# Take 3 – Practical Practice Pointers© January 20, 2020 Edition

## Timing of BP Meds, "Low-T", Supporting Colleagues in Distress

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## From the Literature

## 1) Timing of Taking Blood Pressure Medications – Bedtime Better?

For years, HTN researchers have wondered whether the circadian rhythms of patient's blood pressure regulation and those of the pharmacokinetics of antihypertensive medications could be leveraged to achieve better overall HTN control. Most of the popular antihypertensive medications (ACEIs, ARBs and those in combination with CCBs and diuretics) when taken at bedtime seem to control blood pressure better during sleep without affecting BP control during the day.

Researchers decided to definitively evaluate these ideas in a very practical and well-done trial in primary care, using the gold-standard measurement for blood pressure control (48-hour ambulatory blood pressure monitoring [ABPM]) and CVD outcome events. Over 19,000 adults with HTN, currently on medication, were randomized to taking their medications at bedtime or on awakening and followed for a median of 6.3 years. Once-a-day combination therapies and additional medications were allowed as needed for improved control. Other medications for CVD prevention (statins, aspirin, etc.) were not regulated in the study, and were prescribed according to guidelines.

While the intervention itself could not be blinded, the outcome assessments were. In addition to the ambulatory blood pressure data, the investigators measured rates of a composite CVD endpoint (any one of myocardial infarction, coronary revascularization, heart failure, ischemic stroke, hemorrhagic stroke, or CVD death) as the primary outcome, as well as those individual outcomes as secondary.

There were small, but statistically significant differences in mean ambulatory blood pressures favoring the evening-dose group – on the order of 1-2 mm Hg in the awake measurements and 2-4 mmg Hg in the asleep measurements. That doesn't seem like much, but all primary and most secondary CVD outcomes were improved in the evening dose group in adjusted analysis. The authors provide (after being harangued in the online comments to the article) the NNT to prevent any CVD outcome (the primary outcome) of ~19 and range from 24-85 for the individual CVD events over 6.3 years. By way of explanation for the effect on CVD events, the authors note an increase in physiological nocturnal BP "dipping" in the evening dose group. Importantly, there was no difference in adverse event rates in the two groups (including too-low BP at night), and medication adherence rates were the same in both groups.

**John's Comments:**
The authors are careful to say that this study should be repeated in different ethnic groups (the study was done in Northern Spain, and no ethnic/racial data was collected), but this was a pragmatic, well-done study. There seem to be no real harms associated with bedtime dosing of antihypertensives and since we know that compliance is improved with once-daily dosing, this should be a relatively easy switch for patients on these medications, with the promise of improved cardiovascular outcomes. I plan to try

this with my patients and will look for the outcome studies in different racial/ethnic groups. A brief search reveals that this “nocturnal non-dipping” phenomenon is prevalent in blacks – so could be well-addressed by this intervention.

**Reference:**
Hermida RC, et al. Bedtime HTN treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 22 Oct. 2019. Link

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## From the Guidelines and the American College of Physicians (ACP)

## 2) ACP Testosterone Treatment Guidelines

A gradual, age-associated decline in serum total testosterone levels begins in men in their mid-30s and continues at an average rate of almost 2% per year. This condition is referred to as age-related low testosterone and is accompanied by clinical symptoms associated with androgen deficiency, such as sexual dysfunction, decreases in energy and muscle mass, mood disturbances, depression, decreased libido, erectile dysfunction, decreased volume of ejaculate, loss of body and facial hair, and weakness.

No well-defined, universally accepted threshold of testosterone levels exists below which symptoms of androgen deficiency and adverse health outcomes occur. The incidence of low testosterone in the US is reported to be approximately 20% in men older than 60, 30% in those older than 70, and 50% in those older than 80 years, although the prevalence of syndromic low testosterone (defined as at least 3 sexual symptoms with a total testosterone level < 320 ng/dL) is lower.

Uncertainty exists as to whether the nonspecific signs and symptoms associated with age-related low testosterone are a consequence of age-related low testosterone or whether they are a result of other factors, such as chronic illnesses or concomitant medications. Additionally, the role of testosterone treatment in managing age-related low testosterone is controversial. The U.S. FDA requires the pharmaceutical industry to label all testosterone medications to clearly state that their products are approved for use only in persons with low testosterone levels due to known causes.

