



## MEDICAL POLICY

### COMPOUNDED MEDICATION, MEDICAL FOOD, AND CO-PACKS

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## POLICY

### OVERVIEW:

- **Compounded medication** has traditionally involved combining drug ingredients to meet needs of specific patients for medications that are not otherwise commercially available. For this reason, the FDA has not sought to eliminate all compounded pharmaceuticals. However, the practice of compounding has gotten out of hand as pharmacies and physicians take advantage of very high markups. While traditional compounds involved tailoring medications to the needs of an individual patient, some business are now pre-manufacturing and mass-marketing product.

Although compounded drugs do not require FDA determination that they are safe and effective, the FDA is concerned about their quality, purity, safety, and efficacy as most have not been adequately tested in quality studies. In addition, they often duplicate formulas that are available either over-the-counter or by conventional prescription.

Guidelines are now appearing that address these concerns. These include the ODG, a study commissioned by the California Commission on Health, Safety and Workers' Compensation, and other insurance policies, including those of Aetna. They have concluded that compounded medication is frequently experimental.

- Some compounded drugs include **medical foods** (e.g. Theramine, Sentra, Gabadone). These are formulated to treat patients who are seriously ill or require food as significant treatment. They are to be used under guidance of a physician, but they are exempt from labeling requirements for health claims and nutrient content. Medical food products are not approved or registered with the FDA. As with other many compounds, however, the FDA remains concerned about safety and quality. Today there is little medical evidence supporting their use.
- Medical food marketers have created **co-packs**, which are pre-packaged combinations of a medical food and a generic FDA-approved prescription drug that are convenient to use (e.g. Theracodophen: Hydrocodone, Acetaminophen, & Theramine). The FDA has ruled that such co-packs require FDA registration and has threatened to shut down companies that do not comply.

Under the FDA, co-packs must be registered as a new drug and are not generally recognized as safe and effective. Today co-packs represent a convenience but not a medically necessity.

### **SPECIFIC RECOMMENDATIONS:**

#### **COMPOUNDED MEDICATION:**

- 1. Must contain at least one prescription ingredient** (This would eliminate the use of popular compounds such Dendracin cream, which contains only OTC drugs).
- 2. Must include only drug substances that have been supported as safe and effective for the prescribed indication by the FDA-approval process OR by adequate medical and scientific evidence in the medical literature** (This would allow off-label usage when supported by medical evidence).
- 3. Is not recommended if it contains at least one drug (or drug class) that is not recommended.**
4. Must not be a drug that was withdrawn or removed from the market for safety reasons.
5. Must not be a copy of a commercially available FDA-approved drug product.
6. Must not be used as therapy unless an appropriate rationale is provided in the medical records as to why conventional, non-compounded alternatives would be inadequate.
- 7. Must not be used as first-line therapy unless an appropriate rationale is provided in the medical records.**
8. Must include only bulk ingredients that are components of FDA-approved drugs that have been made in an FDA-registered facility and have an NDC code.

#### **Commonly Compounded Individual Medications:**

- Dendracin/Neurodendraxin (Blends of Methyl Salicylate, Benzocaine & Menthol and Capsaicin, Menthol & Methyl Salicylate respectively): Not recommended as all ingredients are OTC.
- Topical Anti-Epilepsy Drugs: Not recommended. There is no evidence to support their use.
- Topical Capsaicin: Recommended.
- Topical Gabapentin: Not recommended. There is no peer-reviewed literature to support its use.
- Topical Ketamine: Under study. Only recommended for neuropathic pain, for which all primary and secondary treatments have been exhausted.

- Topical Ketoprofen: Not recommended. There are no high quality studies to support its use.
- Topical Lidocaine: Recommended for neuropathic pain.
- Topical Muscle Relaxants: Not recommended. There is no peer-reviewed literature to support its use.
- Topical NSAID's: Diclofenac (Voltaren, Pennsaid) is recommended for soft tissue injuries such as sprain/strains and osteoarthritis pain in a joint that lends itself to topical treatment (ankle, elbow, foot, hand, knee, and wrist). Ketoprofen, piroxicam, and flurbiprofen (Ansaid) are not recommended due to inadequate evidence of safety and efficacy in treating pain.
- Topical Salicylates: Recommended.

