Clinical Challenges

Hypertension II

Peter P. Toth · Domenic A. Sica

FOREWORD BY SUZANNE OPARIL

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CLINICAL CHALLENGES IN HYPERTENSION II

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Foreword

Hypertension is the most common form of cardiovascular disease in economically developed and developing countries, afflicting over 73 million persons in the US and over one billion worldwide. Left uncontrolled, it is a major contributor to death and disability due to stroke, coronary artery disease and chronic kidney disease. While blood pressure reduction has been shown in randomized controlled trials to be highly effective in preventing acute cardiovascular events and death, attainment of guideline specified blood pressure goals in the practice setting has proved difficult. Much of the difficulty experienced by primary care providers and hypertension specialists alike in managing blood pressure comes from conflicting information about the relative efficacy of various antihypertensive measures, both pharmacologic and nonpharmacologic (lifestyle modification). Further, there is a paucity of authoritative information about how to approach blood pressure management in patients with comorbidities that may be driving blood pressure elevation (anxiety and panic disorders, sleep disorders, athletic activities) or that may limit therapeutic choices (acute and chronic stroke, coronary artery disease) and in special patient populations (adolescents and young adults, the very elderly).

Edited by preventive cardiologist Peter Toth and clinical pharmacologist Domenic Sica, this new book fulfils an urgent need of those who care for hypertensive patients by providing answers or at least approaches to practical questions that are not addressed in current guidelines. The volume is organized around frequently asked questions about hypertension that surface time and time again at educational symposia. Issues discussed include both core clinical and scientific concepts and practical everyday patient related issues that are not well covered in most hypertension guidelines.

Chapters by world experts offer advice on such critical questions as: How should we use home (self) blood pressure measurement vs. 24 hour ambulatory blood pressure monitoring vs. office-based blood pressure readings for diagnosis and management of hypertension? What are appropriate treatment goals for systolic and diastolic blood pressure? In what patient groups? Does lifestyle modification play a major-and sustainable-role in hypertension management? If pharmacologic therapy is needed, does it matter what we use? Should we believe, as stated in JNC7, that diuretic therapy should be first step therapy in all (or nearly all) hypertensive patients? Or, should we adopt the recommendations of the more recent European guidelines that several classes of antihypertensive drugs are appropriate for first line treatment, at the discretion of the caregiver? What is more important, getting to goal blood pressure or blocking critical pathways, e.g., the renin-angiotensin-aldosterone system? In other words, when considering antihypertensive treatment, does mechanism matter? Are all angiotensin converting enzyme (ACE) inhibitors equally effective in lowering blood pressure? Protecting target organs? Are angiotensin receptor blockers (ARBs) equivalent or superior to ACE inhibitors in controlling blood pressure and protecting target organs? What is the best way to treat morning surges in blood pressure?

Importantly, there are many hypertensive patients for whom treatment recommendations based on the strongest form of evidence, the randomized controlled trial, are lacking. Chapters in this book address many of these common and difficult to manage situations,

e.g. the patient with anxiety/panic disorder and labile hypertension, the post-stroke (both acute and chronic) patient, the athlete who wishes to continue to compete despite his/her hypertension, the adolescent or young adult with hypertension in whom the short term risk of cardiovascular disease/events is low but the long term prognosis may not be benign, and the patient with a hypertensive emergency. For many of these conditions, there may never be randomized controlled trial data. In the meantime, the caregiver must rely on expert opinion and his/her own experience in caring for patients with these complex problems. *Clinical Challenges in Hypertension II* (along with its companion volume *Challenges in Hypertension*) is a treasure trove of valuable expert opinion on how to deal with many important problems in hypertension management. I recommend it highly.

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Preface

Hypertension (HTN) is a complex, multifactorial disease. In the last four decades an enormous amount of experimental, epidemiologic, and clinical investigation has demonstrated beyond all doubt that elevations in both systolic and diastolic blood pressure exert deleterious effects on the vasculature. Progressive injury stemming from chronically elevated blood pressure increases risk for developing endothelial dysfunction, loss of vascular elasticity and distensibility, atherosclerosis, left ventricular hypertrophy, heart failure, ischemic and hemorrhagic stroke, peripheral arterial disease, as well as proteinuria and nephropathy. Hypertension is widely prevalent throughout the world and constitutes a significant public health issue. The incidence of HTN is increasing in men and women and in people across all ethnic groups.

