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Therapeutic Inertia and Treatment Intensification

Robina Josiah Willock¹, Joseph B. Miller², Michelle Mohyi³, Ahmed Abuzaanona³, Meri Muminovic⁴, and Phillip D. Levy⁵

¹Department of Community Health and Preventive Medicine, Morehouse School of Medicine, Atlanta, GA, USA

²Department of Emergency Medicine and Department of Internal Medicine, Henry Ford Hospital and Wayne State University, Detroit, MI, USA

³Department of Internal Medicine, Henry Ford Hospital, Detroit, MI, USA

⁴Department of Emergency Medicine, Henry Ford Hospital, Detroit, MI, USA

⁵Department of Emergency Medicine and Integrative Biosciences Center, Wayne State University, 6135 Woodward Ave, Detroit, MI 48202, USA

Abstract

Purpose of Review—This review aims to emphasize how therapeutic inertia, the failure of clinicians to intensify treatment when blood pressure rises or remains above therapeutic goals, contributes to suboptimal blood pressure control in hypertensive populations.

Recent Findings—Studies reveal that the therapeutic inertia is quite common and contributes to suboptimal blood pressure control. Quality improvement programs and standardized approaches to support antihypertensive treatment intensification are ways to combat therapeutic inertia.

Furthermore, programs that utilize non-physician medical professionals such as pharmacists and nurses demonstrate promise in mitigating the effects of this important problem.

Summary—Therapeutic inertia impedes antihypertensive management and requires a broad effort to reduce its effects. There is an ongoing need for renewed focus and research in this area to improve hypertension control.

Keywords

Therapeutic inertia; Treatment intensification; Hypertension control; Antihypertensive therapy; HTN management

Phillip D. Levy plevy@med.wayne.edu.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Introduction

Antihypertensive therapy is the cornerstone of effective hypertension (HTN) management, yet poor blood pressure (BP) control among persons with HTN continues to be an ongoing challenge for patients and clinicians. The deleterious effect of poor patient adherence to prescribed antihypertensive therapy is well established and there is extensive ongoing research aimed at mitigating the individual and environmental factors that contribute to this. Despite decades of work in this area, it is clear that the myriad reasons for suboptimal BP control, particularly among ethnic racial minorities and persons of low socioeconomic status, are persistent and multifaceted, making development of comprehensive solutions challenging.

While much emphasis is placed on patient-level contributors to poor BP control, there is growing interest in understanding how therapeutic inertia, which is the failure of clinicians to intensify treatment when BP rises or remains above therapeutic goals, may impact the equation [1]. Uncertainty regarding the BP-lowering effect of antihypertensive medications and a desire to avoid up-titration or treatment intensification in patients with presumed poor adherence may be contributory. Additionally, though various methods of measuring antihypertensive therapeutic intensity have been reported in the literature, there is no uniformly accepted approach to guide therapeutic intensification for HTN in clinical trials or in routine clinical practice. It is clear then that one significant clinical priority in attaining individual and national BP control targets is the implementation of evidence-based approaches for systematically defining and measuring therapeutic intensification across providers and practice types.

Scope of the Problem

Although poor BP control is pervasive, it is difficult to determine how much of this is attributable to therapeutic inertia. In one study conducted in five Department of Veterans Affairs (VA) clinics, researchers found that 40% of male hypertensive patients had a BP that was persistently $> 160/90$ mmHg despite an average of more than six hypertension-related visits per year over a 2-year follow-up period [2•]. Moreover, antihypertensive therapy was found to have been intensified during only 6.7% of visits. Not surprisingly, patients who had more aggressive treatment intensification had greater declines in BP even when adjusting for baseline characteristics (mean decrease in systolic and diastolic BP of 6.3 and 4.5 mmHg, respectively, for those in the highest quintile vs. 4.8 and 0.8 mmHg, respectively, for those in the lowest quintile). Another study from a diabetic cohort treated in an academic medical center clinic setting reported that less than a third of patients with BP above goal received intensification of their antihypertensive therapy [3].

