medication (N=7), and only 2 used biochemical analytic data. Furthermore, most studies have used only one type of adherence measurement, making it difficult to compare the outcomes. Especially considering that differences in measuring methodology may lead to differences in the assessment of adherence levels. Importantly, the fact that self-reported data carries the biases of recall and social desirability, along with its lack of granularity and general overestimation of adherence, is a limitation for the accuracy and precision of the data collected. Third, none of the studies have included patient adherence to treatment across the most common diseases (e.g., cardiovascular, oncology, immunology, neurology, endocrinology, and rare disease), making a comprehensive understanding of patient adherence difficult. In fact, only a limited number of the included studies covered multiple of these condition areas, and most focused only on one area. Another important lesson learned is that most of the studies consider participants from one country only, which makes it challenging to assess generalizability of the obtained results to other countries or regions where socioeconomic and healthcare system-related factors might significantly differ. Remarkably, none of the studies included the cost of treatment in their analyses, although this is an important determinant of adherence to treatment, considering the importance of the socioeconomic factors in selected studies. Fourth, regarding the review process, having such a broad topic and scope (including several kinds of conditions, treatments, measures of adherence, etc.) challenges the proper feeding of the ASReview tool. This limitation has been overcome by performing several additional

training rounds before getting the final prioritization algorithm. Lastly, most of the literature studying factors influencing adherence to treatment relies on patient self-reported data, which, as discussed above, carries its own biases. These are vital lessons learned for future steps in scientific research in patient adherence to treatment.

Conclusion

A better understanding of patients' adherence to treatment is important to maximize the benefit of healthcare provided to patients, in order to improve health related outcomes and reduce costs. The results of this SR show that a large number of studies show the effects and associations of several factors and determinants on adherence to treatment. This study analysed the reported effects of factors related to the patient's characteristics and behaviours, the characteristics of the condition and its treatment, as well as characteristics of the healthcare system and socioeconomic environment. Despite this overview of available data on the scientific literature presented in this document, it is highly relevant to conduct more scientific research using high quality standards (e.g., randomized controlled trials, across disease areas, longitudinal) in patient adherence to maximize the benefit of healthcare provision for patients, which is a key factor for various subsequent health outcomes.

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References

- Ababneh, M., Shamieh, D., Al Demour, S., & Rababa'h, A. (2019). Evaluation of the clinical pharmacist role in improving clinical outcomes in patients with lower urinary tract symptoms due to benign prostatic hyperplasia. In *International Journal of Clinical Pharmacy* (Vol. 41, Issue 5, pp. 1373–1378). Springer Science and Business Media LLC. <https://doi.org/10.1007/s11096-019-00896-2>
- Alfian, S. D., van Boven, J. F. M., Abdulah, R., Sukandar, H., Denig, P., & Hak, E. (2020). Effectiveness of a targeted and tailored pharmacist-led intervention to improve adherence to antihypertensive drugs among patients with type 2 diabetes in Indonesia: A cluster randomised controlled trial. In *British Journal of Clinical Pharmacology* (Vol. 87, Issue 4, pp. 2032–2042). Wiley. <https://doi.org/10.1111/bcp.14610>
- Al-Haj Mohd, M. M. M., Phung, H., Sun, J., & Morisky, D. E. (2016). Improving adherence to medication in adults with diabetes in the United Arab Emirates. In *BMC Public Health* (Vol. 16, Issue 1). Springer Science and Business Media LLC. <https://doi.org/10.1186/s12889-016-3492-0>
- Anglada-Martinez, H., Riu-Viladoms, G., Martin-Conde, M., Rovira-Illamola, M., Sotoca-Momblona, J. M., & Codina-Jane, C. (2015). Does mHealth increase adherence to medication? Results of a systematic review. *International Journal of Clinical Practice*, 69 (1), 9–32. <https://doi.org/10.1111/ijcp.12582>

