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April 1, 2019

Attn: Alicia Richmond Scott
Pain Management Task Force Designated Federal Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Health
200 Independence Avenue SW, Room 736E
Washington, DC 20201

Via Email: paintaskforce@hhs.gov

RE: Docket No. HHS-OS-2018-0027: Request for Public Comments on the Pain Management Best Practices Inter-Agency Task Force Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations

Dear Pain Management Task Force Officer,

The Natural Products Association (NPA) is submitting this letter as general comments to docket HHS-OS-2018-0027, regarding FDA's notice titled, "Request for Public Comments on the Pain Management Best Practices Inter-Agency Task Force Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations," for public comment. These comments are aimed to provide stakeholder feedback regarding the Draft Report on Pain Management Best Practices: Updates, Gaps, Inconsistencies, and Recommendations. NPA would like to highlight the following areas of the HHS Draft Report where patient access to Medical Foods and Foods for Special Dietary Use could provide an alternative to the current opioid crisis.

Section 2.2 Medication - Gaps and Recommendations
Section 2.6 Complementary and Integrative Health
Section 2.7 Special Populations
2.7.2 Older Adults
Gap 1B – Increased risk of side effects
Section 3.3 Access to Pain Care – Inadequate insurance coverage
3.3.2 Insurance for complementary pain management services (gaps)

Section 2.2 Medication

While NSAIDS can provide significant pain relief for inflammation, arthritis, muscle pains, headaches, and acute pains from injury or surgery, the category of "medical foods", recognized by FDA for the dietary management of a disease or condition for which distinctive nutritional requirements, may provide unique benefits in these conditions.[1,2] Medical foods have the potential to improve patient outcomes by alleviating pain and lowering the medication dosage while maximizing tolerability and safety. While analgesic medications are a mainstay of chronic and acute pain therapy,[3] these modalities do not come without the risk of significant adverse events and drug-drug interactions. NSAIDS are commonly prescribed, but their analgesic efficacy is often modest and comes with a number of serious adverse effects.[4]

The mechanism of action behind medical foods in the treatment of chronic pain syndromes arises from an understanding that the metabolic process is disrupted in pain, leading to a depletion of neurotransmitters, synaptic fatigue, increased neurotransmitter precursor turnover and dietary deficiency of the neurotransmitter precursor. Choline, histidine, 5-hydroxytryptophan, serine, and arginine have all been used in medical foods to blunt painful

[1] Bitto A., Squadrito F., Irrera N., Pizzino G., Mecchio A., Galfo F., and Altavilla D. (2014). Flavocoxid, a nutraceutical approach to blunt inflammatory conditions. Mediators Inflamm 790851.
[2] Morgan S.L., Baggott J.E., Moreland L., Desmond R., and Kendrach A.C. (2009). The safety of flavocoxid, a medical food, in the dietary management of knee osteoarthritis. J Med Food 12: 1143-1148.
[3] Slater D., Kunnathil S., McBride J., Koppala R. (2010). Pharmacology of nonsteroidal anti-inflammatory drugs and opioids. Semin Intervent Radiol 27: 400-411.
[4] Gargallo CJ, Sostres C., and Lanas A. (2014). Prevention and treatment of NSAID gastropathy. Curr Treat Options Gastroenterol 12: 398-413.

stimuli.[5,6,7] The nutraceutical flavocoxid has been used to treat the inflammation and joint pain from osteoarthritis in double blind clinical studies.[8,9]

Other physician-prescribed medications to manage pain have not met with optimal success. Acetaminophen is another medication relied on to manage chronic pain, but it is associated with significant adverse events.[10,11] Opioids have their own adverse effects including increased risk of falls, depression, sexual dysfunction, nausea, constipation, hormonal abnormalities, dependence, overdose, and death. Growing concerns about prescribing ever-increasing doses or combinations of analgesics, and an apparent lack of evidence demonstrating any lasting improvement in long-term clinical outcomes, has created heightened urgency for developing safer, more effective therapies to better manage chronic pain conditions. Medical foods provide a new alternative to traditional medication therapies. Utilizing medical foods in combination with traditional medications for chronic pain may manage efficacy safely, while reducing any risks of adverse events.

Medical foods must meet strict FDA safety and efficacy standards. Such products require substantiation to demonstrate efficacy of a clinical endpoint in a target population. Medical foods have the potential to be more cost-effective than standard analgesic medications. Medical foods have been an underutilized option for the treatment of chronic pain. Physicians should have appropriate alternatives to traditional pharmaceuticals to improve patient outcomes by alleviating pain and improving safety.

Section 2.6 Complementary and Integrative Health

> **Gap 2:** There is a gap in the understanding of complementary and integrative health approaches in terms of mechanisms of action, clinical studies examining the feasibility of integrating complementary and integrative health approaches into current care models, the efficacy of individual complementary and integrative health approaches in special populations, and clinical evaluation of complementary and integrative health approaches in the perioperative surgical period as part of a multimodal approach to acute and chronic pain settings.

There should be future research on medical foods as complementary medicines in the treatment of acute and chronic pain. Research should focus on the mechanisms of action, risk and benefit, and economic benefit in the treatment of both acute and chronic conditions, including the acute perioperative surgical pain period as well as other chronic pain conditions and syndromes. FDA should formally recognize more medical foods as examples that qualify under the definition promulgated in the Orphan Drug Act and its amendments. There is a considerable lack of clarity in the understanding of industry as to what products FDA recognizes as a medical food. FDA should rewrite its compliance police guide (CPG) on medical foods and provide more examples, especially in the area of medical foods for acute and chronic pain conditions.

