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REVIEW ARTICLE

Initial non-adherence to antihypertensive medications in the United States: a systematic literature review

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Abstract

An important component of hypertension management is the initiation and continuation of antihypertensive medications. Non-adherence during the long-term use of antihypertensive medications is well studied. However, there is a paucity of research about the frequency and clinical consequences of failing to take the first dose of an antihypertensive, a treatment challenge known as initial medication non-adherence (IMN). This systematic literature review summarizes the published evidence from 2010 to 2019 on the prevalence, associated factors, consequences, and solutions for IMN to antihypertensive medications in the United States. Of the fifteen studies identified, nine studies reported the prevalence of IMN, two studies examined patient-reported reasons for IMN, and four studies evaluated interventions aimed to lower IMN. It is estimated that 5–34% of patients do not obtain their new antihypertensive medications. Factors and reasons cited include patient demographics, patient beliefs or perceptions about medications, cost or financial barriers, and clinical characteristics, such as a new hypertension diagnosis or higher co-morbid disease burden. The clinical, economic, and patient-reported outcomes of IMN are not well researched. In addition, interventions to address IMN have yielded inconsistent results. Significant opportunities exist for further research into this dimension of patient behavior to better understand and address IMN to new antihypertensive medications.

Introduction

The prevalence of hypertension and consequent mortality have increased substantially in the United States over the past decade [1, 2]. Almost one-half of US adults are now estimated to have hypertension (blood pressure [BP] ≥ 130/80 mmHg) with only one-quarter achieving adequate BP control [2, 3].

To improve BP control in patients qualifying for pharmacologic therapy, antihypertensive medications must not only be prescribed, but obtained and taken by patients. However, according to the 2017 Behavioral Risk Factor Surveillance System, of those who report having been told by a doctor that they had high BP, 40.4% were not taking antihypertensive medication, despite guidelines recommending pharmacologic therapy for most patients with a hypertension diagnosis [4].

Medication non-adherence is a well-recognized problem that contributes to suboptimal patient health outcomes and poses a significant burden to the healthcare system [5]. Since 2003, when the World Health Organization's first published the definition of medication adherence—the extent to which a person's medication-taking behavior corresponds with agreed recommendations from a healthcare provider [5]—a body of literature has evaluated the prevalence, associated factors, consequences, and proposed solutions for non-adherence [6, 7]. The literature is rich with reports about ongoing medication adherence or medication utilization patterns after starting a new medication, but studies focused on the first time a patient is expected to obtain a new medication, or initial medication non-adherence (IMN), are rare [8]. The limited research suggests that failure to obtain the first medication may be common. One US retrospective cohort analysis found that 24% of adults with an antihypertensive prescription did not obtain the medication [9]. Patients who do not obtain the

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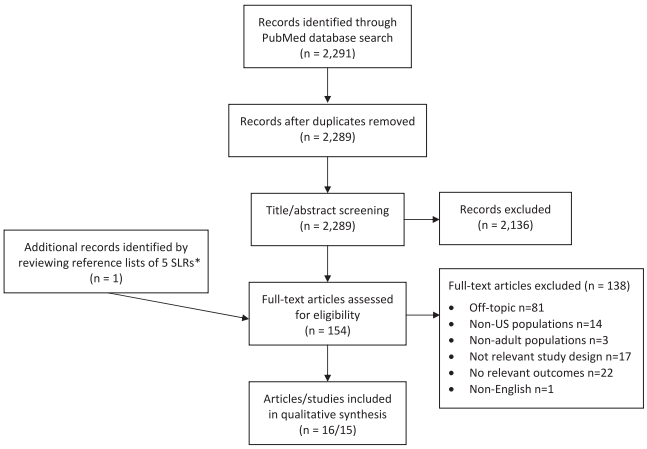

Fig. 1 Flowchart of study selection. *During title/abstract screening, five systematic literature reviews on IMN were found. The reference lists of these articles were reviewed and one additional article was identified for full-text review. Figure template adapted from [37].

initial fill of an antihypertensive medication likely remain untreated or undertreated for some period of time, resulting in increased risk for morbidity or premature death as well as potentially increased costs to society and the healthcare system.