### **MEDICAL FOOD:**

- 1 Must be reported as safe and effective for the recommended indication by adequate medical and scientific evidence in the medical literature.**
- 2. Any compound of medical food that contains at least one food that is not recommended is not recommended.**

#### Common Medical Foods:

- Choline: Not recommended. There is inconclusive evidence to support its use.
- GABAdone™ (Proprietary blend of Choline, Glutamic Acid, 5-Hydroxytryptophan, and GABA): Not recommended because of ingredients that are not recommended.
- Gamma-aminobutyric acid (GABA): Recommended for epilepsy, spasticity, and tardive dyskinesia. There are no high quality peer-reviewed studies to support use for insomnia.
- Glutamic Acid: Not recommended. There is insufficient evidence to support its use.
- Honey & Cinnamon: Recommended for treating arthritic pain.
- 5-Hydroxytryptophan: Recommended for depression, anxiety disorders, fibromyalgia, obesity, and sleep disorders.
- L-Serine: Not recommended. There is no indication for its use.
- L-Arginine: Not recommended. There is no indication for its use in treating pain or inflammation.

- Limbrel (flavocoxid/ arachidonic acid): Under study for treating arthritic pain in patients at risk of adverse effects from NSAIDs. Not yet recommended.
- Sentra PM™ (Proprietary blend of choline, glutamate, and 5-hydroxytryptophan): Not recommended because of ingredients that are not recommended.
- Theramine® (Proprietary blend of gamma-aminobutyric acid [GABA], choline, L-arginine, and L-serine): Not recommended because of ingredients that are not recommended.
- Trepadone™ (Proprietary blend of L-arginine, L-glutamine, choline, L-serine and gammaaminobutyricacid [GABA]): Not recommended because of ingredients that are not recommended.
- Deplin® (L-methylfolate): Not recommended for depressive disorder or peripheral neuropathy.

### **CO-PACKS:**

**Not recommended.** They are not generally recognized by the FDA as safe and effective in their compounded form. They also represent a medical convenience as opposed to a medical necessity.

#### Common Co-Packs:

- Theracodophen-650 Convenience Pack (Hydrocodone 10 mg, Acetaminophen 650 mg, and Theramine);
- Strazepam Convenience Pack (Temazepam 15 mg and Sentra PM);
- Gabazolamine-0.5 Convenience Pack (Alprazolam 0.5 mg and GABAdone);
- Gaboxetine Convenience Pack (Fluoxetine 10 mg and GABAdone);
- Trazamine Convenience Pack (Tradazone 50 mg and Sentra PM);
- Senophylline Convenience Pack (Theophylline 100 mg and Sentra PM);
- Therapentin-60 (Gabapentin 200 mg and Theramine);
- Prazolamine (Carisoprodol 350 mg and Theramine);
- Sentradine (Ranitidine 150 mg and Sentra PM);
- Therafeldamine (Piroxicam 20 mg and Theramine)

