# Important news about low blood pressure, MAOIs, and beta-blockers

## Summary

Beta-blockers prevent both the post-dose elevation of blood pressure that some people experience, especially after larger doses of MAOIs, and the **exercise-induced hypotension**. They may also help the excessive hypotension that is manifest, in the absence of exercise, by some patients on MAOI drugs. That last issue is yet to be verified by controlled experiment in a larger number of patients.

**It is remarkable that this phenomenon has been overlooked for so long**

**This potential solution to the of problem orthostatic hypotension would be of immediate use and benefit to any patient who is currently experiencing symptoms related to hypotension — it simply involves taking a therapeutic dose of one of the beta-blockers, discussed below, either on an as needed basis, or as a regular twice daily dosage.**

Terms: beta-blockers, aka β-blockers, β-adrenoceptor antagonists
[in this text I will use the term beta-blockers because some typefaces do not translate the Greek character, thus, when typeface substitution occurs characters are not rendered correctly]

## Introduction

Recent information and discussion in my MAOI Group is informed by other eminent world experts in pharmacology and related fields. This little-know quirk of pharmacology has generated discussion of what may be a long-overlooked and simple solution for **low blood pressure (hypotension)** problems experienced by those taking MAOIs.

The story started with an observation by one of the group members who is an eminent professor of pharmacology and toxicology (Professor Ian Whyte from Newcastle in Australia, who has published many seminal papers) who demonstrated that beta-blockers prevented **post-exercise hypotension** in an individual patient: this phenomenon was consistent and well documented by reliably done, repeated, and clear differences in blood pressure readings. This was mentioned in discussions on the group around the time the COVID epidemic started; that may have played a part in distracting everyone's attention, because it seems to have been forgotten about. I tested it in one or two patients who sought advice from me over the Internet and it was clear that beta-blockers were preventing the **post-dose hypertension**, but no one produced clear blood pressure readings supporting the idea that it prevented **exercise-induced hypotension**, although several people reported that subjectively it seemed to have solved the problem.

**An important question, that could be resolved simply, is whether they lessen the commonly encountered postural hypotension.**
**Step forward 'citizen scientists'!**

It may be that, because the main thrust of the discussion was preventing post-dose **hypertension**, the idea they might also prevent **hypotension** just did not stick in anyone's mind. Furthermore, the idea that they might prevent both hypertension and hypotension seems counter-intuitive.

Whatever the explanation of our failure to follow up on this idea, something happened recently which made me go back and look at what Professor Whyte had said and recense the discussion and re-present it to the group.

That produced comments and ideas which I hope will generate more systematic research.

## The mechanisms

Beta-blockers are generally regarded as hypotensive agents; however, they produce their effect by slowing the heart rate and by reducing cardiac output, not by reducing resistance to blood-flow (i.e., **systemic vascular resistance [SVR]**).

There are three beta-adrenoceptor subtypes beta-1, beta-2 and beta-3 which are activated by the endogenous agonists (-)-adrenaline and (-)-noradrenaline.

**Beta-1 are in cardiac tissue**, and beta-2 are mainly found in the smooth muscle of arterioles regulating blood flow to various tissues and organs, and in bronchioles etc. Skeletal muscle arterioles express particularly high levels of beta-2 vs. alpha-1 adrenoceptors.

Noradrenaline is a weaker agonist than adrenaline at beta-2 adrenoceptors [1] and https://www.ncbi.nlm.nih.gov/books/NBK559069/.

The resting vascular tone is alpha-1 mediated, phentolamine (an alpha-1 antagonist) produces orthostatic hypotension, because reflex vasoconstriction is reduced.

Antagonism of beta-1 has negative chronotropic and inotropic effects which decrease blood pressure and oxygen demand, hence improving angina. They prolong the atrial refractory periods and have an antiarrhythmic effect.

**Stimulation of beta-2** has vaso-dilatory effects. **Intrinsic sympathomimetic activity (ISA)**, an old term, is now understood and is due to partial agonist activity at beta-2 adrenoceptors — thus producing a lesser response than the endogenous ligands (adrenaline, noradrenaline) and other full beta-agonists.

