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Strategies to Enhance Compliance with Treatment in Patients with Hypertension

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Abstract

Introduction: Limited evidence from systematic reviews and meta-analyses exists on the effectiveness of interventions aimed at improving poor compliance with antihypertensive drugs among patients with hypertension. This review seeks to consolidate findings from these analyses to better comprehend the issues surrounding medication non-compliance in this demographic.

Methods: An exclusive search was conducted in the PubMed database for studies on hypertension management featuring keywords such as "adherence," "drug," "treatment," "outcome," "hypertension," and "randomized controlled trial." A comprehensive search across various databases was performed to identify research published from 2000 to 2022 that focused on self-reported medication adherence among individuals with hypertension. The search yielded 21 randomized controlled trials that evaluated the impact of different interventions on both blood pressure control and medication adherence in hypertensive patients. These studies often implemented complex interventions to enhance adherence, with blood pressure measurements recorded in both outpatient and clinical settings.

Results: A variety of strategies have been explored to boost compliance with antihypertensive medication, including calendar blister packs, combination drug formulations, educational initiatives for patients, direct interactions, and telephonic computer systems. In 62% of the 21 identified randomized controlled trials, these interventions led to significant improvements in adherence, gauged through methods such as self-reports, prescription refill rates, and electronic monitoring of drug intake. Generally, better adherence correlated with improved hypertension management outcomes, with the magnitude of effects varying. Nevertheless, in 8 out of the 21 studies, no enhancement in adherence was observed. While pill counting is straightforward, it fails to capture the timing of medication intake. MEMS caps can detail medication-taking behavior but might induce hypotension without thorough validation. HPLC-MS/MS offers precise drug concentration measurements in biological fluids but is costly and might not reliably indicate long-term compliance.

Conclusions: Noncompliance with antihypertensive medication is widespread and challenging to precisely detect. Health practitioners may not fully recognize the extent of nonadherence, and self-reported measures along with questionnaires could play a crucial role in identifying patient attitudes and obstacles to following prescribed treatment regimes.

Keywords: Blood Pressure, Compliance, Stroke, Death, Medications.

Introduction

Hypertension stands as a significant worldwide health challenge, being a primary cause of death and the third most common reason for disability. Predictions suggest that the number of individuals suffering from hypertension will reach 1.56 billion by 2025. A critical obstacle in managing hypertension effectively is the lack of medication adherence, with patients typically consuming only 50-70% of their antihypertensive medication doses. Furthermore, within the first year of treatment, up to half of the patients discontinue their antihypertensive medications, and as many as 75% fail to meet their blood pressure targets. Adherence is defined as the degree to which a person's actions align with the advice given by their healthcare provider [1]. While patient-related factors are commonly blamed for nonadherence, the issue is multifaceted, involving aspects related to the treatment, illness, healthcare system, healthcare team, and socioeconomic factors. A key factor in starting and adhering to health-related behaviors is self-efficacy, or the belief in one's capability to execute a specific behavior [2].

Enhancing blood pressure management in hypertensive patients is crucial for diminishing the risk of cardiovascular incidents. Despite clinical trials indicating potential control rates of up to 80%, real-world outcomes often do not achieve these levels. According to data from the National Health and Nutrition Examination Survey (NHANES) for 2005-2006, the actual control rate of hypertension was merely 44% among all hypertensive individuals and 64% among those under treatment [3]. The disparity between these figures and the ideal control rates is largely due to poor adherence to medication regimes, which includes both forgetting to take medications and not following the treatment plan consistently. Historically, the term "compliance" was utilized to describe how well patients followed their medication schedules, but the term "adherence" is now preferred to emphasize following healthcare providers' recommendations [4]. Nonadherence, especially with antihypertensive medications, is widespread and results in uncontrolled blood pressure, poor health outcomes, and elevated healthcare expenditures. Previously, measuring adherence was challenging, but advances in technology have introduced chemical adherence testing as a method to verify medication consumption. This approach employs liquid chromatography-tandem mass spectrometry to detect the presence of medications in samples like blood or urine [5].