The treatment of hypertension is one of the true cornerstones in any approach to reducing risk for cardiovascular events in both the primary and secondary prevention settings. Evidence-based, population specific guidelines for the treatment of HTN have been developed by numerous expert bodies. These guidelines are rigorous and based on many well done prospective, randomized clinical trials. They emphasize the critical need to lower elevated blood pressure with lifestyle modification and pharmacologic intervention and to treat patients with end organ injury with specific classes of drugs. Despite the clarity and utility of many of these guidelines, there continues to be low rates of attaining target blood pressure in approximately two-thirds of the patients with HTN. Clearly, more focused efforts at improving the identification and management of HTN need to be implemented. Patient compliance and access to medication must also be improved.

The etiology of HTN depends on specific, highly complex genetic and metabolic backgrounds. Environmental influences (e.g. social/psychological stress, salt intake, diet) also play significant roles. The brain, kidney, and visceral adipose tissue regulate a wide range of biochemical and physiological responses which intimately influence the molecular and histologic dynamics of arterial walls, leading to increased vasomotor tone and HTN.

Hypertension in any given individual is often multifactorial. During the last 60 years, many different drug classes have been developed to antagonize specific mechanisms by which blood pressure is raised (i.e. reducing intravascular volume, inhibiting renin and angiotensin converting enzyme, blocking intravascular catecholamine and angiotensin II receptors, and blocking calcium channels in smooth muscle cells). The majority of patients require combinations of drugs to control their blood pressure, especially in the presence of end organ damage. It requires clinical experience and insight into drug mechanisms to appropriately target specific mechanisms with specific drugs in order to optimally control blood pressure.

There are numerous fine textbooks in the field of hypertension and nephrology. This book is not intended to be encyclopedic. Rather, it is framed as a series of questions with detailed answers that are as evidence-based as possible. The authors are all experts in the field of HTN management. The questions posed are those that often arise at major conferences. These are the sorts of questions that often puzzle clinicians the most, or leave them wondering what the evidence supporting certain approaches really consists of. Issues such

as the need to treat early morning surges in blood pressure, the influence of sleep and anxiety disorders on blood pressure, determining the most efficacious first line agent for HTN, therapeutic equivalency of angiotensin converting enzymes and angiotensin receptor blockers, issues and complications in the management of isolated hypertension, and the nature of endothelial dysfunction, among others, receive detailed, focused, and practical treatment in a manner that emphasizes daily application in clinical and hospital settings. Therapeutic approaches emphasize established guidelines for HTN management. Important biochemical and physiologic pathways are illustrated. The emphasis of each chapter is on improving patient care and encouraging clinicians to expand their scope and efficacy of practice.

It is our sincerest wish that this book facilitates the mission each of us share in improving patient care. The targeted, appropriate management of HTN unequivocally reduces cardiovascular morbidity and mortality. The control of HTN also helps to forestall the development of endstage renal disease and need for dialysis and reduces the rate of progression of heart failure, atherosclerosis, and aortic aneurysms. Increasing the number of patients with well-controlled blood pressure is an important goal as it improves the quality and quantity of life. We hope that this book and its companion volume facilitate more aggressive and thoughtful approaches to blood pressure management.

Peter P. Toth
Domenic Sica

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Do anxiety and panic disorders influence blood pressure?

C. Warren, S. L. Dubovsky

BACKGROUND

The significant comorbidity between hypertension and both generalized and panic anxiety disorders has been recognized for many years [1, 2]. The interaction between anxiety and blood pressure (BP) is complex, involving direct effects of anxiety on BP, lifestyle issues, and effects of psychiatric and antihypertensive medications. In this chapter, we will briefly review the diagnosis and psychiatric comorbidities of anxiety disorders, causes of hypertension in anxious patients, and treatment of anxiety in hypertensive patients.

Anxiety can be broadly divided into generalized, phobic and panic anxiety. Generalized anxiety consists of excessive worry about everyday events. Phobic anxiety is provoked by a particular stimulus or situation. Simple phobias such as fear of snakes or heights are less common than anxiety in social situations (social phobia or social anxiety disorder). Social anxiety may be specific (e.g. anxiety with public speaking or other forms of performance) or it may be generalized (anxiety in all social and performance situations). Panic anxiety is characterized by unprovoked attacks of intense anxiety with substantial physiologic arousal. Recurrent panic attacks are frequently accompanied by anticipatory anxiety (anxiety about having another panic attack) and may lead to agoraphobia, initially manifested as anxiety in any situation in which a panic attack has been experienced or from which escape might be difficult if a panic attack occurred. Agoraphobia may also develop in the absence of panic attacks.