The American College of Physicians (ACP) developed this guideline to provide clinical recommendations based on the current evidence of the benefits and harms of testosterone treatment in adult men with age-related low testosterone. This guideline is endorsed by the AAFP as well. Recommendations include:

- Clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence). The discussion should include the potential benefits, harms, costs, and patient's preferences.
- Clinicians should reevaluate symptoms within 12 months and periodically thereafter and should discontinue testosterone treatment in men with age-related low testosterone with sexual dysfunction in whom there is no improvement in sexual function (conditional recommendation; low-certainty evidence).
- Clinicians should consider intramuscular rather than transdermal formulations when initiating testosterone treatment to improve sexual function in men with age-related low testosterone, as costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.

- Clinicians should not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation; low-certainty evidence).

The guideline does not address screening for or diagnosis of hypogonadism or monitoring of testosterone levels.

**Mark's Comments**
This is an area for which there is still lack of clarity as to the most effective way to both diagnose and treat, particularly given some of the non-specific symptoms that have been associated with the condition. For some of my patients, I have done "trials" (N of 1) to measure the impact on specific symptoms if their baseline free testosterone was low. Note that the annual cost per beneficiary for testosterone replacement therapy was $2,135.32 for the transdermal and $156.24 for the intramuscular formulation, according to 2016 Medicare Part D Drug Claims data, but this does not include costs associated with getting the IM injections.

**Reference:**
Qaseem,A, et al. Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline. Ann Intern Med. 7 January 2020. Link

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## From the AMA and the Physicians Foundation

## 3) Supporting Colleagues Who Are Struggling Emotionally

There is a whole spectrum of factors that contribute to burnout, as well as a number of barriers limiting physicians' willingness to address it. If a colleague is struggling with burnout or other forms of emotional distress, how can you help? A new campaign from the Physicians Foundation called "Vital Signs" aims to equip each of us to help colleagues who might be experiencing significant emotional distress by having the tools to check in with them while also destigmatizing the act of seeking help as well as help giving. The first step is recognizing a colleague who may be experiencing significant emotional distress. The HEART acronym highlights warning signs to look for:
**H**ealth:
- Increasing the use of medications and/or alcohol or illicit drugs
- Talking about wanting to hurt themselves or die

**E**motions
- Experiencing extreme mood swings
- Feeling hopeless or having no purpose

**A**ttitude
- Being negative about professional and personal life
- Having inappropriate outbursts of anger or sadness

**R**elationships
- Withdrawing or isolating themselves from family, friends and coworkers
- Talking about being a burden to others

**T**emperament
- Acting anxious or agitated; behaving recklessly
- Being uncomfortable, tired or in unbearable pain

If any of these warning signs are being demonstrated, here are some initial steps to begin a conversation with a colleague:

- Prepare for the conversation: This begins with your own education. Be aware of local resources and support groups that might offer a next step as well as any bias you might carry regarding help seeking for mental health concerns. Also, consider if you are the best person to approach them, particularly in the context of having developed mutual trust and respect. If not, ask who might be better to do so.
- Find the right time: When addressing such a sensitive topic, timing and location are important. Think about a time when there will not be interruptions, neither person is overly tired and other obligations do not pose as a distraction. At the same time, don't wait for the "perfect time" as this may mean the conversation never happens. A "cup of coffee" conversation is a good setting to consider.
- Choose the right language: "May I share something with you that I'm concerned about" and using "I" statements in general acknowledge that you may be inaccurate in your assessment and decrease the real possibility of defensiveness. It is vital to not come across as critical, accusatory, or shaming.
- Listen actively: Not only is it important to begin a conversation, but it is also vital that you listen well after initiating it. Practice "active listening" by acknowledging what they are saying and show them that you are listening to them. You should also reiterate your support and willingness to help them. Some questions you can ask to focus the conversation on listening, instead of trying to fix the problems, are: "When did you begin feeling like this?" and "How can I best support you?"
- Navigate resistance: Before initiating a conversation, plan for some level of resistance or denial. If this happens, always remain calm and patient. This can help you show your support is authentic. In the moment, you can say, "I can tell you're not ready to talk about this right now but know that I care about you and am here when you are ready." After the initial conversation, continue to follow up with them and be proactive—don't wait for them to check in.

**Mark's Comments:**

The ominous data indicate that you are experiencing distress yourself, are working with someone who is, or both. It is common to both feel alone when experiencing emotional distress and also to isolate oneself (even push others away). Therefore, this is a time when our resisting the temptation to "mind my own business" could potentially save a life or help bring someone "back to life." Our professional well-being is an area for which I have great passion, and addressing it is essential for the quality and sustainability of our medical practice. We can help make a difference for each other now even as we strive together to help improve a very dysfunctional healthcare system.

**References:**


- Berg, S. How to open your heart to fellow doctors struggling with burnout. AMA. Website 24 December 2019. Article
- Physicians Foundation: Vital Signs Program. Link


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*Mark*


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