## **SUPPORTING DOCUMENTATION**

### **COMPOUND DRUGS**

Not recommended as a first-line therapy for most patients, but recommended as an option after a trial of first-line FDA-approved drugs, if the compound drug uses FDA-approved ingredients that are recommended in ODG. (Wynn, 2011) See specific entries for each ingredient. See also Topical analgesics, compounded. In general, FDA-approved drugs should be tried prior to prescribing a compound drug, unless specific patient issues with any appropriate FDA-approved drugs have already been identified. Pharmacy compounding has traditionally involved combining drug ingredients to meet the needs of specific patients for medications that are not otherwise commercially available, and it is undertaken on a patient-by-patient basis for patients who, for example, might be allergic to inactive ingredients in FDA-approved drugs or may need a different dosage strength or route of administration. Unlike commercially available drugs, these products are not approved by the FDA but rather are regulated by the state pharmacy board and state law governing the practice of pharmacy. The FDA does not regulate pharmacy-compounded products in recognition of the important public health function performed by traditional compounding. Recently, some pharmacies have been making and marketing stock compound drugs for the WC patient population. Among the FDA “Red Flags” for Enforcement Action on Compounded Drugs is: "Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to amounts compounded after receiving valid prescriptions." (FDA, 2011) Compound topical analgesics may provide relief by acting locally over the painful site with lower risk of systemic adverse effects on the gastrointestinal system and drug interactions than oral NSAIDs. The issues surrounding compound drugs are due to uncertainties regarding whether the products are medically appropriate and whether payments are reasonable, with the latter issue possibly also involving who dispenses the drug. Medical necessity should be based on the patient's needs combined with the medical and scientific evidence presented in ODG. ODG does not address pricing and fee schedules, but in general there should be consistency within a pharmacy fee schedule for products containing the same active ingredients, so that there is not an inappropriate incentive to use compounding. (Wynn, 2011)

#### Criteria for Compound drugs:

- (1) Include at least one drug substance (or active ingredient) that is the sole active ingredient in an FDA-approved prescription drug, not including OTC drugs.
- (2) Include only bulk ingredients that are components of FDA-approved drugs that have been made in an FDA-registered facility and have an NDC code.
- (3) Is not a drug that was withdrawn or removed from the market for safety reasons.
- (4) Is not a copy of a commercially available FDA-approved drug product.
- (5) Include only drug substances that have been supported as safe and effective for the prescribed indication by the FDA-approval process and/or by adequate medical and scientific evidence in the medical literature. This would allow off-label usage when supported by medical evidence. See specific entries for each ingredient in ODG for the medical and scientific evidence. (Wynn, 2011)

### **TOPICAL ANALGESICS**

Recommended as an option as indicated below. Largely experimental in use with few randomized controlled trials to determine efficacy or safety. Primarily recommended for neuropathic pain when trials of antidepressants and anticonvulsants have failed. (Namaka, 2004) These agents are applied locally to painful areas with advantages that include lack of systemic side effects, absence of drug interactions, and no need to titrate. (Colombo, 2006) Many agents are compounded as monotherapy or in combination for pain control (including NSAIDs, opioids, capsaicin, local anesthetics, antidepressants, glutamate receptor antagonists,  $\alpha$ -adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists,  $\gamma$  agonists, prostanoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor). (Argoff, 2006) There is little to no research to support the use of many these agents. Any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of these compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required. [Note: Topical analgesics work locally underneath the skin where they are applied. These do not include transdermal analgesics that are systemic agents entering the body through a transdermal means. For example, see Duragesic® (fentanyl transdermal system).]

*Non-steroidal anti-inflammatory agents (NSAIDs):* Recommended for the following indications:

*Acute pain:* Recommended for short-term use (one to two weeks), particularly for soft tissue injuries such as sprain/strains. According to a recent review, topical NSAIDs can provide good levels of pain relief for sprains, strains, and overuse injuries, with the advantage of limited risk of systemic adverse effects as compared to those produced by oral NSAIDs. They are considered particularly useful for individuals unable to tolerate oral administration, or for whom it is contraindicated. There appears to be little difference in analgesic efficacy between topical diclofenac, ibuprofen, ketoprofen and piroxicam, but indomethacin is less effective, and benzydamine is no better than placebo. The number needed to treat for clinical success, defined as 50% pain relief, for all topical NSAIDs combined vs. placebo was 4.5 (95% confidence interval [CI], 3.9 - 5.3) for treatment periods of 6 to 14 days. Current studies indicate 6 or 7 out of 10 patients have effective pain control with topical agents vs. 4 out of 10 with placebo. The reason for the high placebo rate is that most sprain/strain injuries improve on their own. (Massey, 2010) (Mason, 2004)

