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SHORT REPORT

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A novel protocol to assess the impact of prescription stimulants on blood pressure in adults using ambulatory blood pressure monitoring

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Abstract

Prescription stimulants are an important cause of secondary hypertension and their use is increasing in adult patients who are also at risk for essential hypertension. Although stimulants increase blood pressure, a systematic approach for assessing their impact in individual patients is lacking. We developed a protocol using ambulatory blood pressure monitoring for up to 36 h to compare blood pressure over two sequential days. Average blood pressure on the first day (without stimulant medication) was compared to average blood pressure on the second day (after re-starting stimulant medication). We describe the outcomes of this protocol for a case series of eleven adults. Patients demonstrated one of three outcomes: normal blood pressure on both days, hypertension on both days, or hypertension only on the day patients received their stimulant medications. This novel protocol provides valuable information on the blood pressure effects of stimulant medications and allows clinicians to make personalized decisions regarding treatment.

1 | INTRODUCTION

The global burden of hypertension is high and steadily rising. Although national definitions vary, conservative estimates suggest that at least 31% of the world's adults (over 1.4 billion people) are impacted.[1] Effective treatment of high blood pressure (BP) involves a thorough assessment that includes identifying and addressing secondary causes of hypertension that can be significant barriers to achieving BP control. Prescription stimulants are one such potential cause[2] and are used to treat attention-deficit/hyperactivity disorder (ADHD) and sleep disorders such as narcolepsy, shift-work disorder, and obstructive sleep apnea with residual daytime sleepiness. Further, use of these medications is increasing dramatically; between 2000 and 2014, the number of stimulant prescriptions dispensed in the United States nearly tripled to 58 million, over half of which are for adults.[3] As the use of these medications increases, it becomes increasingly important to better understand their impact on cardiovascular health.

Although prescription stimulants are known to impact BP,[4] systematic approaches to assess effects in individual patients are lacking. Without a consistent method by which to gauge the effect of stimulants in individual patients, clinicians are left with trial-and-error if they are to personalize treatment decisions and avoid unnecessary under- or over-treatment. To address this clinical scenario, we

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TABLE 1 Cohort characteristics with blood pressure findings off and on stimulants

Patient	Sex	Age	DM (Y/N)	HLD (Y/N)	# of HTN meds	Stimulant	Indication	Day 1: Off Stimulant average BP (mmHg)	Day 2: On Stimulant average BP (mmHg)	BP Change (SBP mmHg/ DBP mmHg)	Outcome
1	M	83	N	Y	0	Armodafinil	Sleep apnea	135/81	139/80	4/−1	Sustained HTN No stimulant effect
2	F	32	N	N	0	Modafinil	Idiopathic hypersomnia	136/86	151/95	15/9	Sustained HTN Stimulant effect
3	F	69	N	N	0	Armodafinil	Sleep apnea	118/62	116/60	−2/−2	Normotension No stimulant effect
4	M	63	N	N	0	Armodafinil	Sleep apnea	128/85	132/85	4/0	Sustained HTN No stimulant effect
5	M	70	Y	Y	2	Methylphenidate	Sleep apnea	165/73	180/84	15/11	Sustained HTN Stimulant effect
6	M	70	N	N	0	Dextroamphetamine ER	Sleep apnea, ADHD	132/86	148/92	16/6	Sustained HTN Stimulant effect
7	F	25	N	N	0	Dextroamphetamine/ amphetamine IR and ER	ADHD	112/69	112/72	0/3	Normotension No stimulant effect
8	F	30	N	N	0	Dextroamphetamine/ amphetamine IR	ADHD	131/89	135/93	4/4	Sustained HTN No stimulant effect
9	F	36	N	N	0	Methylphenidate	ADHD	129/83	128/81	1/2	Normotension No stimulant effect
10	F	76	N	N	4	Dextroamphetamine/ amphetamine IR and ER	ADHD	120/61	128/58	8/-3	Normotension No stimulant effect
11	F	48	N	N	0	Methylphenidate/ methylphenidate ER	Idiopathic hypersomnia	129/74	138/80	9/6	Stimulant-induced HTN Stimulant effect
Average SBP/DBP (SE)								130.5(4.1)/ 77.2(3.0)	136.7(5.6)/ 80(3.7)	6.7(1.9)/ 3.2(1.4)	

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; ER, extended release; HLD, hyperlipidemia; HTN, hypertension; IR, immediate release; SBP, systolic blood pressure; SE, standard error.

developed a standardized protocol using ambulatory blood pressure monitoring (ABPM) that spans two consecutive days, enabling a simple and direct method to quantify pressor effects of stimulants for individual patients.