Section 2.7 Special Populations

2.7.2 Older Adults

Gap 1B – Increased risk of side effects

The most frequent NSAID-related adverse effects are gastrointestinal (GI) related, including GI ulcers, gastritis, GI bleeds, gastroesophageal reflux, and GI bleeds. It is estimated that NSAID-related GI bleeding is

[5] Shell W.E., Pavlik S., Roth B., Silver M., Breitstein M.L., May L., and Silver D. (2016). Reduction in pain and inflammation associated with chronic low back pain with the use of the medical food theramine. Am J Ther 23: e1353-e1362.
[6] Silver D.S., Charuvastra E.H., May L., Pavlik S.L., and Shell W.E. (2012). Theramine (a medical food) versus nonsteroidal anti-inflammatory agents in elderly patients: a pharmacoeconomic analysis. J Pharm Res 5: 2806-2809.
[7] Lautenbacher S., Kundermann B., and Krieg J.C. (2006). Sleep deprivation and pain perception. Sleep Med Rev 10: 357-369.
[8] Levy R.M., Saikovsky R., Schmidt E., Khokhlov A., and Burnett B.P. (2009). Flavocoxid is as effective as naproxen for managing the signs and symptoms of osteoarthritis of the knee in humans: a short-term randomized, double-blind pilot study. Nutr Res 29: 298-304.
[9] Levy R.M., Khokhlov A., Kopenkin S., Bart B., Ermolova T., Kantemirova R., Mazurov V., Bell M., Caldron P., Pillai L., and Burnett B.P. (2010). Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects with osteoarthritis of the knee. Adv Ther 27: 732-742.
[10] Sargiotto B.T., Machado G.C., Ferreira M.L., Pinheiro M.B., Abdel Shaheed C., and Maher C.G. (2016). Paracetamol for low back pain. Cochrane Database Syst Rev 6: CDO012230.
[11] Williams C.M., Maher C.G., Latimer J., (2014). Efficacy of paracetamol for acute low-back pain: a double-blind, randomized controlled trial. Lancet 384: 1586-1596.

responsible for 100,000 hospitalizations and 16,500 deaths per year.[12,13] The annual risk for GI bleeds in patients over age 65 years is estimated to be 2.5%.[14,15] Hematopoietic toxicity (e.g., bleeding risk) may occur, and hepatic, renal, and cardiovascular systems may all be impacted as a result of NSAIDs in elderly patients.[16,17] NSAID-induced adverse events are also dose-related and elderly patients are at highest risk for these negative outcomes.[18] Because the risk of negative outcomes is so high in elderly patients, the American Geriatrics Society recommends that NSAIDS be restricted, or even eliminated in individuals older than 65 years of age.[19] One pharmacoeconomic analysis, comparing a medical food to generic NSAID use in elderly patients, found medical foods to be less costly after evaluating the costs of NSAID-related GI bleeding, laboratory monitoring, and clinical follow up.

Section 3.3 Access to Pain Care

Medical foods are not considered a covered benefit for any diagnosis other than inborne errors of metabolism which are present at birth and permanent in nature. Medical foods and foods for special dietary use aimed at reducing pain outcomes in patients should be a covered benefit. If the medical food or food for special dietary use have substantiation behind the claims for reducing pain scores in patients, then these food products should receive the same benefits afforded to traditional pharmaceuticals. FDA should expand its recognition of medical foods outside of infant diagnoses involving inborne errors of metabolisms.

Conclusion

The growing concerns over polypharmacy, increasing prescription doses, and adverse events from managing acute and chronic pain have created a need to develop safer therapies when treating pain. Medical foods and foods for special dietary use are two categories that are underutilized by physicians. Their claims are substantiated by competent and reliable scientific evidence and there is a labeling requirement that differentiates them from other food products. They must also be given under the supervision of a physician. These products have the potential to provide clinicians with a unique therapeutic modality which improves pain scores while minimizing toxicity risks.

NPA hopes that the U.S. Department of Health and Human Services and its Pain Management Task Force will consider these three pages of comments. We look forward to working with the Department in the future and thank them for the opportunity to comment on this very important matter.

Sincerely,

Daniel Fabricant, Ph.D.
CEO & President
Natural Products Association

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[12] Roth S.H. (2012). Coming to terms with nonsteroidal anti-inflammatory drug gastropathy. Drugs 72: 873-879.
[13] Wehling M. (2014). Nonsteroidal anti-inflammatory drug use in chronic pain conditions with special emphasis on the elderly and patients with relevant comorbidities: management and mitigation of risks and adverse effects. Eur J Clin Pharmacol 70: 1159-1172.
[14] Silver D.S., Charuvastra E.H., May L., Pavlik S.L., and Shell W.E. (2012). Theramine (a medical food) versus nonsteroidal anti-inflammatory agents in elderly patients: a pharmacoeconomic analysis. J Pharm Res 5: 2806-2809.
[15] Gupta A., Zheng L., Ramanujam V., and Gallagher J. (2015). Novel use of pharmacogenetic testing in the identification of CYP2C9 polymorphisms related to NSAID-induced gastropathy. Pain Med 16: 866-869.
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[17] Curiel R.V. and Katz J.D. (2013). Mitigating the cardiovascular and renal effects of NSAIDS. Pain Med 14 (Suppl 1): S23-S28.
[18] Taylor R., Lemtouni S., Weiss K, and Pergolizzi J.V. (2012). Pain management in the elderly: an FDA safe use initiative expert panel's view on preventable harm associated with NSAID therapy. Curr Gerontol Geriatr Res 2012: 196159.
[19] Shell W.E., Pavlik S., Roth B., Silver M., Breitstein M.L., May L., and Silver D. (2016). Reduction in pain and inflammation associated with chronic low back pain with the use of the medical food theramine. Am J Ther 23: e1353-e1362.