It is currently mostly used in research settings, but there is evidence to suggest it could be used in primary care as well. The World Health Organization recommends using the term "adherence" to describe the extent to which a person's behavior (such as taking prescribed medications) aligns with healthcare provider recommendations, rather than using pejorative terms like "compliance" or "difficult" that imply disobedience [6]. There are several methods for assessing adherence to medications, including self-reported measures, prescription records, and electronic monitoring systems. One objective method is chemical adherence testing, which uses liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect medications in patient samples such as blood or urine [7]. This technique is currently used in a limited number of healthcare settings, but there is evidence that it could be feasible for use in primary care as well. Some groups have also developed immunoassays for specific medications, but these lack specificity and require confirmation by mass spectrometry. Urine and blood are the most commonly used sample types for chemical adherence testing, with urine being the more popular choice due to its non-invasive collection and larger quantities that can be obtained. Some groups have also published quantitative methods for

measuring antihypertensive drugs in urine [8]. Chemical adherence testing is a technique used to confirm whether or not a patient is taking their prescribed medications. It is typically conducted using liquid chromatography-tandem mass spectrometry (LC-MS/MS) to detect medications in patient samples, such as blood or urine. While this method is not widely used in primary care, there is evidence to suggest that it could be feasible in both the UK and internationally. Some researchers have suggested that drugs with very short or long elimination half-lives may produce false negative or positive results in chemical adherence testing. However, a recent study found no correlation between half-life and adherence rates for common antihypertensive medications in urine [9, 10]. To date, a little evidence such as systematic review and meta-analysis was conducted to evaluate the interventions that improve non-adherence to antihypertensive medications in hypertensive patients using. A previous review found that nonadherence to these medications is common, with rates ranging from 30-50%. Nonadherence to antihypertensive medications is associated with uncontrolled blood pressure, poor clinical outcomes, and increased costs to the healthcare system. This review aimed to synthesize the data from these studies to provide a better understanding of non-adherence to antihypertensive medications in this population.

Methods

We selectively searched the PubMed database for publications on the treatment of hypertension that contained the terms "adherence," "drug," "treatment, "outcome," "hypertension," and "randomized controlled trial." Researchers conducted a search of several databases to identify studies published between 2000 and 2022 that measured self-reported adherence to antihypertensive medications in hypertensive patients. In summary, the aim of this review was to identify and review randomized controlled trials that focused on interventions to improve adherence to antihypertensive medications in patients with hypertension. A search of the PubMed database was conducted using specific search terms, and the resulting publications were further narrowed down to include only clinical trials.

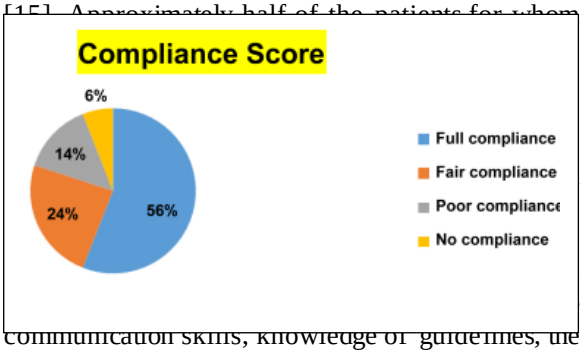
The final search results included 21 randomized controlled trials that examined the effect of various interventions on both blood pressure and adherence to medication in patients with hypertension. Many of these studies used multiple measures, or "complex interventions," to improve adherence. Blood pressure measurements were taken both in outpatient settings and in hospitals or doctors' offices. Two medical researchers helped to develop a list of relevant search terms and two authors screened titles and abstracts for relevance. Full-text articles were obtained and evaluated for inclusion, and a standardized form was used to collect information on the surveys used in each study. The goal of the review was to gather data on intervention aiming at improving nonadherence in hypertensive patients. A systematic review and meta-analysis was conducted to assess the nonadherence rates of antihypertensive medication in patients with hypertension. The study included observational and experimental studies that measured patient-reported barriers to adherence to antihypertensive medication in adults, published in English, and excluded studies that measured adherence to other health behaviors or used patient diaries or open-ended questions to measure adherence. The review focused on sources of bias, including randomization, blinding of the outcome assessor, and losses to follow-up, and reported the results of factorial trials separately.