In order to develop strategies that improve initial adherence to antihypertensive medications, a thorough understanding of the prevalence, determinants, and outcomes of IMN is necessary. Therefore, the objective of this review is to summarize the existing literature on the prevalence, associated factors, consequences, and solutions targeting IMN to antihypertensive medications in the US.

Patients and methods

A systematic literature search was performed in Medline (PubMed) to capture publications in the past decade (January 1, 2010 to December 31, 2019) using the following search terms: (1) medication adherence (MeSH term) and first fill, early, primary, or initial (in the title or abstract), or (2) prescription abandonment. These search terms were chosen based on various terminology that has been used to describe IMN in the literature; these include "primary non-adherence", "primary medication adherence", "primary medication non-adherence", "initial medication adherence", "first-fill failure", "prescription abandonment", "early non-adherence", and "non-filling" [8]. The search was limited to English language studies conducted in the US, as the objective was to understand IMN within the US healthcare system. Two reviewers independently reviewed all titles and abstracts identified from the initial search. During title/abstract review, studies that clearly did not address IMN (e.g., measured ongoing medication adherence without any reference to IMN), solely evaluated non-adult populations (<18 years), employed weaker study designs (i.e., case series or case reports), or were conducted outside of the US were excluded. All non-excluded articles were further evaluated with a full-text review. Two reviewers independently screened the full-text article using the same inclusion and exclusion criteria as for title/abstract screening, but during this stage, an additional requirement was that the study be relevant to IMN to antihypertensive medications. The reference lists of systematic reviews from the PubMed search were also examined to determine whether they included studies that were relevant to IMN to antihypertensive medications. Any discordance in article selection between reviewers was resolved by discussion and the final list of articles included in this review was agreed upon by both reviewers.

Results

The literature search in PubMed identified 2289 unique articles. After title/abstract screening, 153 articles remained, of which 15 were included after full-text review. The reference lists of five systematic reviews [8, 10–13] were reviewed and yielded one additional article, resulting in a total of 16 articles that met inclusion and exclusion criteria (Fig. 1) [9, 14–28]. Since two articles described the same study [18, 19], there were 15 unique studies. Eleven of these studies included antihypertensives along with other medications [15–22, 24–26, 28], but only the data for IMN to antihypertensive medications are described below. Nine studies assessed the prevalence, two studies examined patient-reported reasons, and four studies evaluated interventions aimed to lower IMN.

Prevalence and predictors of IMN ($n = 9$ studies)

Estimates of the prevalence of IMN to antihypertensive therapy ranged from 5.2 to 34.0% of patients, and 1.1 to 47.7% of antihypertensive prescriptions (Table 1) [9, 14–22]. The patient populations, data sources and definitions for new antihypertensive medication and IMN

Table 1 Studies reporting prevalence of initial medication non-adherence (IMN) to antihypertensive medications ($n = 9$).

