Take 3 – Practical Practice Pointers© January 28, 2019 Edition

Omega Fatty Acids, Treatment of Minor Stroke/TIA, Melatonin Primer

From the Literature

1) Omega-3 and 6 Fatty Acids for the Prevention of ASCVD

Research has suggested that omega-3 fatty acids from oily fish (long-chain omega-3, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)), as well as from plants (alpha-linolenic acid (ALA)) benefit CV health. Guidelines recommend increasing omega-3-rich foods, and sometimes supplementation, but recent trials have not confirmed this. Higher intake of marine omega-3 fatty acids (n-3) has also been associated with reduced risks cancer in several observational studies. Whether supplementation with omega-3 fatty acids has such effects in general populations at usual risk for these end points is unclear. A recent randomized trial and Cochrane Review help to shed some additional light on this question.

In the randomized trial, marine n-3 fatty acids (at a dose of 1 g/day) and vitamin D3 (2000 IU per day) were studied in the primary prevention of CV disease and cancer among men $\geq$ 50 and women $\geq$ 55. Primary end points were major CV events (a composite of myocardial infarction, stroke, or death from CV causes) and invasive cancer of any type. Secondary end points included individual components of the composite CV end point, site-specific cancers, and death from cancer.

During a median follow-up of 5.3 years, supplementation with n-3 fatty acids did not result in a lower incidence of major CV events or cancer than placebo.

The Cochrane review came to similar conclusions. They found that moderate- and high-quality evidence suggests that increasing EPA and DHA has little or no effect on mortality or cardiovascular health. Previous suggestions of benefits from EPA and DHA supplements appear to spring from trials with higher risk of bias. Low-quality evidence suggests ALA may slightly reduce CVD event and arrhythmia risk.

Omega-6 fats are polyunsaturated fats vital for many physiological functions, but their effect on cardiovascular disease (CVD) risk is debated, since they are considered to be pro-inflammatory. A recent Cochrane Review also looked at effects of omega-6 fats on CV health, mortality, lipids and adiposity to date, using previously unpublished data.

The reviewers found no evidence that increasing omega-6 fats reduce CV outcomes other than MI, where 53 people may need to increase omega-6 fat intake to prevent 1 person from experiencing MI. They concluded that the benefits of omega-6 fats remain to be proven, thought increasing them may be of benefit in people at high risk of MI.

My Comment:
Given that this Pointer has the potential to be practice-changing for some, I asked John Epling, MD, one of our FM colleagues at Carilion who is also a national expert in critical thinking and appraising/interpreting the literature, to provide his insights. Here are some of John's thoughts: *"The results are consistent. Spoiler alert – we find ourselves in the same place with these interventions as with numerous similar findings from nutritional epidemiology research. Nutritional epidemiology – usually large well-done*

observational studies – can tell us about the association of certain dietary patterns with certain health outcomes. That is indeed helpful information if we can restrain ourselves from converting that information to pill form and administering it in a supplement without doing the proper studies first.

A few commentators, frequently associated with the supplement industry, have ballyhooed the fact that there was a slight reduction in the secondary outcome of myocardial infarction rate. However, the authors rightly urge caution in the interpretation of any of the secondary endpoints because the appropriate statistical controls for these outcomes were not performed.

We continue to try to convert good nutritional advice to pill form. As primary care physicians, our best strategy is to emphasize the broad principles from the good quality nutritional epidemiology work that's been done, and emphasize that these findings are applicable to diet, not supplements."

This is certainly consistent with Beth Polk's commentary guidance from the January 21st Pointer on "Best Diets 2019" – *"Eat food, mostly plants, not too much."* I also want to point out there is much literature on the importance of the omega-6 to omega-3 dietary ratio to our overall health. For those unfamiliar with this topic, the last reference provides a comprehensive yet digestible overview. Based on the present "Standard American Diet (SAD)," I would be quite hesitant to recommend supplementation of omega-6 for anyone without a close examination of their overall diet.

References:

- Abdelhamid AS et al. Omega-3 fatty acids for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018 Nov 30;11: Review
- Hooper L et al. Omega-6 fats for the primary and secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2018 Nov 29;11: Review
- Manson JE et al. Marine n-3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer. N Engl J Med. 2018 Nov 10. Abstract
- Healthline June 2018: How to Optimize your Omega-6 to Omega-3 Ratio: Link

From the Literature

2) Initial Treatment of High Risk TIA and Minor Ischemic Stroke

Single antiplatelet therapy with aspirin or clopidogrel has been shown to be an effective intervention for both short and long term secondary prevention of stroke and transient ischemic attack after an index event. Because they have synergistic action to inhibit platelet aggregation, experts have wondered whether their combination (dual anti-platelet therapy – DAPT) might provide better secondary prevention of stroke than either one alone. Previous studies have shown that:

- They are not useful in the long term after stroke. Several large RCTs have shown that DAPT was no better than single agent therapy.
- They are considered too risky after major stroke. Major strokes, as opposed to minor ones, are treated with single agent only because of the higher risk of hemorrhagic transformation.