A recent longitudinal trend analysis of nationally representative data from the National Ambulatory Medical Care Survey (2005–2012) and National Hospital Ambulatory Medical Care Survey (2005–2011) assessed antihypertensive treatment intensification [4]. Representing approximately 41.7 million yearly primary care visits among US hypertensive adults where treatment intensification may have been beneficial (i.e., those with a documented BP $\geq 140/90$ mmHg), the weighted prevalence of treatment intensification was only 16.8% (15.8 to 17.9%), with a decreasing trajectory overtime. The low prevalence of

intensification was consistent across a wide range of clinical and demographic groups suggesting that therapeutic inertia is indeed a widespread, pervasive problem.

Why Is There Reluctance to Intensify Treatment?

There are many provider-level factors that contribute to therapeutic inertia. For example, providers' concern for unpleasant medication side effects that are known to negatively impact long-term adherence may lead to delays in therapeutic intensification [5]. Part of this concern may stem from existing understanding of changes to cerebral autoregulation that occur in response to chronic, uncontrolled HTN, where patients become more tolerant of high BP and less tolerant of low BP. Rapid intensification of treatment could lead to cerebral hypoperfusion and its associated consequences [6]. Whether these concerns are justified is unclear, but they do appear to impact clinical practice [7].

Workflow constraints during the clinical encounter may also impact treatment intensification as there is often insufficient time to comprehensively assess patients at each visit. Even when clinicians do have time to address issues such as uncontrolled BP, dosing decisions can be challenging. Clinicians often lack clear knowledge of the standard, expected effects of antihypertensive dosing across medication classes [8•]. Dosing uncertainty can be particularly pronounced when patients have cardiovascular comorbidities and are on multiple classes of antihypertensive medications. Discrepancies between office and home BP readings are common and contribute to uncertainty regarding antihypertensive titration as clinicians may not know what the "real" BP is. This leads to an increased tolerance for BP that is only approaching the recommended therapeutic goal. Some of this may reflect uncertainty about the accuracy of BP measurements taken by their staff or "white coat" HTN [9, 10]. Though difficult to quantify, medication costs and associated concern for whether patients can remain adherent to prescribed therapy are additional factors that may contribute to a reluctance to intensify treatment.

A Rational and Safe Approach to Treatment Intensification

Without a doubt, treatment intensification enhances survival and decrease the likelihood of cardiovascular events in patients with HTN [11–13]. The essential facets of treatment intensification include considerations of medication class, dose, and the cadence of medication change. The choice of medication class is largely guided by expert recommendations such as those put forth from panel members of the Eighth Joint National Committee (JNC-8) [14••]. The JNC-8 emphasizes the importance of treatment intensification in aggressively attaining and maintaining target BP early in the course of management. [14••] However, there is a scarcity of randomized controlled trials comparing the superiority of different approaches to medication titration. Initial medication choice usually consists of thiazide-type diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or calcium channel blockers with broad latitude for clinician and, to a lesser degree, patient preference. Depending on the stage of HTN, medication initiation can be either single agent therapy, or a combination of two medication classes separately, or two medications as a fixed-dose combination pill. Titration pathways include either maximizing a single agent or adding a second agent before reaching the maximum

dose of the first medication. Further antihypertensive therapy includes the addition of different antihypertensive classes for those with BP persistently above goal.

There is growing evidence to support the use of fixed-dose combination therapy in the early treatment intensification of uncontrolled BP. The European Society of Hypertension, JNC-8, and the European Society of Cardiology (ESH/ESC) guidelines specifically recommend starting patients diagnosed with stage 2 HTN ($\geq 160/100$ mmHg) on two antihypertensive medication classes [15]. These recommendations stem from the understanding that most patients ultimately require combination therapy to achieve target BP control [16]. When combined antihypertensive medications are required, fixed-dose combination pills have shown superior adherence and BP control [17-19, 20]. Fixed-dose combination pills simplify dosing regimens, making it easier for patients to comply while combatting therapeutic inertia by driving use of more than one medication.