*Osteoarthritis and tendinitis, in particular, that of the knee, elbow, and hand or other joints that are amenable to topical treatment:* Recommended for short-term use (4-12 weeks). (See also the Knee Chapter.) (Underwood, 2008) (Mason, 2004) (Biswal, 2006) (Green, 2002) (Niethard, 2005) (Conaghan, 2008) (Altman, 2009) (Wenham, 2010) (Zhang, 2007) (NICE, 2008) (Zhang, 2010) (Altman, 2011) The American Academy of Orthopedic Surgeons recommends topical NSAIDs if there is increased GI risk with use of NSAIDs as one option for treatment. (Richmond, 2010) There are no studies evaluating topical ketoprofen for treatment of hand osteoarthritis. Topical ketoprofen gel has been compared to oral celecoxib, with WOMAC physical function scores significant for the later but not the topical treatment. (Rother, 2007)

*Osteoarthritis of the hip and shoulder:* There is little evidence to utilize topical NSAIDs for treatment of osteoarthritis of the hip or shoulder.

*Osteoarthritis of the low back:* There is no evidence to recommend a NSAID dosage form other than an oral formulation for low back pain. (Roelofs, 2008) (Haroutiunian, 2010)

*Widespread musculoskeletal pain:* Not recommended.

*Neuropathic pain:* Not recommended as there is no evidence to support use. (Haroutiunian, 2010) (Finnerup, 2005)

*General information:* The theory behind using a topical NSAID is to achieve a therapeutic concentration in the tissue adjacent to the application, allowing for safe serum concentration. This would allow for less adverse GI events, eliminate first-pass metabolism and reduce risk of other GI events associated with higher systemic doses provided with oral formulations. Overall, a high concentration of drug is observed in the dermis and muscles (equivalent to that obtained orally), with less gastrointestinal effect. Plasma concentrations are 5% to 15% of those achieved systemically. (Kienzler, 2010) Topically applied NSAIDs appear to reach the synovial fluid of joints, although the mechanism for delivery remains unclear. The efficacy in clinical trials for this treatment modality has been inconsistent and most studies are small and of short duration. Topical NSAIDs have been shown in meta-analysis to be superior to placebo during the first 2 weeks of treatment for osteoarthritis, but either not afterward, or with a diminishing effect over another 2-week period. (Lin, 2004) (Bjordal, 2007) (Mason, 2004) When investigated specifically for osteoarthritis of the knee, topical NSAIDs have been shown to be superior to placebo for 4 to 12 weeks. The effect appeared to diminish over time and it was stated that further research is required to determine if results were similar for all preparations. (Biswal, 2006) These medications may be useful for chronic musculoskeletal pain, but there are no long-term studies of their effectiveness or safety. In terms of acute pain, topical NSAIDs were found to produce a 50% reduction in pain at one week, with the most significant results obtained with use of ketoprofen, while indomethacin was barely distinguished from placebo. (Mason, 2004)

*Pharmacokinetics and systemic availability:* Absorption and penetration through the skin depends on the active medication, formulation (i.e. gel vs. solution), carrier-medicated transport, and penetration enhancement. Each of these differences produces differences in systemic levels attained. The carrier may also contribute to toxicity. Toxicity by dose has not been established (especially for trials that allowed for more than one joint to be treated). Excessive amounts of topical NSAID may produce higher than desired levels, hindering the advantage of a topical formulation. (Haroutiunian, 2010) (Kienzler, 2010)

*Compounded formulations:* There is little research available in terms of bioavailability and objective clinical endpoints for these agents. (Haroutiunian, 2010)

*FDA-approved agents:* At this time, the only available FDA-approved topical NSAID is diclofenac.