2 | METHODS

2.1 | Population

We present data for an initial case series of 11 adult patients of Beth Israel Deaconess Medical Center (BIDMC) who were referred to the BIDMC Hypertension Center at Healthcare Associates (HCA) in 2018–2019 (Table 1). HCA serves as the hospital-based academic primary care practice and cares for over 42 000 adults, approximately 13 000 of whom have hypertension. The BIDMC Hypertension Center is embedded within this ambulatory practice and is staffed by a multidisciplinary team of faculty physicians, internal medicine residents, pharmacists, licensed practical nurses, and medical assistants.

2.2 | ABPM protocol

We used ABPM to evaluate pre- and post-stimulant systolic BP (SBP) and diastolic BP (DBP) for patients with ongoing stimulant use. Prior to scheduling, patient charts were reviewed by a clinical pharmacist to identify type of stimulant prescribed, its duration of action, and its clinical indication for prescription. If the pharmacist identified safety concerns regarding medication interruption, such as treatment for idiopathic hypersomnia, these were addressed with the appropriate prescribing or referring clinicians prior to scheduling. Patients were instructed to not take their stimulant medication on Day 1 of the protocol. They were then fitted with an ABPM (SpaceLabs 99227 or 90217A of Spacelabs Healthcare) according to manufacturer instructions, which they wore the remainder of that day and overnight. On Day 2, patients were asked to take their stimulant medications as prescribed and extend the duration of the ABPM monitoring afterward by an interval at least equal to the duration of action of their prescribed stimulant (Table 2) for up to an additional 12 h or until they went to bed. The ABPM was programmed to perform measurements every 20–30 min during the day and hourly during sleep using Sentinel 10 software. Patients recorded their sleep and wake times and the timing of any medications taken for the duration of the ABPM study. They were otherwise encouraged to simulate, as closely as possible, their usual diet and activities and to make as few other changes as possible between days. Average daytime BP measurements on Day 1 (off stimulant) were compared to Day 2 (on stimulant). We used a threshold of >70% successful readings overall with a minimum of 20 daytime readings and 7 nighttime readings as our criteria for validity for our protocol.[5]

2.3 | Analysis

We defined normotension as an average daytime BP of <135/<85 on Day 1 and Day 2, sustained hypertension as an average daytime BP of ≥135/≥85 on Day 1 and Day 2, and stimulant-induced hypertension as an average daytime BP of <135/<85 on Day 1 and ≥135/≥85 on Day 2 (Figure 1). We also defined a clinically significant stimulant effect as an increase in daytime SBP of ≥10 mm Hg and/or an increase in daytime DBP of ≥5 mm Hg while on medication.

3 | RESULTS

We assessed eleven patients using our protocol, with an average age of 54.7 (range 25–83) years (Table 1). The most common stimulants prescribed were armodafinil and combination dextroamphetamine/amphetamine. Indications for use were roughly even between sleep disorders and attention-deficit/hyperactivity disorder.

Four patients were normotensive on both days, suggesting that they did not have either essential or drug-induced hypertension. In contrast, six patients demonstrated sustained hypertension on both days, which we interpreted as indicating underlying essential hypertension, although three also showed a clinically significant increase in BP on stimulant therapy. One patient was normotensive off their stimulant medication but hypertensive on the day they took their medication with an average increase in BP between the two days of 9 mm Hg SBP and 6 mm Hg DBP. The overall average increase across eleven patients was 6.7 (SE 1.9) mm Hg SBP and 3.2 (SE 1.4) mm Hg DBP. No serious adverse events occurred during the protocol.

4 | DISCUSSION

We present a novel clinical protocol for utilizing ABPM to assess the impact of prescription stimulants on BP trends in a case series of 11 adults. The protocol was well-tolerated by patients with minimal additional burden on clinic resources and represents a safe and standardized approach for the assessment of BP abnormalities among patients who require stimulant use.

The protocol stratified patients into three diagnostic categories. Some were normotensive throughout the study, some were consistently hypertensive, and one patients' average BP increased enough to cross the diagnostic threshold for hypertension. We defined hypertension as an average daytime BP of ≥135/≥85 by ABPM, a threshold that was commonly used at the time we designed this protocol.[6] We did not expect to find cases in which the average BP was lower while on stimulant medications, and indeed no such examples occurred in this limited patient sample.

Four patients were found to be normotensive both on and off their stimulant medication, none of whom had a clinically significant increase by our definition. Given that they were referred to the

TABLE 2 Stimulant medications and duration of action[7]

Medication	Time to Peak	Duration of action	Recommended monitoring interval after stimulant dose
Armodafinil	2 h	15 h	15 h or until bedtime, whichever is shorter
Dextroamphetamine ER	8 h	8 h	8 h
Dextroamphetamine/amphetamine IR	3 h	4–6 h	4 h after last dose
Dextroamphetamine/amphetamine ER	7–8 h	8–12 h	12 h or until bedtime, whichever is shorter
Methylphenidate IR	1–2 h	3–5 h	4 h after last dose
Modafinil	2–4 h	15 h	8–10 h

Abbreviations: ER, extended release; IR, immediate release.