Results and discussion

There is a wide range of interventions that have been studied to improve adherence to antihypertensive medications, including the use of calendar blister packs, combination preparations, patient education programs, personal encounters, and telephone-based computer systems. In 62% of the 21 randomized controlled studies that were identified, the interventions resulted in improved adherence, as measured by various methods including self-assessment, proportion of prescriptions filled, and electronic recording of medication intake [11]. Improved adherence was generally associated with better clinical outcomes in hypertension, with effect sizes ranging from small to large. However, in 8 of the 21 studies, the interventions did not improve adherence. Hypertension, or high blood pressure, is a major risk factor for mortality and disability

worldwide. It is estimated that by 2025, there will be 1.56 billion people with hypertension. Poor adherence to medications is a common problem in hypertension treatment, with rates of nonadherence ranging from 30% to 50%. This can lead to uncontrolled blood pressure, poor clinical outcomes, and increased healthcare costs [12]. Adherence, or the extent to which a person follows the recommendations of their healthcare provider, can be influenced by various factors including the patient's own characteristics, the therapy itself, the healthcare team and system, and socioeconomic factors.

Studies have shown that improved adherence to hypertension medications is associated with better clinical outcomes, such as a reduced risk of stroke, cardiovascular death, and coronary heart disease. However, many studies have found that adherence rates remain suboptimal, with estimates ranging from 39% to 44% of treated hypertensive patients achieving recommended blood pressure levels [13]. Factors associated with nonadherence include younger age, male gender, Hispanic ethnicity, low income, lack of health insurance, and not visiting a healthcare provider in the past year. Adherence to medications such as ACE inhibitors, ARBs, and beta blockers has also been shown to be associated with a lower risk of all-cause mortality in patients with ischemic heart disease and diabetes [14]. Adherence to medications that prevent cardiovascular disease (CVD) was 57% after two years, with around one-third of patients who had experienced a myocardial infarction being nonadherent. A review of electronic monitoring data from 4783 patients in Phase IV studies found that 2% of patients did not start treatment and 48% of patients had at least one "drug holiday" (defined as omitting doses for three or more consecutive days) per year [15]. Approximately half of the patients for whom



communication skills, knowledge of guidelines, the complexity and adequacy of the prescribed regimen, therapeutic inertia, and time constraints (see Table 1). Adherence is inversely related to the number of daily doses: in patients taking medication four times daily, adherence is approximately 50%. Approximately half of patients thought to have resistant hypertension were actually completely or partially nonadherent, and about one in four patients referred for renal denervation was nonadherent.

A systematic review identified 43 self-report adherence scales, of which 16 were validated in hypertensive patients. Another review identified six questionnaires that were tested for both validity and reliability. Studies using HPLC-MS/MS to assess adherence reported complete adherence in 35-81%, partial adherence in 10-37%, and total nonadherence in 9-35% of hypertensive patients, with the definition of partial adherence varying between studies [16]. A Cochrane review of interventions aimed at improving adherence in various medical conditions found that most of the existing evidence is of insufficient quality (only 17 out of RCTs had low-risk bias), and that the five RCTs reporting improvement in both adherence and clinical outcomes involved complex interventions that would be difficult to implement in a real-world setting. Interestingly, the amount of time spent by the provider with the patient was not statistically associated with adherence, suggesting that the quality of communication (e.g., showing concern and providing information) might be more important than the absolute quantity of time. A meta-analysis of 18,000 patients found that using fixed-dose combinations (FDCs) of two or more antihypertensive agents was associated with a 29% increase in adherence and persistence with treatment compared to using the same two drugs in free combination [17].

Another meta-analysis reported that adherence was higher in patients taking FDCs than in those on free combinations, by 8% in patients naive to prior antihypertensive treatment and by 14% in non-naive patients. Hypertensive patients starting treatment on an FDC were 53% more likely to achieve blood pressure control in the first year than those who started on monotherapy (34% more likely when using free combinations). Furthermore, patients treated with FDCs had fewer hospitalizations and a lower five-year cardiovascular event rate than patients on free combinations [18]. The use of electronic multicompartment medication devices with reminder systems has been shown to have positive effects on adherence, although a systematic review found that these studies had methodological limitations. In terms of mobile health solutions, a meta-analysis of RCTs in patients with chronic diseases found a beneficial effect of text messaging on adherence, although most studies used self-reported adherence assessment and had short duration.