*Voltaren® Gel 1% (diclofenac):* Indicated for relief of osteoarthritis pain in a joint that lends itself to topical treatment (ankle, elbow, foot, hand, knee, and wrist). It has not been evaluated for treatment of the spine, hip or shoulder. Maximum dose should not exceed 32 g per day (8 g per joint per day in the upper extremity and 16 g per joint per day in the lower extremity). The most common adverse reactions were dermatitis and pruritus. (Voltaren® package insert) Clinical trial data suggest that diclofenac sodium gel (the first topical NSAID approved in the US) provides clinically meaningful analgesia in OA patients with a low incidence of systemic adverse events. (Altman, 2009) The labeling for topical diclofenac has been updated to warn about drug-induced hepatotoxicity. (FDA, 2009) Voltaren Gel was effective in adults regardless of age. Treatment-related application site dermatitis was more common with Voltaren Gel, but gastrointestinal AEs were infrequent. It is recommended for osteoarthritis after failure of an oral NSAID, or contraindications to oral NSAIDs, or for patients who cannot swallow solid oral dosage forms. (Baraf, 2011) (Kienzler, 2010) See also Voltaren® Gel separate listing, where it is not recommended as a first-line treatment.

*Pennsaid® (diclofenac topical solution 1.5% containing 45.5% dimethyl sulfoxide):* FDA-approved for osteoarthritis of the knee. A recent study on adverse effects of this agent compared to oral diclofenac found that the latter formulation had significantly higher events. Gastrointestinal AEs orally were 39% vs. 25.4% topically (P<0.0001). Cardiovascular events were 3.5% orally vs. 1.5% topically (P=0.055). Liver function tests were increased more commonly in those taking oral agents. The most common adverse effect was application-site reaction. Dry skin is thought to result from the DMSO component. Long-term studies were recommended. (Roth, 2011) The dose is 40 drops to the knee four times a day. See also

Pennsaid® (diclofenac sodium topical solution) separate listing, where it is not recommended as a first-line treatment.

*Flector® Patch (diclofenac epolamine topical patch 1.3%)*: Indicated for acute strains, sprains, and contusions. Apply one patch twice daily to most painful area. See also Flector® patch (diclofenac epolamine) separate listing, where it is not recommended as a first-line treatment.

*Non FDA-approved agents: Ketoprofen*: This agent is not currently FDA approved for a topical application. It has an extremely high incidence of photocontact dermatitis and photosensitization reactions. (Diaz, 2006) (Noize, 2010) (Hindsen, 2006) (Devleeschouwer, 2008) (Matthieu, 2004) (Barbaud, 2009) Due to the high incidence of these reactions the French government removed this topical drug from the market in December 2009. This was subsequently overturned, with recommendations made to make the topical formulation available by prescription only, and by strengthening warnings as to adverse effects. (Lechat, 2010) Absorption of the drug depends on the base it is delivered in. (Guroi, 1996). Topical treatment can result in blood concentrations and systemic effect comparable to those from oral forms, and caution should be used for patients at risk, including those with renal failure. (Krummel 2000) *Clinical trials*: Numerous clinical trials are ongoing, including a phase III trial for a ketoprofen patch for treatment of soft tissue injury, acute sprain/strain, and non articular rheumatism, tendinitis and bursitis, a phase III trial for ketoprofen 10% cream for treatment of acute soft tissue injury, and a topical ketoprofen gel for muscle soreness. Clinical trials show similar results between Diclofenac gel and a ketoprofen patch formulation. (Esparza, 2007) See also Ketoprofen, topical separate listing, where it is under study as a first-line treatment.

*Piroxicam*: There is no FDA-approved topical piroxicam agent. This drug also is known to produce drug-induced photosensitivity. (Drucker, 2011) (Barbaud, 2009) Numerous adverse effects are noted with systemic delivery of piroxicam including elevated hepatic enzymes in 1-10% in patients who receive the drug.

*Adverse effects of topical NSAIDs in general*: Topical NSAIDs have a high safety margin with fewer severe gastrointestinal adverse effects. Adverse drug events occur on average in about 12% of individuals, with 75% of these including rash and/or pruritus at the application site. A recent systematic review of use of topical NSAIDs in older adults found the withdrawal rates from topical agents to be similar to that of oral NSAIDs. Gastrointestinal complaints and headaches were reported most frequently in both topical and oral NSAID groups. Anemia, liver function tests, renal abnormalities, and severe gastrointestinal events were higher in oral NSAID users. Examination of drug-related effects, including vehicles used and total dose is needed. (Makris, 2010) The use of oral NSAIDs concomitantly with topical agents is not recommended. (Peterson, 2011) See also NSAIDs, GI symptoms and cardiovascular risk; & NSAIDs, hypertension and renal function.