- Asgari, S., Abbasi, M., Hamilton, K., Chen, Y.-P., Griffiths, M. D., Lin, C.-Y., & Pakpour, A. H. (2021). A theory-based intervention to promote medication adherence in patients with rheumatoid arthritis: A randomized controlled trial. In *Clinical Rheumatology* (Vol. 40, Issue 1, pp. 101–111). Springer Science and Business Media LLC. <https://doi.org/10.1007/s10067-020-05224-y>
- Bavel, J. J. V., Baicker, K., Boggio, P. S., Capraro, V., Cichocka, A., Cikara, M., ... & Willer, R. (2020). Using social and behavioural science to support COVID-19 pandemic response. *Nature human behaviour*, 4(5), 460–471. <https://doi.org/10.1038/s41562-020-0884-z>
- Beckers, H. J. M., Webers, C. A. B., Busch, M. J. W. M., Brink, H. M. A., Colen, T. P., & Schouten, J. S. A. G. (2012). Adherence improvement in Dutch glaucoma patients: a randomized controlled trial. In *Acta Ophthalmologica* (Vol. 91, Issue 7, pp. 610–618). Wiley. <https://doi.org/10.1111/j.1755-3768.2012.02571.x>
- Bonetti, A. F., Bagatim, B. Q., Mendes, A. M., Rotta, I., Reis, R. C., Favero, M. L. D., Fernandez-Llimos, F., & Pontarolo, R. (2018). Impact of discharge medication counseling in the cardiology unit of a tertiary hospital in Brazil: A randomized controlled trial. In *Clinics* (Vol. 73, p. e325). Elsevier BV. <https://doi.org/10.6061/clinics/2018/e325>
- Calvo-Arbeloa, M. (2019). Adherencia al tratamiento con adalimumab, golimumab y ustekinumab en pacientes con enfermedad inflamatoria intestinal [JB]. *FARMACIA HOSPITALARIA*, 44(02), 62–67. <https://doi.org/10.7399/fh.11325>
- Chesney, M. A., Morin, M., & Sherr, L. (2000). Adherence to HIV combination therapy. *Social Science & Medicine*, 50(11), 1599–1605. [https://doi.org/10.1016/S0277-9536\(99\)00468-2](https://doi.org/10.1016/S0277-9536(99)00468-2)
- Colvin, N. N., Mospan, C. M., Buxton, J. A., Waggett, J. “Davie,” & Gillette, C. (2018). Using Indian Health Service (IHS) counseling techniques in an independent community pharmacy to improve adherence rates among patients with diabetes, hypertension, or hyperlipidemia. In *Journal of the American Pharmacists Association* (Vol. 58, Issue 4, pp. S59–S63.e2). Elsevier BV. <https://doi.org/10.1016/j.japh.2018.04.024>
- Crowley, M. J., Grubber, J. M., Olsen, M. K., & Bosworth, H. B. (2012). Factors Associated with Non-Adherence to Three Hypertension Self-Management Behaviors: Preliminary Data for a New Instrument. In *Journal of General Internal Medicine* (Vol. 28, Issue 1, pp. 99–106). Springer Science and Business Media LLC. <https://doi.org/10.1007/s11606-012-2195-1>
- Crowley, M. J., Zullig, L. L., Shah, B. R., Shaw, R. J., Lindquist, J. H., Peterson, E. D., & Bosworth, H. B. (2014). Medication Non-Adherence After Myocardial Infarction: An Exploration of Modifying Factors. In *Journal of General Internal Medicine* (Vol. 30, Issue 1, pp. 83–90). Springer Science and Business Media LLC. <https://doi.org/10.1007/s11606-014-3072-x>
- Cutler, R. L., Fernandez-Llimos, F., Frommer, M., Benrimoj, C., & Garcia-Cardenas, V. (2018). Economic impact of medication non-adherence by disease groups: A systematic review. *BMJ Open*, 8(1), e016982. <https://doi.org/10.1136/bmjopen-2017-016982>
- DiMatteo, M. R. (2004). Variations in patients’ adherence to medical recommendations: A quantitative review of 50 years of research. *Medical Care*, 42(3), 200–209. <https://doi.org/10.1097/01.mlr.0000114908.90348.f9>
- Dobler, C. C. (2021). Adherence to treatment. *Breathe*, 17 (2).
- Flicoteaux, R., Protopopescu, C., Tibi, A., Blanchon, T., Werf, S. V. D., Duval, X., Mosnier, A., Charlois-Ou, C., Lina, B., Leport, C., & Chevret, S. (2017). Factors associated with non-persistence to oral and inhaled antiviral therapies for seasonal influenza: a secondary analysis of a double-blind, multicentre, randomised clinical trial. In *BMJ Open* (Vol. 7, Issue 7, p. e014546). BMJ. <https://doi.org/10.1136/bmjopen-2016-014546>
- Gillespie, D., Hood, K., Farewell, D., Stenson, R., Probert, C., & Hawthorne, A. B. (2014). Electronic Monitoring of Medication Adherence in a 1-year Clinical Study of 2 Dosing Regimens of Mesalazine for