Anxiety disorders are defined by the predominant type of anxiety and the circumstances in which it occurs [3]. For example, generalized anxiety disorder is characterized by chronic, relapsing anxiety involving everyday issues such as worry about something happening to loved ones or about getting sick. Panic disorder is defined by recurrent panic attacks, with or without agoraphobia. Social anxiety disorder and phobias involve anxiety restricted to specific situations or stimuli. Post-traumatic stress disorder is classified with the anxiety disorders, although anxiety is only part of a syndrome of re-experiencing, avoidance, numbing and arousal in response to a severe traumatic event. In obsessive compulsive disorder (OCD), anxiety occurs when patients are not able to engage in compulsions (rituals), which often arise in response to obsessions (for example, when patients with contamination fears

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Table 1.1 Physical symptoms commonly experienced by anxious patients.

- Shortness of breath
- Light headedness
- Paresthesias
- Difficulty concentrating
- Insomnia
- Generalized aches and pains
- Jaw clenching
- Back pain
- Multiple somatic complaints
- Choking
- Chest pain
- Tremor
- Sweating
- Palpitations
- Feeling easily fatigued

are not able to wash their hands after getting them dirty). Anxiety is a prominent secondary symptom in other psychiatric disorders. For example, 70% of depressed patients are also anxious and anxiety can be a symptom of impending overstimulation or mental disorganization in patients with mania or psychosis. Anxiety disorders are most frequently comorbid with other disorders, depression and bipolar disorder; common medical comorbidities include hypertension, dyslipidemias, asthma, and chronic obstructive pulmonary disease [4]. Patients with anxiety and hypertension have an increased rate of non-adherence with medical therapy because they experience more adverse effects and have a lower threshold for discontinuing treatment [2]. Such patients are also less likely to seek medical care in the first place [5].

Psychological dimensions of anxiety involve hyperfocus on the possibility of danger and a sense of being helpless to master it. While mental manifestations of anxiety are obvious (e.g. worry, tension, fears of losing control, difficulty concentrating, avoidance of situations that provoke anxiety), physical symptoms are often the presenting complaint, especially in a non-psychiatric setting (Table 1.1). Physical symptoms represent a combination of exaggerated awareness of minor bodily dysfunction that most people ignore and somatic consequences of high levels of arousal.

PHYSIOLOGY OF ANXIETY

From a physiologic standpoint, anxiety is a state of high arousal. [6, 7]. Arousal in anxiety is mediated by the locus coeruleus, the major brainstem noradrenergic nucleus. Stimulation of the locus coeruleus, can occur with the perception of danger or in response to substances known to induce anxiety such as caffeine, sodium lactate, adrenal medullary hormones, stress, hypotension, hypercapnia or hypoglycemia. Connections to the amygdala result in mental orientation toward the possibility of danger, and activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis results in tremor, tachycardia, elevated BP, altered blood flow, metabolic changes favoring energy production and other dimensions of the 'fight or flight' response.

Whereas anxiety increases central and peripheral release of norepinephrine and its metabolites, catecholamines themselves induce anxiety by activating the locus coeruleus. As a result, stress responses can become self-perpetuating, with the physiology of anxiety leading to more catecholamine release and more arousal. Other stress hormones such as arginine

vasopressin, corticotrophin releasing factor and cortisol can also activate the locus coeruleus and induce anxiety. Cholecystokinin also seems to participate in inducing anxiety and may participate in some gastrointestinal symptoms of anxiety.