Treatment intensification also depends on dosing decisions. Step-wise dose escalation may avoid medication side-effects but can produce delays in reaching goal. Understanding what BP-lowering effect may be achieved with antihypertensive therapy is key to effective medication titration. In a meta-analysis of 354 randomized, double-blind, placebo-controlled trials of fixed-dose combination antihypertensive therapy involving close to 40,000 active treatment patients, Law et al. estimated the BP-lowering effect of three concurrent, half-dose medications to be 20 mmHg systolic and 11 mmHg diastolic [21]. More recently, Levy et al. sought to quantify the effect of antihypertensive treatment using a novel, normalized measure of medication dosing called the therapeutic intensity score (TIS) [8]. The TIS is a calculated, proportional measure of prescribed to maximum U.S. Food and Drug Administration approved daily dosage for antihypertensive agents that can be summated as a single, aggregate value. For example, a patient on half the maximum recommended dose of lisinopril, half the maximum dose of chlorthalidone, and half the maximum dose of amlodipine would have TIS of 1.5 (0.5 for lisinopril, 0.5 for chlorthalidone, and 0.5 for amlodipine). Using mixed-effect linear modeling of BP change over time, they demonstrated that each 1 point increase in TIS would result in a 14–16 mmHg reduction in systolic blood pressure—a finding largely consistent with the Law et al. meta-analysis. An overview of the TIS and other scoring methods to standardize antihypertensive therapeutic intensity is provided in the accompanying Table 1.

Clinical guidelines rest on expert opinion as to the cadence of medication titration. The JNC-8 panel recommends follow-up after starting pharmacological treatment or titrating an existing therapy [14]. European guidelines recommend a follow-up every 2–4 weeks after the initiation or titration of antihypertensive drug therapy until blood pressure target is achieved [15]. A more rapid cadence is possible, particularly with the aid of pharmacists or nurse-driven protocols. Nevertheless, the safety and tolerability of more aggressive approaches is not well studied. Using TIS and JNC-8 recommendations as a basis, we propose an algorithm that targets achievement of BP control focused on objective treatment intensification goals in the accompanying Fig. 1.

Overcoming Therapeutic Inertia

While algorithms can facilitate practice change, additional approaches will be needed to overcome therapeutic inertia. One strategy is to increase provider awareness of the pervasiveness of therapeutic inertia while initiating quality improvement programs and decision tools to encourage more active treatment of uncontrolled BP. In the absence of standardized metrics and feedback, clinicians often overestimate the quality of BP management among the populations they care for [22]. The creation of quality improvement programs that incorporate feedback metrics provides clinicians the data needed to drive improvement. Though non-adherence is often thought to be a primary driver of poor BP control, reinforcing the need for progressive treatment intensification is important [4]. Even among patients with resistant HTN, treatment intensification is significantly associated with better BP control at 1 year [13]. There is precedence for system level intervention with such a strategy to reduce therapeutic inertia. A large quality improvement initiative involving 650,000 patients within the Kaiser Permanente Northern California Hypertension registry program demonstrated the efficacy of standardized metrics and feedback in BP control [20•]. Their approach included creation of a system-wide registry, reporting of HTN control rates every 1–3 months for each system medical center, and implementation of system-wide practice guidelines. This comprehensive effort led to an 80% rate of BP control in their hypertensive population compared to a national mean of 64%. Kaiser Permanente Southern California has implemented a similar quality improvement initiative that reaches over 650,000 hypertensive adults [23].

A second strategy calls for shifting the burden of BP control from physicians to other clinical professionals, including nurses, nurse practitioners and pharmacists. Although improvements in individual physician behavior remain important, incorporating systems of care that transcend this paradigm offer promise. Existing studies support the inclusion of diverse healthcare workers in improving BP control. Within the quality improvement program in the Kaiser Permanente system, medical assistants were used to conduct follow-up BP measurements 2–4 weeks following a medication change [20•]. Nurse-driven protocols can also be effective. A recent systematic review and meta-analysis demonstrated positive, albeit modest effects of a nurse-driven approach on BP control [24]. As shown in a recent cluster randomized trial performed among low-income patients using community health workers (CHWs) [25•] and other para-professionals can also be instrumental in overcoming therapeutic inertia at the practice level. In a recent study, CHWs made home visits for health coaching and training in home BP monitoring and provided additional patient support via text-messaging reminders about BP management.