- Adults in Remission with Ulcerative Colitis. In *Inflammatory Bowel Diseases* (Vol. 20, Issue 1, pp. 82–91). Oxford University Press (OUP). <https://doi.org/10.1097/01.mib.0000437500.60546.2a>
- Grigoryan, L., Pavlik, V. N., & Hyman, D. J. (2012). Predictors of Antihypertensive Medication Adherence in Two Urban Health-Care Systems. In *American Journal of Hypertension* (Vol. 25, Issue 7, pp. 735–738). Oxford University Press (OUP). <https://doi.org/10.1038/ajh.2012.30>
- Hohmann, C., Neumann-Haefelin, T., Klotz, J. M., Freidank, A., & Radziwill, R. (2014). Providing systematic detailed information on medication upon hospital discharge as an important step towards improved transitional care. In *Journal of Clinical Pharmacy and Therapeutics* (Vol. 39, Issue 3, pp. 286–291). Wiley. <https://doi.org/10.1111/jcpt.12140>
- Hovland, R., Bremer, S., Frigaard, C., Henjum, S., Faksvag, P. K., Saether, E. M., & Kristiansen, I. S. (2020). Effect of a pharmacist-led intervention on adherence among patients with a first-time prescription for a cardiovascular medicine: a randomized controlled trial in Norwegian pharmacies+. In *International Journal of Pharmacy Practice* (Vol. 28, Issue 4, pp. 337–345). Oxford University Press (OUP). <https://doi.org/10.1111/ijpp.12598>
- Jahn, P., Kuss, O., Schmidt, H., Bauer, A., Kitzmantel, M., Jordan, K., Krasemann, S., & Landenberger, M. (2014). Improvement of pain-related self-management for cancer patients through a modular transitional nursing intervention: A cluster-randomized multicenter trial. In *Pain* (Vol. 155, Issue 4, pp. 746–754). Ovid Technologies (Wolters Kluwer Health). <https://doi.org/10.1016/j.pain.2014.01.006>
- Kamal, A. K., Shaikh, Q., Pasha, O., Azam, I., Islam, M., Memon, A. A., Rehman, H., Akram, M. A., Affan, M., Nazir, S., Aziz, S., Jan, M., Andani, A., Muqet, A., Ahmed, B., & Khoja, S. (2015). A randomized controlled behavioral intervention trial to improve medication adherence in adult stroke patients with prescription tailored Short Messaging Service (SMS)-SMS4Stroke study. In *BMC Neurology* (Vol. 15, Issue 1). Springer Science and Business Media LLC. <https://doi.org/10.1186/s12883-015-0471-5>
- Kim, J., Tran, K., Seal, K., Fernanda, A., Glenda, R., Messier, R., . . . & Kaunelis, D. (2017). Interventions for the treatment of obstructive sleep apnea in adults: a health technology assessment. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Mar. (CADTH Optimal Use Report, No. 6.1b.) Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535532/>
- Kuypers, D. R. J., Peeters, P. C., Sennesael, J. J., Kianda, M. N., Vrijens, B., Kristanto, P., Dobbels, F., Vanrenterghem, Y., & Kanaan, N. (2013). Improved Adherence to Tacrolimus Once-Daily Formulation in Renal Recipients. In *Transplantation Journal* (Vol. 95, Issue 2, pp. 333–340). Ovid Technologies (Wolters Kluwer Health). <https://doi.org/10.1097/tp.0b013e3182725532>
- Laba, T. L., Lung, T., Jan, S., Scaria, A., Usherwood, T., Brien, J. A., . . . & Leeder, S. (2018). Medication non-adherence in a cohort of chronically ill Australians. *Australian Journal of General Practice*, 47(8), 556–562. <https://doi.org/10.31128/AFP-10-17-4351>
- Llorca, C. V. y, Cortes Castell, E., Ribera Casado, J. M., de Lucas Ramos, P., Casteig Ayestaran, J. L., Casteig Blanco, A., Gil Guillen, V. F., & Rizo Baeza, M. (2021). Factors associated with non-adherence to drugs in patients with chronic diseases who go to pharmacies in Spain. In *International Journal of Environmental Research and Public Health* (Vol. 18, Issue 8, p. 4308). MDPI AG. <https://doi.org/10.3390/ijerph18084308>
- Martin, L. R., Williams, S. L., Haskard, K. B., & DiMatteo, M. R. (2005). The challenge of patient adherence. *Therapeutics and Clinical Risk Management*, 189–199.
- Matsumura, K., Arima, H., Tominaga, M., Ohtsubo, T., Sasaguri, T., Fujii, K., Fukuhara, M., Uezono, K., Morinaga, Y., Ohta, Y., Otonari, T., Kawasaki, J., Kato, I., & Tsuchihashi, T. (2013). Impact of antihypertensive medication adherence on blood pressure control in hypertension: the COMFORT study. In *QJM* (Vol. 106, Issue 10, pp. 909–914). Oxford University Press (OUP). <https://doi.org/10.1093/qjmed/hct121>