Study	Study design	Antihypertensive population	Data sources	New Rx definition	Measurement of IMN	Prevalence of IMN	Predictors of IMN
Comer et al. [14]	Retrospective cohort	791 patients with HTN prescribed a new antihypertensive from a multi-location primary care practice in Delaware	EHR and pharmacy claims	Without history of same medication class	No paid pharmacy claim within 30 days	34.0% (269/791) of patients	Lower diastolic blood pressure Medicare (vs. private, Medicaid, self-pay/other) insurance
Cooke et al. [9]	Retrospective cohort	7061 members of a Mid-Atlantic managed care organization with new antihypertensive Rxs from physicians who were e-prescribing at least 75% of the time	Pharmacy claims	Coded as new in the pharmacy claim (includes initial and ongoing medications for which a new Rx was issued)	Pharmacy claim status as denied or reversed	24.3% (1713/7061) of patients 15.6% (2289/14,693) of Rxs	New antihypertensive medication (no pharmacy claims for same medication within prior 6 months) New HTN diagnosis Brand medication Higher copayment HMO or PPO (vs. indemnity) insurance
Fischer et al. [15]	Retrospective cohort	30,211 e-Rxs for antihypertensives in adults (6145 were new antihypertensives) from community-based practices in Massachusetts.	e-Rx transactions and pharmacy claims	No prior Rx claim for same medication within available data (range of 6–12 months prior)	No paid pharmacy claim during study window (range of 1 day to 12 months)	19.5% (5879/30,211) of antihypertensive Rxs (28.4% [1744/6145] of antihypertensive Rxs in those without prior history of medication)	NR
Fischer et al. [16]	Retrospective cohort	75,182 e-Rxs for antihypertensives (23,033 for new antihypertensives) and in those with any history of Rx claim, 68,513 e-Rxs for antihypertensives (16,364 for new antihypertensives) from e-prescribing database available in all 50 states	e-Rx transactions and pharmacy claims	No prior Rx claim for same medication within 6 months	No paid pharmacy claim within 6 months	17.8%[a] of antihypertensive Rxs (47.7%[a] of antihypertensive Rxs in those without prior history of medication) In those with any history of a Rx claim, 9.8%[a] of antihypertensive Rxs (26.4%[a] of antihypertensive Rxs in those without prior history of medication)	NR
Jackson et al. [17]	Retrospective observational analysis	11,771 e-Rxs for new direct renin inhibitors, angiotensin-receptor blockers (ARBs), or angiotensin-converting enzyme (ACE) inhibitors in adults from a retail pharmacy chain located in the Mid-South region	Pharmacy records	No previous Rx for the same drug in the prior 180 days	Prescribed medication or an appropriate alternative not obtained from the pharmacy within 30 days	11.3% (1335/11,771) of Rxs	NR
Raebel et al. [18]; Raebel et al. [19]	Retrospective cohort	6,393 members with a new antihypertensive Rx from an integrated healthcare delivery system in Colorado	EHR and pharmacy records	No Rx for a drug with the same therapeutic indication in the prior 365 days	Prescribed medication not obtained from the pharmacy within 30 days	5.2% (331/6393) of patients	Within subset of 4721 patients comparing IMN to ongoing adherence (excluded patients who obtained the medication within 30 days, but had no refills after): Hispanic or other race/ethnicity compared to non-Hispanic whites Shorter length of health plan enrollment Non-HMO health plan

Table 1 (continued)

Study	Study design	Antihypertensive population	Data sources	New Rx definition	Measurement of IMN	Prevalence of IMN	Predictors of IMN
							compared to HMO Fewer healthcare contacts in the 6 months after the new Rx ≥4 comorbidities
Romanelli et al. [20]	Retrospective cohort	5,350 adults with Rxs for antihypertensives and a completed experience of care survey from a multispecialty ambulatory healthcare delivery system in California	EHR and pharmacy claims	New Rx which could be for a new or an ongoing medication	No paid pharmacy claim through expected end date of Rx	19.6% (1046/5350) of patients	NR
Shin et al. [21]	Retrospective cohort	45,178 e-Rxs for a new cardiovascular agent from an integrated healthcare system in California	EHR and pharmacy records	No prior dispensing in the same class during the prior 12 months	Prescribed medication not obtained from the pharmacy within 14 days	7.8% (3804/48,982) of Rxs	NR
Shrank et al. [22]	Cross-sectional cohort	642,376 Rxs for a new antihypertensive from a national pharmacy chain	Pharmacy records and pharmacy claims	No prior dispensing in the same class during the prior 6 months	Prescribed medication returned to stock and no paid pharmacy claim for an alternative medication within same class within 30 days	1.1% (7160/642,376) of Rxs	NR

EHR electronic health record, *e-Rx* electronic prescription, *HMO* health management organization, *HTN* hypertension, *NR* not reported, *PPO* preferred provider organization, *Rx* prescription.

[a]Absolute numbers not reported.

varied in these nine studies. Patients were identified from integrated healthcare systems in two studies [18, 19, 21], primary, community or ambulatory care practices in three studies [14, 15, 20] and pharmacies in three studies [16, 17, 22]. Only one study identified patients from their membership in a managed care organization [9].