Pharmacist-driven approaches to reduce therapeutic inertia may be among the most effective ways to leverage this strategy. Community-based pharmacists are uniquely positioned to improve BP control among outpatient populations because of the pharmacists' expertise and widespread availability. In studies conducted outside the USA, pharmacists have played a large role in intensifying antihypertensive treatment. The World Health Organization (WHO) has promoted pharmacist-driven protocols since 2005 as part of its integrated chronic disease prevention and control program [26]. In Canada, a pharmacist-led intervention demonstrated a more than 2-fold improved odds for patients reaching their BP target [27].

Another Canadian study that used a pharmacist and nurse team intervention also saw improved rates in BP control compared to usual care [28]. Within the USA, there is evidence of increased efficacy and cost-savings resulting from pharmacist-driven strategies as well. A study by Margolis et al. randomized patients to usual care versus a pharmacist-led home BP telemonitoring intervention. Patients used home BP monitors to transmit readings to pharmacists, who adjusted their medications accordingly. This intervention led to BP control in 72% in the intervention arm versus 57% in the control arm at 18 months [29•]. Similar studies have also shown cost savings by using a pharmacy intervention [30]. A recent meta-analysis of 39 randomized controlled trials involving pharmacist interventions demonstrated overall larger improvements in BP among programs where pharmacists were directly involved in monthly efforts to educate patients, provide feedback to physician, and manage medications [31] suggesting the more they are integrated into care, the better the care is.

Though somewhat more punitive, a third strategy is to implement pay for performance tied to quality metrics. One cluster randomized trial in the VA evaluating the impact of physician and practice-level incentives demonstrated that only individual financial incentives led to improved BP control among hypertensive patients [32]. On the other hand, data from the UK following a 2004 implementation of a pay for performance incentive did not demonstrate significant changes in BP control attributable to this incentive [33]. Ultimately pay for performance incentives can be quite diverse in their design and implementation within a health care system. As such, the success of these types of incentives is largely dependent on the local context [34].

Future Directions

Ongoing studies continue to refine our approach to therapeutic intensification. The National Institutes of Health (NIH) funded Blood Pressure Visit Intensification Study in Treatment (BP- VISIT) currently tests a multimodal intervention designed to increase office visit frequency [35]. The intervention involves clinician training on engagement of patients using collaborative partnerships to improve their BP. It also includes standardized order sets, staff training in blood pressure measurements, and monthly feedback on quality metrics. Another NIH-funded study is the mHealth to Improve Blood Pressure Control in Hypertensive African Americans (MI- BP) [36]. This study tests the efficacy of a mobile health platform to initiate behavioral changes that improve BP control. Both of these ongoing trials involve increased engagement of patients in their own care, a design feature that may positively impact treatment intensification decisions in the future. With near ubiquitous access to quality home BP monitoring and digital health devices, there is much that can be done to test the effectiveness of such tools to augment typical face-to-face clinical evaluations, and reduce therapeutic inertia through more efficient information exchange.

Conclusion

Therapeutic inertia impedes critically important antihypertensive treatment intensification, and broad efforts to combat this are needed if we hope to reduce the population attributable risk of HTN. We outline multiple key aspects in this review which can have immediate and lasting impact on efforts to overcome therapeutic inertia and improve BP control.

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Fig. 1.

Clinical algorithm for treatment intensification based on therapeutic intensity score and JNC-8 guidelines. Primary medication classes for treatment per JNC-8 guidelines include thiazide-type diuretic, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or calcium channel blocker *TIS*, therapeutic intensity score; *JNC-8*, Eighth Joint National Committee

Table 1
Overview of existing scoring systems to standardize antihypertensive therapeutic intensity

Study (year)	Measure	Estimated blood pressure lowering
Levy (2016)	Therapeutic intensity score: proportion of prescribed to maximum recommended antihypertensive medication dose	14.5 mmHg for 1 point TIS
Berlowitz (1998)	Norm-based score: number of observed minus expected number of antihypertensive medication change divided by number of patient visits	6.3 mmHg if score >0.18
Okonofua (2006)	Standard-based score: expected minus observed rate of antihypertensive medication change	6.8 mmHg if score <0.10