- McAlister, F. A., Ye, C., Beupre, L. A., Rowe, B. H., Johnson, J. A., Bellerose, D., Hassan, I., & Majumdar, S. R. (2019). Adherence to osteoporosis therapy after an upper extremity fracture: a pre-specified substudy of the C-STOP randomized controlled trial. In *Osteoporosis International* (Vol. 30, Issue 1, pp. 127–134). Springer Science and Business Media LLC. <https://doi.org/10.1007/s00198-018-4702-7>
- Meggetto, O., Maunsell, E., Chlebowski, R., Goss, P., Tu, D., & Richardson, H. (2017). Factors Associated With Early Discontinuation of Study Treatment in the Mammary Prevention.3 Breast Cancer Chemoprevention Trial. In *Journal of Clinical Oncology* (Vol. 35, Issue 6, pp. 629–635). American Society of Clinical Oncology (ASCO).<https://doi.org/10.1200/jco.2016.68.8895>
- Mitchell, B., Chong, C., & Lim, W. K. (2015). Medication adherence 1 month after hospital discharge in medical inpatients. In *Internal Medicine Journal* (Vol. 46, Issue 2, pp. 185–192). Wiley.<https://doi.org/10.1111/imj.12965>
- Mohan, A., Riley, B., Schmotzer, B., Boyington, D. R., & Kripalani, S. (2014). Improving medication understanding among Latinos through illustrated medication lists. *Am J Manag Care*, 20(12), e547-e555.
- Mugo, P. M., Sanders, E. J., Mutua, G., van der Elst, E., Anzala, O., Barin, B., Bangsberg, D. R., Priddy, F. H., & Haberer, J. E. (2014). Understanding Adherence to Daily and Intermittent Regimens of Oral HIV Pre-exposure Prophylaxis Among Men Who Have Sex with Men in Kenya. In *AIDS and Behavior* (Vol. 19, Issue 5, pp. 794–801). Springer Science and Business Media LLC.<https://doi.org/10.1007/s10461-014-0958-x>
- Nascimento, T., Braz, N., Gomes, E., Fernandez-Arche, A., & De La Puerta, R. (2016). Self-care improvement after a pharmaceutical intervention in elderly type 2 diabetic patients. In *Current Diabetes Reviews* (Vol. 12, Issue 2, pp. 120–128). Bentham Science Publishers Ltd. <https://doi.org/10.2174/1573399811666150722130232>
- Nieuwkerk, P. T., Nierman, M. C., Vissers, M. N., Locadia, M., Greggers-Peusch, P., Knappe, L. P. M., Kastelein, J. J. P., Sprangers, M. A. G., de Haes, H. C., & Stoes, E. S. G. (2012). Intervention to Improve Adherence to Lipid-Lowering Medication and Lipid-Levels in Patients With an Increased Cardiovascular Risk. In *The American Journal of Cardiology* (Vol. 110, Issue 5, pp. 666–672). Elsevier BV. <https://doi.org/10.1016/j.amjcard.2012.04.045>
- OECD, & European Union. (2018). Health at a Glance: Europe 2018: State of Health in the EU Cycle. https://doi.org/10.1787/health_glance_eur-2018-en
- Park, L. G., Howie-Esquivel, J., Whooley, M. A., & Dracup, K. (2015). Psychosocial factors and medication adherence among patients with coronary heart disease: A text messaging intervention. In *European Journal of Cardiovascular Nursing* (Vol. 14, Issue 3, pp. 264–273). Oxford University Press (OUP). <https://doi.org/10.1177/1474515114537024>
- Reddy, A., Huseman, T. L., Canamucio, A., Marcus, S. C., Asch, D. A., Volpp, K., & Long, J. A. (2017). Patient and Partner Feedback Reports to Improve Statin Medication Adherence: A Randomized Control Trial. In *Journal of General Internal Medicine* (Vol. 32, Issue 3, pp. 256–261). Springer Science and Business Media LLC.<https://doi.org/10.1007/s11606-016-3858-0>
- Sabate, E. (2003). Adherence to long-term therapies. World Health Organization, 30(4). <https://apps.who.int/iris/handle/10665/42682>
- Shankari, G., Ng, S. C., Goh, S. Y., Woon, F. P., Doshi, K., Wong, P. S., Fan, Q., Tan, I. F., Narasimhalu, K., & De Silva, D. A. (2020). Modifiable Factors Associated with Non-Adherence to Secondary Ischaemic Stroke Prevention Strategies. In *Journal of Stroke and Cerebrovascular Diseases* (Vol. 29, Issue 12, p. 105395). Elsevier BV. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105395>
- Sieben, A., A.W. van Onzenoort, H., J.H.M. van Laarhoven, K., Bredie, S. J. H., & van Dulmen, S. (2021). Identification of Cardiovascular Patient Groups at Risk for Poor Medication Adherence. In *Journal of*