To determine whether there was a match between prescribing and obtaining the medication, seven studies used two separate data sources. The lack of a match identified IMN. In six of these studies, antihypertensive prescriptions were identified using data from electronic medical records or electronic prescribing (e-prescribing) transactions and matched to pharmacy records or claims data to determine whether the medication had been obtained by the patient [14–16, 18–21]. One study (Shrank et al.) used pharmacy records to identify prescriptions for a new antihypertensive and matched them to pharmacy claims [22]. However, this study relied on pharmacy records to report whether the medication had been returned to stock—which occurs when the medication is not picked up after 14 days, and then the authors reviewed pharmacy claims data to determine whether the patient picked up a different antihypertensive medication within the same class. Patients who did not obtain the initially prescribed medication or one in the same class were considered to have IMN.

Only one data source was used in two studies. In Cooke et al., the status of the pharmacy claim was used to determine IMN [9]. Claims that were reversed or denied were labeled as IMN with prevalence determined by that proportion in relation to all claims (paid, reversed, or denied). In Jackson et al., pharmacy records were used to identify IMN when there was no sale transaction date for the prescribed medication or an appropriate alternative within 30 days of the fill date of an electronically prescribed new antihypertensive [17].

The definition of 'new' antihypertensive medication also varied across studies. Five studies considered new to mean there was no history of the same medication product, while four studies considered new to be without history of the same medication class or indication. In one study (Cooke et al.), a code found in the pharmacy claim was used to identify whether the medication fill is for the first fill of a prescription or a refill [9]. Thus, in this study, the 'new' category includes both initial and ongoing antihypertensive therapy for which a new prescription was written. When describing predictors of IMN, this study also used the traditional definition for 'new' to include those with no prior history of that specific agent.

Of note, one study (Raebel et al.) included only patients considered to be treatment-naïve (i.e., patients without any history of antihypertensive medications) as new to antihypertensive medication [18, 19].

The prevalence studies also differed in their look-back periods to define new (e.g., 6 or 12 months, all available data within 6–12 months).

In two studies, the definition of IMN was expanded to include failure to pick up the prescribed medication or any medication considered to be a therapeutic alternative [17, 22].

The timeframe for measuring IMN to identify whether a match occurred between prescribing and obtaining the antihypertensive medication ranged from days to months. The most common time period was 30 days ($n = 4$ studies) [14, 17–19, 22].

Three studies described predictors of IMN to antihypertensive medications, including new diagnosis of hypertension, lower diastolic BP, higher cost or insurance type/coverage, non-white non-Hispanic race/ethnicity, fewer healthcare contacts within 6 months after the prescription, and ≥4 comorbidities [9, 14, 18, 19]. In one study, patients who received new antihypertensives (no prior claim within 6 months of that medication) were 49 times more likely to experience IMN compared to those who had filled the medication previously ($p < 0.001$) [9]. Of these three studies describing predictors, none found age or sex to be associated with IMN [9, 14, 18, 19]. Two other studies did not evaluate predictors, but reported higher percentages of IMN when the antihypertensive did not appear in the claims history, compared to when it did [15, 16].

Reasons for IMN ($n = 2$ studies)

In one study, four focus group interviews with a total of 26 adult participants with IMN to a new antihypertensive medication identified barriers resulting in IMN [23]. These participants were asked to identify their reasons—other than forgetting, traveling, or receiving a duplicate prescription—for IMN. Half of the participants were men and 88% lived in urban settings. Most patients were white (65%) or black (27%) and came from all educational backgrounds. Barrier-related themes included distrust, concern for side effects, cost, pill burden, and preference for lifestyle management or complementary alternatives rather than the prescription medications. Participants also expressed that having information about diagnosis, an explanation for the choice of drug therapy, side effects, and cost may influence their adherence. There was also interest in hearing about alternative management of hypertension through lifestyle or complementary medications.

