Letters to the Editor

Clinical Considerations for the Management of Hypertriglyceridemia

Original Article: Management of Hypertriglyceridemia: Common Questions and Answers

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See additional reader comments at: https://www.aafp.org/afp/2020/0915/p347.html

To the Editor: We commend Drs. Oh, Trivette, and Westerfield for providing an updated guide on the management of hypertriglyceridemia—an underappreciated risk factor that is often overshadowed by low-density lipoprotein cholesterol and other chronic conditions family physicians see every day. We would like to offer additional comments to help family physicians with this important update.

Pitavastatin (Livalo, Zypitamag) is a currently available therapy and a good choice as a last resort for patients who are otherwise intolerant of statins because it uses a less common clearance pathway, rendering it less susceptible to pharmacokinetic interactions. We discourage clinicians from prescribing the 80-mg dose of simvastatin (Zocor) because it has been shown to significantly increase muscle-related adverse events without benefit (the U.S. Food and Drug Administration rescinded its approval for initiating this dose).[1]

A low-carbohydrate diet is also a good strategy for managing hypertriglyceridemia. However, it should not be a universal recommendation in patients with triglyceride levels greater than 500 mg per dL (5.65 mmol per L) because some of these patients may have familial chylomicronemia syndrome, a rare genetic disorder where loss-of-function mutations limit the ability to effectively break down triglycerides. Instead of a low-carbohydrate diet, patients with familial chylomicronemia syndrome should be placed on a very low-fat diet. This diagnosis should be considered in patients with triglyceride levels greater than 1,000 mg per dL (11.30 mmol per L) without an obvious secondary cause; occurrence at a young age; and debilitating physical, emotional, and cognitive symptoms.[2]

Intensive therapies such as insulin infusions, plasmapheresis, or parenteral heparin are not standard care or sufficiently supported by the literature to recommend their use; these therapies also carry substantial risks and expense. As mentioned by Dr. Oh and colleagues, expert consultation is required in these cases.

The statement that icosapent (purified eicosapentaenoic acid; Vascepa) may not be cost-effective should be updated because a recent cost-effectiveness analysis from the REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial) U.S. cohort demonstrated that icosapent was dominant (lower cost with a better outcome) for secondary prevention and cost-effective (incremental cost-effective ratio less than $50,000 per quality-adjusted life-year) for primary prevention.[3]

Additionally, we disagree that there are no data demonstrating cardiovascular risk reduction with hypertriglyceridemia treatment. Although no individual trial has met this primary end point, meta-analyses have consistently demonstrated a reduction in cardiovascular risk from triglyceride-lowering therapies.[4-6]

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In Reply: We appreciate the letter from Drs. Elkhal and Warden. We agree that caution is warranted before prescribing simvastatin, 80 mg, because of the increased risk of muscle injury and recommend not starting new patients on this dose. Pitavastatin is a newer statin, but there are currently

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no generic equivalents in the United States. It costs approximately $300 per month compared with generic statins, which range from $10 to $15 per month.[1] For patients with significant hypertriglyceridemia leading to acute pancreatitis, we suggest that other medications be considered to reduce pancreatitis-associated morbidity and mortality. Insulin has been successfully used in the hospital setting and is supported in the literature.[2,3] Physicians without experience using insulin and other intensive therapies for this indication should consult an expert.

Familial chylomicronemia syndrome is a rare genetic condition that should be considered if hypertriglyceridemia is refractory to traditional management, including nutrition, exercise, and medication. Lowering fat intake is important to consider in the management of familial chylomicronemia syndrome because of the inability of lipoprotein lipase to metabolize triglycerides and fat. Reduction of refined carbohydrates, including sucrose and fructose, is critical in the management of familial chylomicronemia syndrome because of their conversion in the liver to triglycerides. A diet lower in refined carbohydrates, higher in lean protein, and lower in fat can be an option for patients with familial chylomicronemia syndrome.[4] Essential carbohydrates, although important, are a nonessential dietary macronutrient. However, even patients with familial chylomicronemia syndrome require dietary intake of essential proteins and fatty acids.

Studies of hypertriglyceridemia as an independent risk factor for cardiovascular disease are difficult to interpret because of the complex relationship between triglycerides and other cardiovascular risk factors. Recent guidelines identify hypertriglyceridemia as a risk enhancer and not an independent risk factor.[5] REDUCE-IT is the first study of its kind, demonstrating a reduction of mortality in high-risk patients who have elevated triglycerides despite statin therapy. However, another similarly designed study did not show benefit.[6] Additionally, drug therapy should always be the last resort. The most cost-effective therapy is a healthy diet, physical activity, and nonpharmaceutical interventions to lower cardiovascular risk. This approach is especially important for patients who may have difficulty with payment or insurance coverage for expensive medications. We implore family physicians to double down on nonpharmaceutical interventions while we wait for more data and experience with icosapent to determine its appropriate role in primary or secondary prevention.

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Evidence-Based Use of Opioids

Original Article: Appropriate Use of Opioids for Chronic Pain [Lown Right Care]

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To the Editor: I disagree with Drs. Roth and Lazris that prescribing opioids for knee osteoarthritis pain in an older woman with chronic kidney disease is an appropriate use of opioids. Although abrupt discontinuation of chronic opioid therapy is medically and ethically inappropriate, continuing oxycodone for this indication is also not practicing evidence-based medicine.