*Cost effectiveness*: Current FDA-approved topical agents are approximately six to ten times more expensive than oral over-the-counter preparations. Savings may occur due to lack of serious adverse GI effects, and the lack of necessity of taking an ulcer-protection medication. **Lidocaine**: Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology. See Criteria for use below. Topical lidocaine, in the formulation of a dermal patch (Lidoderm®) has been designated for orphan status by the FDA for neuropathic pain. Lidoderm is also used off-label for diabetic neuropathy. No other commercially approved topical formulations of lidocaine (whether creams, lotions or gels) are indicated for neuropathic pain. Further research is needed to recommend this treatment for chronic neuropathic pain disorders other than post-herpetic neuralgia. Formulations that do not involve a dermal-patch system are generally indicated as local anesthetics and anti-pruritics. In February 2007 the FDA notified consumers and healthcare professionals of the potential hazards of the use of topical lidocaine. Those at particular risk were individuals that applied large amounts of this substance over large areas, left

the products on for long periods of time, or used the agent with occlusive dressings. Systemic exposure was highly variable among patients. Only FDA-approved products are currently recommended.

Indications: Recommended for localized pain that is consistent with a neuropathic etiology after there has been evidence of a trial of first-line therapy (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica). Topical lidocaine patches are generally not recommended for non-neuropathic pain (including osteoarthritis or myofascial pain/trigger points). See Criteria for use below. Most studies have utilized the Neuropathic Pain Scale (NPS) as measure of neuropathy when there are questions of whether this is the cause of pain. There is limited information as to long-term efficacy and continued information as to outcomes should be provided to allow for on-going use. (Argoff, 2004) (Galer, 2004) (Argoff, 2006) (Dworkin, 2007) (Khaliq-Cochrane, 2007) (Knotkova, 2007) (Lexi-Comp, 2008) (Fishbain, 2006) (Affaitati, 2009) (Burch, 2004) (Gimbel, 2005) (Dworkin, 2003) (Finnerup, 2005) (O'Connor, 2009)

Trigger points & myofascial pain: Not recommended. (Affaitati, 2009) (Dalpaiz, 2004)

Osteoarthritis of the knee: Not generally recommended unless a component of neuropathy is indicated using measures such as the Neuropathic Pain Scale. All current available studies were sponsored by the manufacturer of lidocaine patches and are non-controlled, and of short-term in duration. (Burch, 2004) (Kivitz, 2008)

Axial back pain (including osteoarthritis): Not recommended unless neuropathy is suggested. Current studies as to use of Lidoderm patches for non-neuropathic low back pain are non-controlled, may or may not evaluate for the presence of neuropathic quality, have included multiple stages of pain (from acute to chronic), have included multiple diagnoses, show limited results in pain reduction, and are generally sponsored by the manufacturer. Acute groups have had better results than chronic pain patients, which may be attributed to natural recovery. (Gimbel, 2005) (Galer, 2004) (Argoff, 2004)

Capsaicin: Recommended only as an option in patients who have not responded or are intolerant to other treatments. Formulations: Capsaicin is generally available as a 0.025% formulation (as a treatment for osteoarthritis) and a 0.075% formulation (primarily studied for post-herpetic neuralgia, diabetic neuropathy and post-mastectomy pain). There have been no studies of a 0.0375% formulation of capsaicin and there is no current indication that this increase over a 0.025% formulation would provide any further efficacy. Indications: There are positive randomized studies with capsaicin cream in patients with osteoarthritis, fibromyalgia, and chronic non-specific back pain, but it should be considered experimental in very high doses. Although topical capsaicin has moderate to poor efficacy, it may be particularly useful (alone or in conjunction with other modalities) in patients whose pain has not been controlled successfully with conventional therapy. The number needed to treat in musculoskeletal conditions was 8.1. The number needed to treat for neuropathic conditions was 5.7. (Robbins, 2000) (Keitel, 2001) (Mason-BMJ, 2004) Neither salicylates nor capsaicin have shown significant efficacy in the treatment of OA. (Altman, 2009) See also Capsaicin.