Cardiovascular Nursing (Vol. 36, Issue 5, pp. 489–497). Ovid Technologies (Wolters Kluwer Health). <https://doi.org/10.1097/jcn.0000000000000702>

Siregar, F. A., & Andayani, L. S. (2020). Analysis Social Determinant of Adherence to Treatment in Pulmonary Tuberculosis Patients in Medan City. Proceedings of the International Conference of Science, Technology, Engineering, Environmental and Ramification Research (942–945). <https://doi.org/10.5220/0010104709420945>

Stange, D., Kriston, L., von-Wolff, A., Baehr, M., & Dartsch, D. C. (2013). Reducing Cardiovascular Medication Complexity in a German University Hospital: Effects of a Structured Pharmaceutical Management Intervention on Adherence. In Journal of Managed Care Pharmacy (Vol. 19, Issue 5, pp. 396–407). Academy of Managed Care Pharmacy. <https://doi.org/10.18553/jmcp.2013.19.5.396>

Suffoletto, B., Calabria, J., Ross, A., Callaway, C., & Yealy, D. M. (2012). A Mobile Phone Text Message Program to Measure Oral Antibiotic Use and Provide Feedback on Adherence to Patients Discharged From the Emergency Department. In Academic Emergency Medicine (Vol. 19, Issue 8, pp. 949–958). Wiley. <https://doi.org/10.1111/j.1553-2712.2012.01411.x>

Tola, H. H., Shojaeizadeh, D., Tol, A., Garmaroudi, G., Yekaninejad, M. S., Kebede, A., Ejeta, L. T., Kassa, D., & Klinkenberg, E. (2016). Psychological and Educational Intervention to Improve Tuberculosis Treatment Adherence in Ethiopia Based on Health Belief Model: A Cluster Randomized Control Trial. In D. Fernandez-Reyes (Ed.), PLOS ONE (Vol. 11, Issue 5, p. e0155147). Public Library of Science (PLoS). <https://doi.org/10.1371/journal.pone.0155147>