A systematic review included 15 randomized controlled trials and 6,266 patients with osteoarthritis who were followed for 10 days to 24 weeks. Overall, 47% of patients taking opioids reported meaningful pain relief compared with

43% of patients taking placebo (number needed to treat = 32; number needed to harm = 8), with no differences in pain relief after four weeks.[1] A 2018 randomized controlled trial similarly found that opioids were not superior to nonopioid medications for osteoarthritis at 12 months, and patients taking opioids had more medication-related harms.[2]

Opioids relieve the withdrawal symptoms they create, but the long-term pain benefit is minimal. Patients often interpret opioid withdrawal as their underlying pain condition. Opioid-induced hyperalgesia and other harms, such as impaired cognition, falls, and overdose, increase with age.

We need to carefully, slowly, and compassionately taper many patients with noncancer pain off of opioids. Stanford's BRAVO (broaching the subject, risk-benefit calculation, addiction, velocity and validation, other strategies) method is effective for these discussions between patients and physicians.[3] Clinicians should consider gradually tapering the opioids over nine to 12 months or transitioning to buprenorphine.[4] Many patients without opioid use disorder have difficulty tapering. Buprenorphine is an effective, safer choice in these circumstances.[5] Topical diclofenac, a front-wheeled walker with a seat, and an orthopedic consultation may also help relieve pain and improve function.

Patients and communities deserve better than the continued overuse of opioids masquerading as evidence-based practice.

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In Reply: We thank Dr. Perez for his reply but disagree that prescribing opioids for knee osteoarthritis pain in an older woman with chronic kidney disease is "masquerading as evidence-based practice" and inconsistent with current Centers for Disease Control and Prevention (CDC) guidelines.[1] Since the publication of our article, the CDC released data highlighting that chronic pain affects 20.4% of adults, and 7.4% of adults have severe pain that limits life or work activities, with the highest impact in adults 65 years and older.[2]

Selecting the appropriate treatment for adults with chronic pain requires a systematic, patient-centered approach that involves shared decision-making. Integrative approaches, orthopedic consultation, the use of walking assistance devices, and nonopioid and adjuvant medications, are the cornerstone of therapy and should be first-line options for all patients with chronic pain.[3] However, many nonopioid choices have limited evidence of benefit, contraindications, significant adverse effects, or limited effectiveness. When nonopioid modalities have not adequately controlled pain or improved functional status, use of opioids can be an effective and acceptable choice. A National Institutes of Health Pathways to Prevention Workshop consensus statement concluded that "patients, providers, and advocates all agree that there is a subset of patients for whom opioids are an effective treatment method for their chronic pain, and that limiting or denying access to opioids for these patients can be harmful."[4]

We agree that the evidence for long-term benefits of opioid use is not strong; however, significant evidence for the safety and benefits of the judicious use of opioids in appropriate patients is compelling.[5] The judicious use of low-dose opioid therapy (less than 50 morphine milligram equivalents), with careful monitoring and a continued risk-benefits analysis, is an appropriate and evidence-based approach to care.[1,4-6] The use of other approaches (e.g., nonopioid and adjuvant medications) should continue with the lowest effective dose of opioids. Tapering is indicated only in patients who have not shown a significant improvement in pain or functional status. Doses greater than 90 morphine milligram equivalents

should be avoided unless the benefits clearly outweigh the risks and appropriate safety strategies have been implemented.[5,6]

As the CDC states, chronic pain is a high-impact chronic condition associated with significant functional status limitations and patient distress. To assert that there is no role for opioids in treating chronic osteoarthritis pain is not evidence based.

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Oral and Dental Injury Prevention in Children and Adolescents

Original Article: Prevention of Unintentional Childhood Injury

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I applaud Drs. DeGeorge, Neltner, and Neltner for their thoughtful coverage of the important topic of preventing unintentional childhood injury. One important preventable injury topic was not included: oral and dental injuries. In children younger than six years, oral injuries are the second most common injury, accounting for approximately 20% of all injuries.[1] The greatest incidence of trauma to the primary teeth occurs at two to three years, when motor coordination is developing.[2] By age 14, one-third of all children will have experienced a dental trauma,[3] with 11,000 emergency department visits annually for sports-related dental injuries in children and teens.[4] The American Dental Association (ADA) recommends the use of mouth guards in 29 sports and exercise activities.

Oral trauma prevention can easily be worked into other injury-prevention messages during well-child visits, much in the way the authors promoted discussing the use of bicycle helmets and wrist and elbow pads. According to the ADA, athletes are 60 times more likely to suffer harm to their teeth when not wearing a mouth guard. Individuals who wear mouth guards are between 82% and 93% less likely to incur dental injuries.[5] A mouth guard can cost as little as a few dollars for a "boil and bite" style and more for custom-fitted guards (which are covered by public dental insurance in many states). This messaging is consistent with the 2018 American Academy of Family Physicians policy that encourages its members to be aware of the serious disparities surrounding oral health, and to advocate for and engage in strategies that address the underlying social determinants of oral health (https://www.aafp.org/about/policies/all/oral-health.html).

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Editor's Note: This letter was sent to the authors of "Prevention of Unintentional Childhood Injury," who declined to reply. ■