ASSOCIATION OF ANXIETY AND HYPERTENSION

Anxious patients have an elevated risk of hypertension, and hypertensive patients are more likely than normotensive patients to experience anxiety. In a study of 891 hypertensive outpatients, 11.6% had an anxiety disorder, and levels of anxiety on a self-rating scale were positively correlated with severity and duration of hypertension [8]. State and trait anxiety are both increased in patients with primary hypertension [9]. Similarly, a comparison of 80 hypertensive patients with 80 matched controls reported that anxiety, stress and anger turned inward were more common in hypertensive patients [10], and anxiety and depression but not stress levels were more common in a group of 73 hypertensive patients than in 73 matched controls [11]. A very large Scandinavian population survey found that hypertension was almost twice as common in anxious patients as in controls, while the incidence of hypertension was not increased in patients with schizophrenia [12]. In a retrospective data analysis of 6647 patients with anxiety disorders followed for a year, 22% were hypertensive [4]. A 15-year prospective follow-up of 3308 adults from the Coronary Artery Risk Development in Young Adults (CARDIA) study found that time urgency/impatience and hostility but not anxiety or depression predicted the later development of hypertension [13]; alternatively, in a cross sectional nationally representative telephone and postal survey study of 3032 adults aged 25–74 in the continental US, generalized anxiety disorder in the absence of depression was associated with an increased risk of coronary heart disease [1].

WHAT CAUSES HYPERTENSION IN ANXIOUS PATIENTS?

Anxiety and elevations of BP clearly are associated, but does one cause the other, or are they both consequences of a common factor? Hypertension and anxiety can both result from a number of illnesses and substances [14–17]. A well-known example is pheochromocytoma, which causes both paroxysmal hypertension and anxiety. Hyperthyroidism, hypoglycemia and hypercalcemia are also associated with both anxiety and hypertension. Obesity, which increases the risk of hypertension, is more common in psychiatric disorders, including chronic anxiety disorders [18]. It is not known whether anxious people ingest more salt than the general population, but the average anxious inpatient drinks 20 cups of coffee per day.

Medications such as adrenal steroids, stimulants, sympathomimetics (e.g. phenylephrine), modafinil, progesterone, ergot alkaloids and ropinirole can cause both anxiety and hypertension. Antipsychotic drugs usually cause orthostatic hypotension, but they occasionally elevate BP. These medications also cause akathisia, a sense of inner restlessness, which can make patients markedly anxious. Central nervous system depressants such as the benzodiazepines and barbiturates reduce anxiety acutely, but withdrawal, which frequently occurs between doses of shorter acting medications like alprazolam, causes both anxiety and hypertension, often along with other signs of discontinuation such as tachycardia and tremor. Substances that regularly induce both anxiety and hypertension include caffeine, ephedra, amphetamines and cocaine; tolerance does not develop to the pressor effect of many of these substances, including caffeine [19]. Over-the-counter preparations containing ephedra (banned in the United States since 2004) and caffeine have been reported to cause severe hypertension, sometimes with life-threatening hypertensive encephalopathy [16]. Withdrawal from alcohol induces anxiety, insomnia and hypertension, which may become chronic with ongoing intermittent drinking.

Most antihypertensive medications do not usually cause anxiety, but reserpine, methyldopa, a-adrenergic blocking agents and nifedipine can cause depression, which may then be

complicated by anxiety [20]. Beta-adrenergic blocking agents occasionally can cause mania and confusion, which may be accompanied by anxiety. On the other hand, a number of medications commonly used to treat anxiety are associated with hypertension as a side-effect. This is particularly true of medications that increase neurotransmission with dopamine and/or norepinephrine (e.g. tricyclic antidepressants [TCAs], bupropion, venlafaxine, stimulants) [14]. Venlafaxine can cause severe elevations in BP and hypertensive crises [21]. While they are not directly noradrenergic, the serotonin reuptake inhibitors (SSRIs) indirectly stimulate norepinephrine release, which can then elevate BP. The monoamine oxidase inhibitors (phenelzine, isocarboxazid, tranylcypromine, selegeline), which are used to treat refractory and bipolar depression and some anxiety disorders, interact with tyramine containing foods such as cheese to cause severe hypertension because monoamine oxidase catalyzed degradation of tyramine, a naturally occurring pressor amine, is inhibited by these medications. Occasional cases of spontaneous hypertensive reactions in the absence of dietary indiscretion have been reported with Tranylcypromine. These cases of apparent autoinduction of hypertensive reactions are presumably attributable to metabolic conversion of tranylcypromine to metabolites with pressor activity, although this has not been shown to occur *in vivo*.