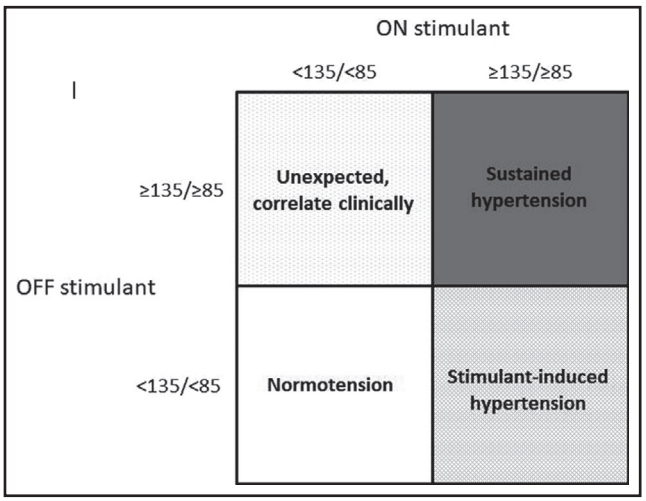

FIGURE 1 Classification of hypertension subtypes based on daytime average BP on and off prescription stimulant medication

BIDMC Hypertension Center on the basis of hypertension measured elsewhere, the results of this protocol suggest that a white coat effect was responsible for their previously elevated BP measurements. As a consequence, the protocol enabled these patients to continue stimulant therapy without modification.

A total of four of the eleven patients (36%) demonstrated increases in their BP that we considered clinically significant. This "stimulant effect" was observed in three of the patients who had sustained hypertension on both days and in one patient determined to have stimulant-induced hypertension. These results suggest that the pressor effect of stimulants may be greatest among individuals with higher baseline BP, but confirmation would require a larger study.

Two additional details of the protocol warrant elaboration. First, we used established pharmacodynamic data to drive the duration of the ABPM for each patient. The length of time the ABPM was worn on Day 2 (while on stimulant) was determined in advance for each patient based on the duration of action for the prescribed stimulant (Table 2). Duration of action is a commonly used parameter to assess the clinical impact of a medication. Second, we tailored changes in therapy for individual patients based on these results which are beyond the scope of the protocol presented here. In practice, this meant increases in antihypertensive medication (and continued stimulant use) for nearly all patients, but our findings suggest that a range of treatment options might be reasonable. For example, most patients with sustained hypertension also exhibited a significant increase with stimulant use, suggesting that continued use might require more intensive pharmacological therapy. We defer to individual clinicians to work with their patients as they navigate this clinical dilemma.

Our protocol has several strengths. We utilized a gold-standard clinical tool (ABPM) for the evaluation of BP along with the underlying pharmacologic properties of stimulant medications to assess their impact on BP in a real-world setting. Our case series included a broad patient age range and multiple underlying clinical diagnoses for prescribing stimulants.

There were also several limitations to our protocol. Our small sample limited our ability to make meaningful observations for individual classes of stimulants or the underlying conditions for which they were prescribed. As these ABPMs were limited to approximately 36 h, it is possible that results would vary with a wider assessment period. We used stimulant duration of action to inform how long patients were instructed to wear the ABPM on Day 2; while we acknowledge that this is an imperfect measure given individual variations in pharmacokinetics, our goal was to capture the bulk of pharmacologic impact of the medication prescribed in a manner that was patient-centered. Suggested durations for ABPM after dosing stimulant medications are listed (Table 2) but these could be tailored to different clinical scenarios.

Lastly, although this case series was performed with a historic ABPM threshold for hypertension (≥135/≥85), it can be readily adapted to other thresholds.

Future work in this area could include larger case series that may allow for more robust conclusions to be drawn regarding different underlying conditions and individual prescription stimulants.

In summary, we describe a simple, standardized protocol that could be rapidly adopted at hypertension centers or any practice that performs ABPM. Our approach provides valuable information

to the patient's care team regarding the BP impact of their simulant medication and allows treatment decisions to be personalized. As prescription stimulant use grows, we encourage more widespread use of protocols like this to maximize safety for patients who use these medications.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

JLC and AMI contributed to protocol design and implementation, data collection, review and analysis and manuscript preparation and review. KJM and SPJ contributed to data review and analysis as well as manuscript preparation and review.

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