**The main currently available beta-blocker with significant partial agonist (ISA) activity is pindolol.**

The effect of beta-blockers may vary according to the existence or absence of a pathological condition, such as essential hypertension, and according to the basal state of the system. This will be particularly relevant to dilation and constriction of arterioles.

The effect of beta-blockers is to block vaso-dilation of the arterioles which control vascular resistance and thus influence blood flow to tissues and organs. Normally, on exercise, arterioles in muscular tissue dilate under the influence of **adrenaline-induced beta-2 stimulation** facilitating increased blood flow — this lowers SVR and BP.

Beta-2 blockade prevents this effect and, if the alpha-adrenoceptors are functioning normally, may even result in vasoconstriction with increased SVR and BP.

## The drugs

There are more than a dozen different beta-blockers in clinical use worldwide and they should not be regarded as a homogenous group, their differing pharmacological properties are described here [2].

**The three drugs of relevance in the context of this commentary are propranolol, metoprolol, and atenolol.**

The clinically used beta-blockers generally show a low degree of selectivity for the beta-1 vs. beta-2 receptor, many are slightly more beta-2 selective [3].

Lipophilicity strongly influences brain penetration, and the only one of these drugs with low lipophilicity and low brain penetration is atenolol, which may thus have less CNS effects.

The half-lives of metoprolol and propranolol are 3–4 hours only, atenolol is 6–9 hours.

**Atenolol is notable in that it has a longer half-life and less CNS effect**

## Physiology

Circulating adrenaline stimulates: increased heart rate and inotropy (beta-1 mediated), vasoconstriction in most systemic arteries and veins via post-junctional alpha-1 and alpha-2 adrenoceptors, but vaso-dilation in muscle at lower concentrations (beta-2). Alpha-mediated vasoconstriction is a factor at higher concentrations. Adrenaline is the predominant stimulator of beta-2 receptors in the physiological state because the threshold concentration for activation of beta-2 adrenoceptors is lower than that for alpha-receptors. Both types of receptors are activated at high concentrations of adrenaline when the response to alpha-adrenoceptors predominates.

In the presence of alpha-adrenoceptor blockade/dysfunction, which may be the reason for the orthostatic hypotension in patients on MAOIs*, the vasoconstriction does not occur, and the vasodilation is greater.

An alpha-adrenoceptor antagonist, or relative alpha-blockade due to false neurotransmitters*, will cause the vasodilation in muscle to be more pronounced, SVR is decreased, and blood pressure decreases. Thus, in the presence of significant alpha-adrenoceptor antagonist activity (direct or indirect), unopposed beta-2 adrenoceptor activity produces a fall in blood pressure instead of the expected rise — this occurs during exercise when adrenaline is released.

*Because MAOIs lead to the increase of octopamine and similar compounds, which are taken up into sympathetic nerve terminals and act as false neurotransmitters, thereby reducing the affective noradrenaline.

**Systemic vascular resistance falls due to activation of vascular beta-2 adrenoceptors**

## Uses and contra-indications

Clinically beta-blockers are commonly used for hypertension, ischaemic heart disease, heart failure, anxiety, tremor, migraine, and glaucoma.

Side effects include: bradycardia, gastrointestinal issues, abdominal pain, nausea, erectile dysfunction, bronchospasm, and cold extremities. Propranolol can also cause drowsiness, fatigue, bad dreams — there is no evidence it precipitates depression. As well as causing cold hands and feet they can precipitate Raynaud's phenomenon. Reduction of renal blood-flow may have adverse consequences.

# Conclusion

The effect of beta-blockers on the post-dose hypertension and exercise induced hypotension appears paradoxical: that paradox is explained above in the context of the administration of MAOIs. They prevent both the hypertension and the hypotension. The question yet to be answered is whether — contrary to expectation — they might also ameliorate the 'normal' orthostatic hypotension that is sometimes problematic.

Straightforward clinical observations that can be made by patients themselves, and clinicians, should settle this important and relevant issue now that it has been described.

References

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