Activation of the sympathetic nervous system with anxiety can elevate BP, as was demonstrated by the observation that the prospect of injection of local anesthesia increased systolic and diastolic pressures by 24–26% and 4–5%, respectively [22]. The possibility that anxiety leads directly to hypertension was suggested in a prospective study of 31 healthy men [23]. Over 4.8 years of follow-up, hypertension was significantly more likely to develop in subjects with higher levels of anxiety and irritability and in those with greater BP reactivity in response to stress, but not those with higher salt sensitivity. In a population-based cohort of 3310 initially normotensive healthy individuals followed for up to 22 years, the combination of symptoms of anxiety and depression at baseline are predictive of the risk of later development of hypertension (risk ratio [RR] = 1.73) [24].

A well-known model of the impact of anxiety on BP is the white coat phenomenon (white coat hypertension). In 226 subjects, anxiety in the clinic was significantly associated with higher diastolic BP during clinic visits than at home during ambulatory monitoring [25]. Anxiety during clinic visits is associated with a greater perception of being hypertensive and a larger white coat effect. However, debate continues about the degree to which the white coat phenomenon is a model of clinically important hypertension. In a summary of four prospective cohort studies, white coat hypertension increased the risk of stroke after 9 years of follow-up [26]. In contrast, a 10-year follow-up of 1332 people with either white coat hypertension or hypertension on ambulatory monitoring but not in the doctor's office found that the composite risk of cardiovascular mortality and stroke morbidity was increased in the latter but not the former [27]. This observation seems consistent with other research suggesting that ambulatory monitoring is a better predictor of complications of hypertension than is monitoring in the office, especially by the physician [28].

DOES TREATMENT OF ANXIETY REDUCE BLOOD PRESSURE?

To the extent that anxiety or high levels of arousal contribute to BP elevation, reduction of anxiety should reduce BP. The benzodiazepine diazepam was as effective as sublingual captopril in reducing BP in patients with "excessive" hypertension (BP >190/100 mmHg) referred to an emergency room setting [29]. Thirty years of experience has demonstrated that biofeedback and relaxation therapy can be effective treatments for mild hypertension [30], possibly by attenuating the sympathetic response to stress [31]. In a recent study, a Chinese system of therapy for anxiety resulted in both better BP control and quality of life in hypertensive patients compared with usual care [32]. Controlled studies have demonstrated that transcendental meditation reduces BP, carotid artery intimal thickness, myocardial ischemia, left ventricular hypertrophy and mortality in hypertension [33].

Table 1.2 Some commonly prescribed benzodiazepines.

Drug	*Lipid solubility*	*Half-life*	*Active metabolites?*	*Usual daily dose (mg)*	*Comments*
Diazepam	High	Long	Yes	5–30	Rapid onset and offset of action acutely but accumulates over time
Chlordiazepoxide	Low	Long	Yes	25–200	Accumulates with repeated dosing
Clonazepam					
Clorazepate	Low	Short	Yes	7.5–30	Prodrug for desmethyldiazepam
Oxazepam	Low	Short	No	30–60	Useful in liver disease
Lorazepam	Low	Short	No	0.5–2	Slow onset and offset of action in acute dosing
Alprazolam	High	Short	No	0.125–3	Higher doses needed for panic disorder; interdose withdrawal common
Temazepam	Low	Short	No	7.5–30	Usually used as hypnotic but has anxiolytic properties

TREATMENTS FOR ANXIETY IN HYPERTENSIVE PATIENTS

Acute anxiety is usually treated with benzodiazepines [34]. Predictors of a good response include anxiety in response to a specific stress and awareness that symptoms are psychological. These medications all act at benzodiazepine receptors, which allosterically modulate the activity of adjacent gamma-aminobutyric acid (GABA) receptor complexes, organized around a chloride ion channel. Occupation of benzodiazepine receptors increases affinity of GABA receptors for their agonist, increasing chloride influx and hyperpolarizing neurons in limbic, cortical and arousal centers, including the locus coeruleus. Reduction of activity in the locus coeruleus reduces activation of the sympathetic nervous system, with the potential to ameliorate hypertension associated with sympathetic overactivity.