In the other study, a survey asking about reasons for IMN in various chronic disease states, 49 respondents with hypertension answered 'yes' to receiving, but not filling a prescription in the last year [24]. These respondents selected one or more reasons for IMN from a list of ten provided in the survey. The most common reason was cost (61.2%),

Table 2 Studies reporting interventions for initial medication non-adherence (IMN) to antihypertensive medications ($n = 4$).

Study	Study design	AntiHTN population	Intervention	Control	New Rx definition	Measurement of IMN	Results: IMN
Fischer et al. [25]	Retrospective cohort	Patients who had not picked up their new antihypertensive medication from a community pharmacy chain	Automated phone calls to patients on the 3rd and 7th days after not picking up their Rxs ($n =$ 814,187 Rxs) Live phone call from a pharmacist or technician to patients who had not picked up their Rxs after 8 days (n = 82,373 Rxs)	Patients born on randomly selected birthdays received usual care ($n = 8718$ Rxs for comparison to automated phone calls and $n = 1993$ Rxs for comparison to live call)	No Rx claims for a drug in same therapeutic class in the prior 6 months	No Rx claims for a drug in same therapeutic class within 30 days of prescription processing at the pharmacy	Automated calls: 3.6% (29, 683/ 814,187) in the intervention group and 4.1% (361/8718) in the control group ($p = 0.06$) Live call: 35.3% (29,106/82,373) in the intervention group and 42.2% (841/1993) in the control group ($p <$ 0.0001)
Fischer et al. [26]	RCT	Patients from primary care practices of an integrated healthcare delivery network in Pennsylvania who did not pick up a newly prescribed antihypertensive medication within 14 days	Phone call from a nurse working with the prescriber ($n =$ 37)	Usual care ($n = 32$)	No Rx for a drug in same subclass within the prior year	Patients who did not pick up their antihypertensive medication from the pharmacy within 30 days	53.1% (17/32) in the intervention group and 73.0% (27/37) in the control group (p $= 0.09$)
Kerner and Knezevich [27]	Prospective intervention with historical control group	Patients with hypertension from primary care clinics in Nebraska who did not pick up an e-prescribed antihypertensive within 7 days	Weekly electronic messages via EHR patient portal beginning 7 days after e-Rx ($n = 9$ patients/9 Rxs)	Historical group from the 6 months prior to the intervention ($n =$ 7 patients/8 Rxs)	New antihypertensive agent or increased strength not previously taken	Medication not picked up before the earlier date of the patient's next clinic visit or within 30 days of prescribing	22.2% (2/9) in the intervention group and 62.5% (5/8) in the control group
O'Connor et al. [28]	RCT	Patients prescribed a new medication for uncontrolled BP from a multispecialty medical group in California, Pennsylvania, Wisconsin or Washington with at least 60 days of follow-up	Phone call from a nurse health manager, diabetes educator/ trainee or pharmacist ($n = 296$)	Usual care ($n = 317$)	No fill of same medication class within prior 180 days	Patients who did not pick up their antihypertensive medication within 60 days of prescribing	14.2% (42/296) in the intervention arm and 17.0% (54/317) in control arm, $p =$ 0.35

BP blood pressure, *EHR* electronic health records, *e-Rx* electronic prescription, *HTN* hypertension, *RCT* randomized controlled trial, *Rx* prescription.

followed by concern for side effects (34.7%), concern for taking the medication (28.6%), and change in health insurance (24.5%). Of the respondents, 18.4% did not think the medication was needed. Less frequently reported reasons included a lack of understanding about the importance of treating their condition or the medication's purpose, and concern that the drug would be ineffective, inconvenient, and interact with other medications.

Consequences of IMN

None of these studies evaluated the clinical consequences of IMN (e.g., chronic kidney disease, stroke, myocardial infarction, mortality). Likewise, there were no studies of the economic burden (e.g., overall and direct/indirect cardiovascular-related costs), nor of patient-reported outcomes (e.g., quality of life) associated with IMN to antihypertensive prescriptions.

Interventions to address IMN ($n = 4$ studies)

Four studies evaluated interventions to address IMN to antihypertensive therapy using a variety of methods, including electronic messages, automated phone calls, and live calls from a nurse, pharmacist/technician or health educator (Table 2) [25–28]. Interventions were provided to patients from care networks or medical groups ($n =$ 3 studies), and a community pharmacy chain ($n =$ 1 study).