Van de Schoot, R., de Bruin, J., Schram, R., Zahedi, P., De Boer, J., Weijdem, F., ... & Oberski, D. L. (2021). An open source machine learning framework for efficient and transparent systematic reviews. Nature Machine Intelligence, 3(2), 125–133. <https://doi.org/10.1038/s42256-020-00287-7>

Wan, L.-H., Zhang, X.-P., Mo, M.-M., Xiong, X.-N., Ou, C.-L., You, L.-M., Chen, S.-X., & Zhang, M. (2016). Effectiveness of Goal-Setting Telephone Follow-Up on Health Behaviors of Patients with Ischemic Stroke: A Randomized Controlled Trial. In Journal of Stroke and Cerebrovascular Diseases (Vol. 25, Issue 9, pp. 2259–2270). Elsevier BV. <https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.05.010>

Wang, M.-Y., Shen, M.-J., Wan, L.-H., Mo, M.-M., Wu, Z., Li, L.-L., & Neidlinger, S. H. (2020). Effects of a Comprehensive Reminder System Based on the Health Belief Model for Patients Who Have Had a Stroke on Health Behaviors, Blood Pressure, Disability, and Recurrence From Baseline to 6 Months. In Journal of Cardiovascular Nursing (Vol. 35, Issue 2, pp. 156–164). Ovid Technologies (Wolters Kluwer Health). <https://doi.org/10.1097/jcn.0000000000000631>

Wooldridge, K., Schnipper, J. L., Goggins, K., Dittus, R. S., & Kripalani, S. (2015). Refractory primary medication nonadherence: Prevalence and predictors after pharmacist counseling at hospital discharge. In Journal of Hospital Medicine (Vol. 11, Issue 1, pp. 48–51). Wiley. <https://doi.org/10.1002/jhm.2446>

Zullig, L. L., Stechuchak, K. M., Goldstein, K. M., Olsen, M. K., McCant, F. M., Danus, S., Crowley, M. J., Oddone, E. Z., & Bosworth, H. B. (2015). Patient-Reported Medication Adherence Barriers Among Patients with Cardiovascular Risk Factors. In Journal of Managed Care & Specialty Pharmacy (Vol. 21, Issue 6, pp. 479–485). Academy of Managed Care Pharmacy. <https://doi.org/10.18553/jmcp.2015.21.6.479>

Tables

Table 1. Basic search string developed for this systematic review

Search String

(Treatment Adherence and Compliance[mh] OR Patient Compliance[mh] OR Patient Dropouts[mh] OR Therapeutic Adher

Table 2. Summary of inclusion and exclusion criteria.

Evidence	Publications of studies that assess the effect of one or more factors on treatment adherence
Publication characteristics	Peer reviewed articles published in English within the last ten years (2012-2022).
Population	Studies considering adult human participants ([?] 16 years old). For reviews and overviews
Condition type	Both, chronic and acute physical conditions. Studies focused on patients suffering from me
Treatment type	The studies eligible for this review were those that analyse adherence to any kind of treatm
Data included	Studies that at least report, for the analysed factors, the direction of the effect and its stat

Table 3. Reported evidence on the effect of socioeconomic factors on treatment adherence.

Socioeconomic	Exp. studies evaluating the factor	Experimental studies
<i>Social or environmental factors</i>	<i>Social or environmental factors</i>	<i>Social or environmental factors</i>
Social interaction and support networks	9	n = 11 (Tola et al)
Social stigma of a condition, socioeconomic status	1	n = 1 (Colvin et al)
Access to treatment centre, culture and lay beliefs about illness and treatment	4	n = 1 (McAlister et al)
Health-related media use (e.g., searching for information)	1	n = 1 (McAlister et al)
<i>Economic factors</i>	<i>Economic factors</i>	<i>Economic factors</i>
Financial status	9	n = 11 (Tola et al)
Education and literacy	18	n = 1 (Colvin et al)
Employment	11	n = 1 (McAlister et al)
Living condition	5	n = 1 (Colvin et al)
Insurance access and coverage	3	n = 1 (McAlister et al)
<i>Patients' lifestyle factors</i>	<i>Patients' lifestyle factors</i>	<i>Patients' lifestyle factors</i>
Substance (ab)use (Including smoking and alcohol)	10	n = 1 (McAlister et al)
Physical activities	3	n = 1 (McAlister et al)

Note. Total number of experimental studies = 47.