Information about preparations and dosing of benzodiazepines is available in any psychopharmacology text [14]. Table 1.2 categorizes some of the commonly used benzodiazepines according to their lipid solubility and elimination half-life. In general, more lipid soluble medications enter and leave the brain rapidly and therefore have a rapid onset and offset of action after a single dose. If a highly lipid soluble benzodiazepine also has a short elimination half-life, it should be administered more frequently to prevent interdose withdrawal. This problem is most marked with alprazolam, which is also a high potency medication, with rebound of symptoms occurring as the brain level of the medication drops between doses. Medications that are less lipid-soluble have a slower onset of action, and the effect wears off more slowly after a single dose. Benzodiazepines that are relatively low in lipid solubility and have longer elimination half-lives and lower potency (e.g. chlordiazepoxide) accumulate with repeated dosing, resulting in adverse effects beginning some time after starting the medication and persisting for some time after it is discontinued. Diazepam has a long elimination half-life but is highly lipid soluble and it is about five times as potent as chlordiazepoxide. As a result, a single dose works rapidly and the effect wears off quickly, but the medication accumulates with repeated doses. Lorazepam has a relatively short elimination half-life and high potency, but it is low in lipid solubility. Consequently, a single dose has a slower onset and offset of

action than a single dose of diazepam, but lorazepam is less likely to accumulate with repeated doses. Oxazepam, an intermediate half-life agent that is the final active metabolite of chlordiazepoxide and diazepam, has no active metabolites of its own. Clorazepate itself has a short half-life but it is a prodrug of desmethyldiazepam with no pharmacologic activity of its own. Its true properties are therefore closer to those of diazepam.

The most important side-effects of the benzodiazepines are sedation and impairment of memory and psychomotor function. The equivalent of 10 mg of diazepam has the potential to impair driving to a degree that would meet criteria for 'driving under the influence'. Tolerance develops to the sedating effects but not the psychomotor impairment that occurs with benzodiazepines. On the other hand, addiction to benzodiazepines is rare in patients who do not have a past history of substance misuse. Discontinuation syndromes, which include return of anxiety, rebound anxiety (anxiety that is more intense than prior to starting the medication), and withdrawal (new physiologic signs such as hypertension, labile BP, tachycardia, myoclonus, confusion and seizures), occur with all benzodiazepines. Drugs with longer half-lives and lower potency (e.g. chlordiazepoxide) are associated with attenuated but more prolonged withdrawal syndromes while benzodiazepines with short half-lives, especially if they are high in potency (e.g. alprazolam) produce more intense withdrawal that appears sooner but does not last as long. Benzodiazepines have additive sedative side-effects with other central nervous system (CNS) depressants and they may have additive hypotensive effects with antihypertensives.

Antidepressants are now the mainstay of treatment of chronic anxiety (Table 1.3). All currently available antidepressants except bupropion are effective for generalized, panic and social anxiety. As was noted earlier, most antidepressants, including the SSRIs, have an initial noradrenergic action that can increase anxiety and BP, in addition to causing related side-effects such as tremor and sweating. However, over time this is followed by down-regulation of β-adrenergic receptors and reduction of noradrenergic activity. Because anxious patients are so sensitive to all adverse effects, antidepressants should be started at a very low dose and the dose should be increased very slowly to allow tolerance to develop to the noradrenergic effect. Beginning treatment with a benzodiazepine can block initial activation by the antidepressant. The benzodiazepine can often be gradually withdrawn when the anxiolytic effect of the antidepressant is fully established. As with the treatment of depression, this can take 1–2 months. Since most anxiety disorders are chronic or recurrent, continuous treatment is often necessary.

The TCAs have been replaced by the SSRIs as first-line treatments because the latter medications have fewer adverse effects and simpler dosing. However, TCAs are still used for more severe and refractory forms of depression as well as for chronic pain and migraine prophylaxis. Anticholinergic side-effects of the TCAs (tachycardia, dry mouth, blurred vision, urinary retention, constipation) are most marked with tertiary amines such as amitriptyline, imipramine, trimipramine and doxepin and less prominent with secondary amines such as desipramine and nortriptyline. Postsynaptic α_1 adrenergic blockade results in hypotension with all TCAs, but noradrenergic TCAs such as desipramine can elevate BP. Alpha-adrenergic blockade also interferes with the pressor action of adrenergic agents such as norepinephrine and dopamine. All of the TCAs have the potential to increase appetite and weight gain, and they all have type 1A antiarrhythmic properties with the potential to aggravate atrioventricular block.