Of the three studies that examined the impact of live phone calls on IMN, one study reported a statistically significant improvement [25]. In this study, patients who did not pick up their newly prescribed antihypertensive medication at a community pharmacy chain after 8 days received a live phone call from a pharmacist or technician [25]. 'New' prescriptions included initial prescriptions for treatment-naive patients as well as those for continuing therapy. Compared to a control group of patients with randomly selected birthdates that did not receive the intervention, participants who received live calls had a 6.9% lower IMN (35.3% vs. 42.2%, $p < 0.0001$). This study also reported the impact of an automated call to patients who did not pick up their newly prescribed antihypertensive medication between days 3 and 7. Compared to a control group, IMN was 0.5 percentage points lower after receiving an automated call ($p = 0.06$).

The other two studies that evaluated the impact of live calls demonstrated no statistically significant difference in IMN compared to usual care [26, 28]. In Fischer et al., patients who did not pick up their prescription after two automated and one live call (part of an existing program) were randomized to receive a nurse call to assess reasons for IMN and encourage prescription pickup ($n = 37$) or usual care ($n = 32$) [26]. In the nurse call group, IMN was 19.8 percentage points lower than usual care ($p = 0.09$).

In the study by O'Connor et al., the authors randomized patients to a structured phone call from a nurse health manager, diabetes educator/diabetes educator trainee, or pharmacist ($n = 388$) versus usual care ($n = 403$) [28]. Different subpopulations were used to report the effect of the intervention on IMN and BP control. Study participants with at least 60 days of follow-up were included in IMN results (intervention, $n = 296$; usual care, $n = 317$). The absolute difference in IMN between the intervention and usual care was 2.8 percentage points lower with intervention ($p = 0.35$). Study participants with baseline and follow-up BP values were included in BP results. There were also no significant differences in systolic BP (-18.1 mmHg in intervention arm [$n = 363$] and -16.4 mmHg in control arm [$n = 368$], $p = 0.26$). Notably, this study included many patients (79.1% and 76.0% in the intervention and control groups, respectively) who had already obtained their medication before the intervention.

In another study, weekly electronic messaging to patients who did not pick up their new e-prescribed antihypertensive medications within 7 days was compared to a historical control group [27]. The absolute difference in IMN of 40.3 percentage points between the message group ($n = 9$ prescription) and a historical control ($n = 8$ prescriptions) was not statistically significant. This study also provided data for the intervention and control groups, respectively, on the mean number of days to prescription pickup (12.6 vs. 24.5 days), capping the days for those who did not pick up the prescription at 30 days, and mean systolic/diastolic BP ($-17.3/-6.6$ and $-0.8/-2.3$ mmHg) changes from the initial visit where the antihypertensive was e-prescribed to the follow-up visit.

Discussion

IMN to antihypertensive medications affects 5–34% of patients and may contribute to the burden of uncontrolled hypertension. The wide prevalence range is due to differences in data sources and study methods (i.e., definition for a new antihypertensive prescription, and variations in how IMN is measured). Prescriptions, and the patients they represent, were captured from a range of local and regional healthcare entities to national pharmacy chains. Some studies required patients to have a diagnosis of hypertension, while others did not.

Studies also differed in that a 'new' antihypertensive medication could be for a particular drug (e.g., lisinopril), a new therapeutic class (e.g., calcium channel blocker), or a new therapeutic indication (e.g., hypertension). The look-back period used to define a new antihypertensive

medication could be from months to a year. Similarly, the length of follow-up used to measure IMN also varied from days to months.

Other systematic reviews have described an inability to compare studies reporting IMN due to heterogeneity [8, 11]. In one of these systematic reviews, the authors reported an unweighted mean IMN of 20.3% across all studies, which included different disease states and medications [11]. Another systematic review of IMN in chronic disease reported the meta-analytic effect of IMN to antihypertensives to be 16%, but it was unclear whether this was the percentage of patients or prescriptions [13]. Although not antihypertensive-specific, IMN rates were significantly lower when prescriptions were the unit of measure assessed [13].