Table 4. Reported evidence on the effect of healthcare related factors on treatment adherence.

Healthcare related factors	Exp. studies evaluating the factor	Experimental studies
<i>Related to the patient - HCP relationship</i>	<i>Related to the patient - HCP relationship</i>	<i>Related to the patient - HCP relationship</i>
Relationship with HCP	3	No significant effect
Communication abilities	2	No significant effect
Trust in provider	1	n = 1 (McAlister et al)
Provision of patient education, training and follow up	21	n = 11 (Tola et al)
Time availability of consultation (Incl. Frequency of visits)	4	n = 1 (Colvin et al)
<i>Directly related to the healthcare system</i>	<i>Directly related to the healthcare system</i>	<i>Directly related to the healthcare system</i>
Access or barriers to the system	2	No significant effect
Insurance coverage and co-payment	2	No significant effect
Provision of feedback and training to HCPs	3	n = 1 (Grigoryan et al)
Community support available to patients	2	n = 1 (Mitchell et al)

Note. Total number of experimental studies = 47.

Table 5. Reported evidence on the effect of Condition or disease-related factors on treatment adherence.

Disease related factors	Exp. studies eval
Progress, duration, and severity of the condition and its symptomatology	8
Level of disability caused by the condition at the physical, psychological, social, and vocational levels	6
Existence of co-morbidities (including depression)	15

Note Total number of experimental studies = 47.

Table 6. Reported evidence on the effect of Treatment related factors on treatment adherence.

Treatment related factors	Exp. studies eval
<i>Treatment regimen</i>	
Complexity and duration of the treatment (including dosing regimen, tooling, and amount of medicines taken & irregularity	
Patient friendliness of the regimen	
Variation and changes of the treatment	
<i>Treatment effects</i>	
Appearance of the beneficial effects or side effects (Treatment beliefs)	
Experience of failures in previous treatments	
<i>Treatment properties</i>	
Formulation and physical properties of the medication	

Note Total number of experimental studies = 47.

Table 7. Reported evidence on the effect of patient related factors on treatment adherence.

Patient-related factors	Exp. studies evaluating t
<i>Unalterable characteristics</i>	<i>Unalterable characteristics</i>
Demographics	26
Experience with treatment and treatment setting	2
Physical characteristics of the patients (including clinical features (BP, pulse, haematocrit))	12
<i>Cognitive and psychological factors</i>	<i>Cognitive and psychological f</i>
Health literacy	4
Perceptions, beliefs, and concerns of the patients regarding their condition	8
Motivation and ability to manage the condition	5
Patients' knowledge about the treatment	7
Patients' knowledge about the disease	8
<i>Behavioral factors</i>	<i>Behavioral factors</i>
Lifestyle of the patients	9
Organization	2
Planning abilities	9

Note. Total number of experimental studies = 47.

Table 8. Inclusion of covariates in studies analysing the effect or association of diverse factors and the level of treatment adherence.

Covariates considered	Covariates considered
Socioeconomic	Socioeconomic Social or environmental factors [a) social interaction and support networks; b) social stigma of Economic factors [a) financial status; b) education and literacy; c) employment; d) living condi Patient's lifestyle factors [a) substance abuse; b) social situations; c) physical activities]
Healthcare system related	Healthcare system related Related to the patient-HCP relationship [a) communication abilities; b) trust in provider; c) pr Directly related to the different figures and institutions involved in healthcare [a) access of barr
Disease related	Disease related a) progress, duration, and severity of the condition and its symptomatology; b) level of disabili
Treatment related	Treatment related Treatment regimen [a) complexity and duration of the treatment; b) patient friendliness of the Treatment effects [a) appearance of the beneficial effects or side effects; b) experience of failure Treatment properties [a) formulation and physical properties of medication; b) cost of treatment
Patient related	Patient related Unalterable characteristics [a) demographics; b) experience with treatment and treatment setti Cognitive and psychological factors [a) health literacy; b) perceptions, beliefs, and concerns of t Behavioral factors [a) lifestyle of the patient; b) organization; c) planning abilities]

Figure legends

Figure 1. PRISMA flow diagram. Diagram adapted from Page et al. (2021).