- The balance of benefit and harm is uncertain for short term use after minor stroke or high risk transient ischemic attack. In the days and weeks after such an event there is an increased risk of a second ischemic event.

This systematic review and meta-analysis of randomized, placebo controlled trials is intended to assess the effectiveness and safety of DAPT combining clopidogrel and aspirin to prevent recurrent thrombotic and bleeding events compared with aspirin alone in patients with acute minor ischemic stroke (defined as a score of 3 or less on the National Institutes of Health Stroke Scale - NIHSS, and no persistent disabling neurological deficit) or transient ischemic attack (TIA).

The review concluded:

- People with high risk transient ischemic attack or minor ischemic stroke are at an increased risk of recurrent stroke and death
- Aspirin and clopidogrel decrease this risk, even more so when used in combination
- DAPT with clopidogrel and aspirin should be started within 24 hours in patients who have had a high risk transient ischemic attack or minor stroke
- DAPT should be continued for 10-21 days, at which point patients should continue with single antiplatelet therapy
- DAPT is not to be used for major stroke because of the increased risk of intracranial bleeding in these patients

My Comment:
I thought it was important to highlight this article, as many of us will be seeing these patients in the interim between hospital discharge and the follow-up appointment with a Neurologist (if such an appointment is even scheduled). We know that often in the transition from hospital discharge, miscommunication happens. It thus becomes important for us to know when to stop DAPT so that our patients are not at increased longer term risk of bleeding from the unnecessary use of this combination.

Reference:
Hao Q, et al. Clopidogrel plus aspirin versus aspirin alone for acute minor ischaemic stroke or high risk transient ischaemic attack: systematic review and meta-analysis. BMJ. 2018 Dec 18;363:k5108: Rapid Recommendation Article

From the Literature

3) Melatonin Primer

Up to 25% of children and 50% of adults experience difficulty sleeping. Because of this, and the fact that many of the traditional sedative-hypnotic medications have the potential to be habit forming (schedule IV) or have potential long-term risk on memory (anti-cholinertics), interest in and the use of melatonin has grown rapidly.

Melatonin is hormone present in almost every life form from bacteria to humans. In vertebrates, melatonin is centrally synthetized by the neuroendocrine organ, the pineal gland. Endogenous melatonin production is influenced by day/night cycles. In the brain, melatonin increases the binding of gamma-aminobenzoic acid (GABA) to its receptors. Its primary roles seem to be regulation of the body's circadian rhythm, endocrine secretions, and sleep patterns.

Disruption of the timing of melatonin release or decreased melatonin production can contribute to insomnia. The problem is particularly pronounced when changing time zones or during shift work. Melatonin production also wanes with age, which may be partially responsible for the sleep difficulties experienced by older adults.

Melatonin has been extensively studied. A 2013 meta-analysis found that melatonin at doses of 0.1 mg to 5 mg decreased sleep latency by 7.1 minutes, increased total sleep time by 8.3 minutes, improved overall sleep quality, and had minimal side-effects. The impact on sleep latency is only slightly less that that from prescription medications.

When considering whether to recommend melatonin, sleep hygiene should be a first priority (see references). The presence of indoor lights during the night and the profuse use of electronic devices whose screens are rich in blue wavelength light during the night are a particular problem, as they delay the beginning of the secretory episode of melatonin and blunt its peak. This includes cell phones and laptop computers.

How Should Melatonin Be Best Used?

- The majority of formulations take 45 minutes to become bioavailable, so it should be taken around an hour before the usual bedtime at exactly the same time every day. It is likely most effective for general use in in those $\geq$ 55.
- A dose of 1.0 mg would result in a plasma concentration of approximately 500 to 600 pg/mL, which is much higher than the physiological concentration. The standard starting does is 3 mg. Studies indicate there is great intra- and inter manufacturer variation regarding the actual amount of melatonin in any product.

If it doesn't work after a few weeks, it probably is not going to help. Long term safety and impact on normal physiological function is unknown.

My Comment:
My sense is that many of us are recommending melatonin as being a "benign option" instead of the other existing options. My rule is that there is no such thing as a "benign" pill, so the more we know about what we're recommending, the better. Melatonin appears to be "relatively benign" based on what we know, but as noted above, long term safety at the standard dose is unknown. Sleep hygiene is still a vital first step, and in particular nocturnal "screen time (see references). One review described nocturnal light as an "environmental toxin." Also, remember that because melatonin is not regulated by the FDA and purity varies widely among products, reviewing third-party product evaluations is recommended to determine product quality.

Reference:

- Cipola-Neto J, et al. Melatonin as a Hormone: New Physiological and Clinical Insights *Endocrine Reviews*, 39(6), 1 December 2018, Pages 990–1028. Link
- Sleep Hygiene Tips: National Sleep Foundation: Link CDC: Link

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Mark

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