Higher percentages of IMN are anticipated in patients with certain clinical characteristics (e.g., new hypertension diagnosis, higher comorbidity burden), demographic features (e.g., ethnicity/race), or prescription attributes (e.g., higher cost). However, there are other factors, such as prescriber characteristics or type of care system which may impact IMN but were not investigated. Previous research shows that integrated delivery systems may offer improved secondary medication adherence, but the effect on IMN is unknown [29]. In our systematic review, two of the included studies in an integrated delivery system reported lower percentages of IMN, 5.2% of patients and 7.8% of prescriptions [18, 19, 21].

As with studies of ongoing medication adherence, the reasons for IMN are complicated and may vary considerably across individuals and settings. Some of the reasons cited include patient beliefs or perceptions about medications and cost/financial barriers [23, 24]. Interestingly, none of these studies evaluated which barriers are unique to IMN and perhaps require a different set of interventions than those for ongoing medication adherence. Although the most noted reason for IMN relates to the cost or financial burden to the patient, it would be an oversimplification to declare cost as the primary reason. One can imagine that providing a prescription at no charge to a patient who does not accept the diagnosis, or who does not believe in the value of the therapy, will not solve IMN.

Studies have not captured important clinical, economic, or patient-reported outcomes of IMN to antihypertensive medications. Only one intervention study assessed changes in BP but included a limited number of patients with IMN to their antihypertensive [28]. Thus, the consequences of IMN are under-researched and poorly understood. In contrast, there is evidence of higher risk for life-threatening consequences in those who do not take their antihypertensive medication as frequently as prescribed or stop all together [30]. It seems logical that patients with IMN who do not even take the first dose are at higher risk for adverse consequences of uncontrolled BP.

Part of the lack of research in this area is due to the challenges associated with linking prescribing with other data sources. Unsurprisingly the study which relied solely on pharmacy records to identify prescriptions at a time when e-prescribing was uncommon reported the lowest prevalence of IMN: 1.1% of new antihypertensive prescriptions [22]. Selection bias may be of concern as patients who never took their written prescription to the pharmacy would not have been included.

The proliferation of e-prescribing facilitates capture of a wider array of prescribing activities, with 79% of prescribers using this technology as of 2019 [31]. As such, linking this information with data from claims or pharmacy records improves the accuracy of calculations. Additional linkages to outcomes data are required to assess the consequences of IMN. The benefits of e-prescribing, however, should not preclude the use of other methods to assess IMN. An example could be incorporating related questions into national surveys, such as the Behavioral Risk Factor Surveillance System [32].

Based on limited evidence, automated phone calls and reminders do not appear to reduce IMN. Personal calls from a healthcare provider may be an option, as one study found that outreach calls from the patient's community pharmacy reduced IMN to antihypertensive medications. However, when pharmacists were added to a list of callers including nurse health managers and diabetes educators, or when nurses were the only caller, there was no difference in IMN compared to control groups. A systematic review of interventions for ongoing medication adherence found that there is no one intervention that works across all patient populations [33]. Likewise, a targeted approach that identifies the reason for IMN and selects an intervention to address specific barriers may be needed. If reasons are similar across IMN and ongoing non-adherence, interventions that work for ongoing adherence could be systematically tested to see whether these are suitable for IMN.

Clinical implications

Most striking is that none of the studies appeared to have engaged the prescriber, who may have the greatest insight to the patient's condition and could play a significant role in mitigating the health impact of medication non-adherence. Currently, physicians and other prescribers are not informed when IMN occurs, and typically only find out if and when the patient returns to the clinic or office [34]. Although many of the consequences of hypertension are chronic in nature (e.g., chronic kidney disease, coronary artery disease, stroke, etc.) and arguably may be addressed at follow-up, medication non-adherence is also one of the most common

causes of hypertensive crises, an acute problem that can result in permanent end-organ damage, as well as preventable healthcare expenditures [2]. In addition, patients who are non-adherent to medications may be less likely to follow-up with appointments, enhancing the risk for long-term consequences of uncontrolled hypertension. In patients who do follow-up, additional medications may be unnecessarily prescribed if the prescriber is unaware of the failure to obtain the original prescription. Thus, IMN may contribute to inefficient prescribing and treatment ineffectiveness. In addition, while this work focuses on hypertension specifically, it is possible that other chronic disease states also require IMN awareness and attention.