Regardless of manufacturers' claims, all SSRIs have similar efficacy and the same incidence of side-effects, including sexual and gastrointestinal side-effects, headache, sedation and jitteriness. Medications in this class differ in their elimination half-lives and inhibition of CYP450 enzymes. For example, fluoxetine and paroxetine are potent inhibitors of CYP2D6, which metabolizes antihypertensive medications like carvedilol, metoprolol and nebivolol, fluvoxamine inhibits CYP3A4, the isozyme that metabolizes verapamil, diltiazem, and eplerenone.

Table 1.3 Antidepressants.

Drug	*Neurotransmitter action*	*Usual dose (mg)*	*Blood pressure effects*	*Comments*
Tricyclic antidepressants				
Imipramine	5-HT, NE uptake inhibition	150–300	Postural hypotension	Adjusted by blood level
Desipramine	NE uptake inhibition	150–300	Increased BP	What about the therapeutic window
Amitriptyline	5-HT, NE uptake inhibition	150–300	Postural hypotension	Anticholinergic
Nortriptyline	NE uptake inhibition	75–150	Increased pulse and BP	What about the therapeutic window
Doxepin	NE uptake inhibition; H1 blockade	150–300	Postural hypotension	Useful as antihistamine and for peptic ulcer disease
Trimipramine	NE, 5-HT uptake inhibition	150–300	As for doxepin	
Maprotiline	NE uptake inhibition	150–225	Tetracyclic structure; seizures at doses >225 mg/day	
Amoxapine	NE uptake inhibition, D2 blockade	150–300	Increased BP or postural hypotension	Neuroleptic effect can cause extrapyramidal side-effects; seizures at high doses
Clomipramine	5-HT, NE uptake inhibition	150–250	Postural hypotension	Only TCA effective for OCD
Serotonin reuptake inhibitors				
Fluoxetine		10–40		Half-life 3 days
Paroxetine	5-HT uptake inhibition	10–50		Anticholinergic; causes weight gain; not for use in children
Sertraline		50–200	Negligible	Minimal P450 effects
Fluvoxamine		150–300		Only SSRI to require divided dosing
Citalopram		20–40		No P450 interactions
Escitalopram		10–20		S-enantiomer of citalopram with similar effects
Third-generation antidepressants				
Trazodone	5-HT_2, α_1 antagonism	50–600	Hypotension	Can cause priapism at any dose; requires divided dosing as antidepressant
Nefazodone	5-HT_2 antagonism, 5-HT uptake inhibition	200–600	Hypotension	Can improve sleep structure; rare cases of severe/fatal hepatotoxicity reported
Bupropion	NE, DA uptake inhibition	150–450	Mild hypertension	No sexual or cardiac effects; seizure risk at doses >450 mg

Table 1.3 Continued.

Drug	*Neurotransmitter action*	*Usual dose (mg)*	*Blood pressure effects*	*Comments*
SNRIs				
Venlafaxine	5-HT, NE, DA uptake inhibition	75–375	Severe hypertension possible at higher doses	Useful for severe and treatment-resistant depression; divided dose necessary at higher doses of XR formulation
Duloxetine	5-HT, NE uptake inhibition	60–120	Mild hypertension possible	BID dosing
Monoamine oxidase inhibitors				
Phenelzine	Inhibition of intraneural metabolism of 5-HT, NE, DA	30–90	Hypotension; hypertension with dietary interactions	Anticholinergic; causes weight gain
Isocarboxazid	As for phenelzine	20–60	As for phenelzine	Less sedation and weight gain than phenelzine
Tranylcypromine	As for phenelzine; metabolite releases DA	30–90	Less hypotension than phenelzine; spontaneous hypertension possible	More activating; amphetamine-like actions
Selegiline	As for tranylcypromine	20–50	No hypotension; no dietary interactions at doses ≤ 10 mg	Minimal antidepressant effect at doses below 20 mg; patch available but benefit may not justify cost

5-HT = serotonin; 5-HT_2 = serotonin-2 receptor; BID = twice a day; BP = blood pressure; DA = dopamine; D2 = dopamine 2 receptor; H1 = histamine 1 receptor; HR = heart rate; NE = norepinephrine; OCD = obsessive compulsive disorder; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = serotonin reuptake inhibitor; TCA = tricyclic antidepressant; XR = extended release.

