BETA-BLOCKER DRUGS AND SLEEP DISTURBANCES
By Regina Patrick, RST, RPSGT

Beta1-adrenergic receptor inhibitor (i.e., beta blocker) drugs are used to reduce blood pressure in people with hypertension (i.e., high blood pressure). However, many people report nightmares, insomnia, and changes in sleep architecture when being treated with these drugs. These adverse effects can lead to a person with hypertension discontinuing treatment. Beta blocker drugs may have these negative effects on sleep because they reduce melatonin production.

Melatonin is a neurotransmitter that promotes sleep. In recent years, scientists have noted it plays a role in the maintenance of blood pressure. However, the mechanism for how melatonin plays a role in maintaining blood pressure is unclear. One possibility may be through its vasoconstrictive and vasodilatory effects since blood vessels contain receptors for melatonin. Some research indicates that vasoconstriction occurs at low melatonin levels (which may increase blood pressure), and vasodilation occurs at high melatonin levels (which may reduce blood pressure).

Blood pressure is normally maintained by the interplay of the enzyme renin (pronounced “REE-nin”), the hormones angiotensin I and angiotensin II, and the adrenal hormone aldosterone. When the arterial pressure in the body is too low, the kidneys release rennin, which is involved in the production of angiotensin I. Angiotensin I is converted into angiotensin II through the action of angiotensin converting enzyme (ACE). Angiotensin II is a powerful vasoconstrictor that stimulates the secretion of the hormone aldosterone. Aldosterone causes fluid retention within the blood vessels, thereby increasing blood pressure.

Hypertension results when there is an excessive amount of pressure from blood pressing against the arterial wall. Some factors that can increase blood pressure are an increased heart rate, vasoconstriction (i.e., narrowing of the blood vessels), fluid retention, and increased viscosity of the blood.

Hypertension can be essential (i.e., idiopathic, meaning its cause can not be determined) or it can be secondary (i.e., caused by another problem). The most common form of hypertension is essential hypertension. Secondary hypertension can result from renal disease, endocrine disorders (e.g., hyperthyroidism), blood disorders, or the use of certain substances (e.g., cocaine, epoetin alfa [a drug that increases the red blood count in people undergoing chemotherapy]). Hypertension may be diagnosed in an adult 50 years or younger if the person persistently has a systolic pressure (i.e., the arterial blood pressure when the heart contracts) greater than 140 mm Hg and a diastolic pressure (i.e., the arterial blood pressure when the heart relaxes) greater than 90 mm Hg. Hypertension in an adult older than 50 years may be diagnosed if the person persistently has a systolic pressure greater than 150 mm Hg and a diastolic blood pressure greater than 95 mm Hg.

Chemotherapeutic approaches for reducing blood pressure in a person with essential hypertension may involve using an ACE inhibitor or otherwise altering the function of the renin-angiotensin-aldosterone system (RAAS); using a diuretic to reduce fluid level in the blood; or using an adrenergic receptor blocker. The development of beta blocker drugs as a treatment for hypertension was an outgrowth of efforts in the 1950s to improve treatment for people with angina pectoris (i.e., sudden, spasmodic chest pain resulting from insufficient blood flow to the heart muscle). At the time, a common treatment for angina pectoris was nitroglycerin pills. Nitroglycerin quickly dilates blood vessels, which increases blood flow and oxygenation to the heart, thereby reducing chest pain. Whereas many researchers were focused on developing treatments for angina pectoris that improved oxygenation of the heart, Scottish pharmacologist James Black theorized that reducing the heart’s demand for oxygen (for example, by slowing the heart rate) could be a treatment approach. However, for a drug to slow the heart rate, it would have to block the stimulant effects of adrenaline on the heart (i.e., the drug would have to be anti-adrenergic).

The anti-adrenergic drugs that were then available for treating hypertension could cause a sudden drop in blood pressure when a person stood (an effect called postural hypotension). This could cause the person to suddenly faint. Research ultimately determined that two types of adrenergic receptors existed – alpha and beta receptors – and that each type had the subtypes alpha1, alpha2, beta1 and beta2. Postural hypotension resulted when an anti-adrenergic drug blocked the activity of alpha1 adrenergic receptors.

With the thought that allowing the alpha1 receptors to remain functional would prevent postural hypotension, Black focused on finding a chemical that was specific for the beta1 receptor. In 1959, he developed the first beta-blocker drug pronethalol. However, before pronethalol could be marketed extensively, animal studies showed that it was a carcinogen (i.e., cancer-causing substance). Black altered the structure of the molecule, which in 1964 led to the development of propranolol (marketed as Inderal). Propranolol was ten times more active than pronethalol, less toxic, and not carcinogenic. Several beta1 blocker drugs have been developed and introduced to the market since then.

Despite their effectiveness in reducing blood pressure, many people stop taking beta blocker drugs because of adverse effects (e.g., cold hands, slow heart rate, fatigue) and because of their effect on sleep. The exact mechanism for how beta blocker drugs impact sleep is unclear. One thought is that beta blocker drugs may affect sleep by interacting with serotonergic receptors (i.e.,
receptors that respond to or secrete the neurotransmitter serotonin). In the brain, serotonergic receptors play a role in different aspects of sleep such as the initiation and maintenance of sleep and in rapid eye movement (REM) sleep. Another thought is that blocking the activity of the beta1 receptor prevents the neurotransmitter norepinephrine (a form of epinephrine) from stimulating the synthesis and release of melatonin. This may lead to a decreased level of melatonin and contribute to nightmares, insomnia, and sleep architecture changes (e.g., increased total wake time, increased wakefulness after sleep onset, decreased REM sleep, decreased slow wave sleep).

Restoring melatonin levels through the administration of exogenous melatonin has been shown to increase the number of REM sleep periods in study participants and to consolidate sleep in elderly people with insomnia. Based on these findings, German researcher Auda Fares proposes that restoring melatonin levels through taking exogenous melatonin may improve sleep in people using beta blocker drugs. However, the use of melatonin to improve sleep in people using beta blocker drugs has not been extensively studied.

The compliance rate of patients who use beta blocker drugs is low because of their adverse effects. For example, an analysis of various studies indicates that the risk of treatment withdrawal was 80% greater with beta blockers than with diuretics and 41% greater with beta blockers than with RAAS blockers.

A person with untreated or improperly treated hypertension is at greater risk of stroke, heart attack, heart failure, kidney failure, and other problems. Therefore, withdrawing beta blocker therapy may be detrimental for a patient if other therapies for controlling blood pressure are ineffective. Improving sleep in patients for whom beta blocker drug therapy has resulted in sleep difficulties may enhance their compliance. Restoring melatonin levels to normal may be one approach to counteract the adverse effects of beta blocker drugs on sleep. However, more definitive studies are needed to determine how to effectively administer melatonin and the extent to which melatonin treatment improves sleep in a person taking beta blocker drugs.

REFERENCES