A randomized trial involving 1372 patients found that text messaging improved adherence compared to usual care, regardless of whether the messages were information-only or interactive. A European study estimated that increasing adherence to antihypertensive therapy to 70% of patients in five European countries (Italy, Germany, France, Spain, and England) would result in total savings of €332 million over a 10-year period and lead to 82,235 fewer cardiovascular events. Another study estimated that increasing adherence to 100% of hypertensive patients in the United States would save approximately $72 billion and reduce the number of strokes, myocardial infarctions, renal, and cardiac events by 8.5 million. A 2010 review compared the cost-effectiveness of published interventions that improved adherence to antihypertensive and lipid-lowering treatment and found that a pharmacist/nurse management program and a combination of self-monitoring, reminders, and educational materials were the most cost-effective interventions [19]. Using fixed-dose combinations (FDCs) was associated with better adherence and fewer hospitalizations and emergency room visits. A retrospective analysis of United States health insurance claims data found that in patients treated with a valsartan/amlodipine FDC, compared to those treated with a free combination of an angiotensin receptor blocker (ARB) and a calcium channel blocker (CCB), adherence was significantly higher and total healthcare costs were 16-20% lower ($P < 0.0001$). Adherence was also strongly correlated with total healthcare costs, with costs being 9-13% lower in patients who were adherent to their medication. Poor adherence to antihypertensive medications is common, especially in patients with apparent resistant hypertension, where it can be as high as 25-50%. Patients with high adherence were 45% more likely to achieve blood pressure (BP) control than those with medium or low adherence, and observational data from the Lombardy region showed that adherence to antihypertensive drug therapy reduced the risk of cardiovascular outcomes by 37% and the risk of hospitalization due to heart failure [20]. Hypertension is usually an asymptomatic condition, which can lead patients, especially younger, active individuals without comorbidities, to underestimate the necessity or benefit of treatment.

They may also fear possible or experienced adverse effects or be unwilling to fit treatment into their schedule. Intensifying antihypertensive treatment does provide greater protection against cardiovascular events, but this potential advantage is accompanied by an increasing rate of treatment discontinuation due to adverse effects, which means that an increasing number of patients are not protected. Lower perception of treatment need and higher levels of concern about treatment are associated with intentional nonadherence, which is an active process that occurs when the patient decides to skip or alter doses [21]. The number of medications is also a strong predictor of nonadherence: 79.3% of UK patients prescribed at least six BP-lowering medications were nonadherent. Changes in pill color and shape were associated with increased odds of nonadherence, and the increasing use of generic medications with regular changes in appearance could cause confusion in elderly patients [22]. Therefore, physicians should identify the specific factors driving nonadherence in each patient so that they can tailor adherence-improving interventions to the patient's profile in an attempt to optimize their effectiveness. When BP control is not achieved, screening for adherence is

useful, especially in patients taking many medications, where nonadherence is more likely.

Conclusions

Nonadherence to antihypertensive medications is common and can be difficult to accurately identify. Healthcare providers may underestimate nonadherence and self-report measures and questionnaires may be useful in understanding patient beliefs and barriers to adherence. Pill counting is a simple method but does not provide information on timing of doses. MEMS caps can provide precise information on medication-taking patterns but may also cause hypotension and have not been extensively tested. HPLC-MS/MS can provide accurate measurements of medication in urine or serum but is expensive and may not accurately reflect long-term adherence.

Conflict of interests

The authors declared no conflict of interests.

References

1. Burnier, Michel. and Burnier, . Medication Adherence and Persistence as the Cornerstone of Effective Antihypertensive Therapy. (2006) American Journal of Hypertension. 19(11); 1190-1196.

2. Gosmanova, Elvira. and Kovesdy, Csaba. Adherence to antihypertensive medications: is prescribing the right pill enough?. (2015) Nephrol. Dial. Transplant. 30(10); 1649-1656.

3. Poulter, Neil., Borghi, Claudio., Parati, Gianfranco., Pathak, Atul., Toli, Diana., Williams, Bryan., Schmieder, Roland. and Sci, Fmed. Medication adherence in hypertension. (2020) 38(4); 579-587.

4. Alghurair, Suliman., Hughes, Christine., Pharm, Bsc., Simpson, Scot., Guirguis, Lisa. and Pharm, . A Systematic Review of Patient Self-Reported Barriers of Adherence to Antihypertensive Medications Using the World Health Organization Multidimensional Adherence Model. (2012) 14(12); 877-886.

5. and Elliott, William. Improving Outcomes in Hypertensive Patients: Focus on Adherence and Persistence With Antihypertensive Therapy. (2009) 11(7); 376-382.

6. Hamdidouche, Idir., Jullien, Vincent., Boutouyrie, Pierre., Billaud, Eliane., Azizi, Michel. and ´phane Laurent, Ste. Drug adherence in hypertension. (2017) 35(6); 1133-1144.