Trazodone is primarily an antagonist of serotonin 5-HT_2 receptors. Given in doses of 300–600 mg/day on a thrice-daily schedule, trazodone is an antidepressant, but it is too sedating for many patients to tolerate at these high doses. On the other hand, its short elimination half-life makes it useful as a hypnotic. Nefazodone combines SSRI and 5-HT_2 antagonist properties. It has negligible effects on BP but occasional cases of severe hepatotoxicity with the proprietary formulation have limited its use. Norepinephrine and to some extent dopamine reuptake inhibition by bupropion carries the potential to increase BP.

Venlafaxine, which is particularly useful for treatment-resistant depression, inhibits serotonin reuptake at doses below 75 mg. As the dose increases, norepinephrine reuptake and then dopamine reuptake are also inhibited. The latter effect produces a risk of significant hypertension in some patients and this medication generally should not be given to hypertensive patients. Duloxetine inhibits reuptake of serotonin and norepinephrine, but not dopamine, at all doses, resulting in a lower risk of hypertension. Mirtazepine antagonizes serotonin 5-HT_2 and 5-HT_3 receptors as well as presynaptic norepinephrine α_2 receptors, which increases norepinephrine release, with the potential to elevate BP. Venlafaxine, bupropion and mirtazepine therefore are not appropriate initial choices for hypertensive patients.

Monoamine oxidase (MAO) inhibitors are usually prescribed by psychiatrists to treat refractory depression and anxiety disorders. The MAO inhibitor selegiline is also used for Parkinson's disease. Despite their potential to cause dangerous hypertensive reactions when combined with tyramine containing foods and some dopaminergic agents, these medications have a primary hypotensive effect, especially phenelzine and isocarboxazid. Additive hypotensive effects with medications used to treat hypertension are more common than are hypertensive reactions with these compounds.

Buspirone, a 5-HT_{1A} receptor partial agonist, is frequently administered for milder forms of chronic anxiety. As with the antidepressants, buspirone has a slow onset of action. As it does not cause sedation, psychomotor impairment, dependence or withdrawal, it is preferred for patients who cannot tolerate these side-effects (e.g. professional drivers, pilots, patients with pulmonary disease) and for patients with a history of substance abuse. Because of its serotonergic action, buspirone can have dangerous interactions with MAO inhibitors.

The anticonvulsants valproate, gabapentin and pregabalin have been found to have antianxiety properties, and gabapentin and pregabalin also have antidepressant effects. These medications are preferable for anxious epileptic patients, and they are second-line treatments for chronic anxiety in patients who should not take or do not respond to the medications listed above. Anticonvulsants do not have predictable BP effects,

A few antihypertensive medications are also used to treat certain anxiety disorders such as 10–20 mg of propranolol being used acutely for performance anxiety. Prazosin has recently been shown to decrease nightmares and agitation in patients with post-traumatic stress disorder [35], although it does not treat other symptoms of this condition. Clonidine is occasionally used to treat severe anxiety, but it is more frequently used to reduce the hyperactivity in attention deficit disorder.

Behavioral therapies such as relaxation, biofeedback, meditation and hypnosis should be considered for all chronically anxious patients. These therapies not only are effective in their own right, but they increase patients' active involvement in treatment, creating a sense of mastery that counteracts the feelings of helplessness that are intrinsic to anxiety. In contrast, waiting for a pill to start working without a sense of personal engagement can intensify feelings of passivity. Since behavioral therapies can also ameliorate hypertension, they may reduce the total amount of medication that is needed.

SUMMARY

Anxiety disorders are common conditions that frequently coexist with hypertension. The physiology of anxiety can contribute to moderate hypertension but by itself it is probably

not sufficient to cause persistent severe elevations of BP. Clinicians treating anxious patients should consider medical causes and side-effects of medications and non-prescription substances before adding anti-anxiety medications. Acute anxiety is generally treated by addressing the cause of the anxiety and as necessary with the addition of a benzodiazepine. Anticonvulsants may be useful anxiolytics for patients with a history of substance abuse. When antidepressants and buspirone are used in the treatment of anxiety their delayed onset of action should be taken into account.

Behavioral therapies should be considered for all chronically anxious patients. Treatment of anxiety often improves BP control but by itself is not likely to be fully effective when more severe hypertension is present. Anxious patients are less likely than other patients to seek treatment for hypertension in the first place, and when they do they are more likely to discontinue treatment prematurely because of high sensitivity to side-effects.

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