Prescribers want to be informed and can be [34]. Standalone e-prescribing systems and those embedded within electronic health records can increase awareness of IMN. The medication history transactions list can be examined to see whether the medication has been obtained, but the list must be available and accessible. Viewing it is often a manual process that occurs at an in-office visit (i.e., when the patient returns) and may require knowing what was prescribed so it can be compared to the transactions list.

There is a more automated process for finding out about IMN, but most clinicians are unaware [34]. In the newest standard for e-prescribing (SCRIPT version 2017071), physicians can request a specific notification about the pharmacy fill status for a patient's electronically prescribed medication (e.g., dispensed vs. not dispensed) [35]. As of January 2020, the Centers for Medicare and Medicaid Services requires the use of this standard for e-prescribing in the Medicare prescription drug benefit (Part D) program [36]. If the patient does not obtain the medication within a timeframe specified by the prescriber, the pharmacy notifies the prescriber through the electronic record. This automated notification would then prompt outreach to the patient to investigate and address barriers to obtaining the newly prescribed medication.

Limitations

The result of any systematic review is highly dependent on the strength of the search protocol and the reviewers' decisions for determining whether studies met the inclusion and exclusion criteria. The medical literature was searched using PubMed but did not include other databases or the gray literature. EMBASE was not searched since the inclusion criteria was IMN within US populations and resources did not allow for review and analysis of the many non-US populations included in this database. A post hoc search of Cochrane Collaborative did not reveal any publications addressing IMN, only ongoing medication adherence. This is not surprising considering the low number of IMN studies included in this review, with only four of those addressing interventions to improve IMN.

Given the paucity of literature on this topic, the purpose of this review was to provide a comprehensive summary of all studies in the US that addressed IMN to antihypertensives. Therefore, a formal risk of bias assessment, where studies of low quality would be excluded, was not conducted. However, the included studies may have been biased due to the methods used. The definitions used to classify a patient or prescription as IMN were different, as well as how subjects were included within the studies. The other inherent limitation is that the prevalence of IMN to antihypertensives is dependent on the populations studied; therefore, the range reported must be interpreted with caution.

For the intervention studies, there were concerns with small sample sizes [26, 27], use of an historical control group [27], and the inclusion of patients who picked up their medications prior to the intervention [28].

What is known about topic

- Limited understanding of IMN
  Initial medication adherence (IMN) which occurs when a patient fails to obtain and take a new medication is less well studied that ongoing medication adherence.
- E-prescribing advances IMN research
  The proliferation of e-prescribing provides new methods to research IMN.

What this study adds

- Prevalence of IMN
  IMN to antihypertensive therapy was reported in 5.2-34.0% of patients and 1.1 to 47.7% of antihypertensive prescriptions.
- Predictors of IMN
  A new diagnosis of hypertension, lower diastolic blood pressure, higher cost or insurance type/coverage, non-white non-Hispanic race/ethnicity, fewer healthcare contacts within 6 months after the prescription, and ≥4 comorbidities were found to be predictors of IMN to antihypertensive therapy.
- Reasons for IMN
  Distrust, concern for side effects, cost, and lack of perceived need for the medication were patient-reported reasons for IMN to antihypertensive therapy.

Conclusion

Non-adherence to initially prescribed antihypertensive medication occurs in ~5–34% of patients. The consequences of this have not been studied; however, it is

likely that these patients have inadequate BP control. The limited research in this area is coupled with a lack of evidence-based interventions to address the problem. In particular, interventions have not involved the prescribers who manage these medications. There is a need for further research on the modifiable predictors and consequences of IMN (short term and long-term; economic, clinical, and humanistic), as well as testing of interventions that can be implemented across practice settings.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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