7. Morgado, Manuel., Morgado, Sandra., Mendes, Liliana., Pereira, J., Castelo-Branco, Miguel., Beira, Da., Sandra, Covilhã. and Morgado, . Pharmacist interventions to enhance blood pressure control and adherence to antihypertensive therapy: Review and meta-analysis. (2011) 68(3); 241-253.

8. Gupta, Pankaj., Lane, Dan., Lawson, Alexander., Burns, Angela., Azizi, Michel., Burnier, Michel., Jones, Donald., Kably, Benjamin., Khunti, Kamlesh., Kreutz, Reinhold., Patel, Prashanth., Persu, Alexandre., Spiering, Wilko., Toennes, Stefan., Tomaszewski, Maciej., Williams, Bryan. and Dasgupta, Indranil. Nonadherence in Hypertension: How to Develop and Implement Chemical Adherence Testing. (2022) Hypertension. 79(1); 12-23.

9. Izeogu, Chigozirim., Kalinowski, Jolaade. and Schoenthaler, Antoinette. Strategies to Improve Adherence to Anti-Hypertensive Medications: a Narrative Review. (2020) Curr Hypertens Rep. 22(12);

10. Clark, Luther., Uther, J., Clark, T., Mi>, ., Medicine, . and Clarkson, Ave. Currently, for adults living in developed societies, hypertension and its complications are among the. ( )

11. Melaku Abegaz, Tadesse., Shehab, Abdulla., Gebreyohannes, Alemayehu., Srikanth Bhagavathula, Akshaya. and Elnour, Ahmed. Nonadherence to antihypertensive drugs. (2017) 96(4); e5641.

12. Dubois, Dominique., Criscuolo, Domenico., Godman, Brian., Institutet, Karolinska., Sweden, ., Vrijens, Bernard., Antoniou, Sotiris., Burnier, Michel., De La Sierra, Alejandro. and Volpe, Massimo. Current Situation of Medication Adherence in Hypertension. (2017) Front. Pharmacol. 8;

13. Fahey, Schroeder., Schroeder, Knut., Fahey, Tom., Ebrahim, Shah., Hypertension, Cochrane., Jj, Casado-Martinez., Ramos-Perez, J., Jp, Moreno-Garcia., Celotti-Gomez, ., Gascon-Vivo, J.,

Randomized, Feldman., Burt, ., Vl, Burt., Ja, Cutler., Mf, Horan., Sieber, ., Wj, Sieber. and Kaplan, R. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. (2004) 2010(1);35-45.

14. Burnier, M. (2017). Drug adherence in hypertension. Pharmacological research, 125, 142-149.

15. Gwadry-Sridhar, F. H., Manias, E., Lal, L., Salas, M., Hughes, D. A., Ratzki-Leewing, A., & Grubisic, M. (2013). Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. Value in health, 16(5), 863-871.

16. Roldan, P. C., Ho, G. Y., & Ho, P. M. (2018). Updates to adherence to hypertension medications. Current hypertension reports, 20(4), 1-7.

17. Choudhry, N. K., Kronish, I. M., Vongpatanasin, W., Ferdinand, K. C., Pavlik, V. N., Egan, B. M., ... & American Heart Association Council on Hypertension; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. (2022). Medication adherence and blood pressure control: a scientific statement from the American Heart Association. Hypertension, 79(1), e1-e14.

18. Burnier, M., Polychronopoulou, E., & Wuerzner, G. (2020). Hypertension and drug adherence in the elderly. Frontiers in cardiovascular medicine, 7, 49.

19. Schlenk, E. A., Dunbar-Jacob, J., & Engberg, S. (2004). Medication non-adherence among older adults: a review of strategies and interventions for improvement. Journal of gerontological nursing, 30(7), 33-43.

20. Granger, B. B., & Bosworth, H. (2011). Medication adherence: emerging use of technology. Current opinion in cardiology, 26(4), 279.

21. Gupta, A. K., Arshad, S., & Poulter, N. R. (2010). Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension, 55(2), 399-407.

22. Tan, J. P., Cheng, K. K. F., & Siah, R. C. J. (2019). A systematic review and meta-analysis on the effectiveness of education on medication adherence for patients with hypertension, hyperlipidaemia and diabetes. Journal of Advanced Nursing, 75(11), 2478-2494.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