Baclofen: Not recommended. There is currently one Phase III study of Baclofen-Amitriptyline-Ketamine gel in cancer patients for treatment of chemotherapy-induced peripheral neuropathy. There is no peer-reviewed literature to support the use of topical baclofen.

Other muscle relaxants: There is no evidence for use of any other muscle relaxant as a topical product.

Gabapentin: Not recommended. There is no peer-reviewed literature to support use.

Other antiepilepsy drugs: There is no evidence for use of any other antiepilepsy drug as a topical product.

Ketamine: Under study: Only recommended for treatment of neuropathic pain in refractory cases in which all primary and secondary treatment has been exhausted. Topical ketamine has only been studied for use

in non-controlled studies for CRPS I and post-herpetic neuralgia and both have shown encouraging results. The exact mechanism of action remains undetermined. ([Gammaitoni, 2000](#)) ([Lynch, 2005](#))

*Salicylate topical*: Recommended as an option. Topical salicylate (e.g., Ben-Gay, methyl salicylate) is significantly better than placebo in acute and chronic pain, but especially acute pain.

## MEDICAL FOOD

Recommended as indicated below. *Definition*: Defined in section 5(b) of the Orphan Drug Act (21 U.S.C. 360ee (b) (3)) as “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” To be considered the product must, at a minimum, meet the following criteria: (1) the product must be a food for oral or tube feeding; (2) the product must be labeled for dietary management of a specific medical disorder, disease, or condition for which there are distinctive nutritional requirements; (3) the product must be used under medical supervision. See Food labeling; Reference Daily Intakes and Daily Reference Values; Mandatory Status of Nutrition Labeling and Nutrition Content Revision proposed rule (56 FR 60366 at 60377, November 27, 1991). Medical foods are exempted from the labeling requirements for health claims and nutrient content claims under the Nutrition Labeling and Education Act of 1990 (see 21 U.S.C. 343 (q) (5) (A) (iv)). Medical foods do not have to be registered with the FDA. ([CFSAN, 2008](#))

*Current available medical food products*:

*Choline*: Choline is a precursor of acetylcholine. There is no known medical need for choline supplementation except for the case of long-term parenteral nutrition or for individuals with choline deficiency secondary to liver deficiency. There is inconclusive evidence that this product is indicated for an endurance aid, memory, seizures, and transient ischemic attacks. Side effects of high-dose choline include hypotension, acute GI distress, and cholinergic side effects (such as sweating and diarrhea). A fishy odor may occur with use. ([AltMedDex, 2008](#)) ([Clinical Pharmacology, 2008](#))

*Glutamic Acid*: This product is used for treatment of hypochlorhydria and achlorhydria. Treatment indications include those for impaired intestinal permeability, short bowel syndrome, cancer and critical illnesses. It is generally used for digestive disorders in complementary medicine. ([AltMedDex, 2008](#)) ([Lexi-Comp, 2008](#))

*5-hydroxytryptophan*: This product has been found to be possibly effective in treatment of anxiety disorders, fibromyalgia, obesity and sleep disorders. It has been found to be effective for depression. In alternative medicine it has been used for depression, anxiety, insomnia, obesity, aggressive behavior, eating disorders, fibromyalgia, chronic headaches and various pain disorders. It should be used with caution in individuals using SSRI antidepressants. This product has been linked to a contaminant that causes a condition called eosinophilia-myalgia syndrome. ([De Benedittis, 1985](#)) ([Klarskov, 2003](#)) ([AltMedDex, 2008](#)) ([Lexi-Comp, 2008](#))

*Gamma-aminobutyric acid (GABA)*: This medication is indicated for epilepsy, spasticity and tardive dyskinesia. There is no high quality peer-reviewed literature that suggests that GABA is indicated for treatment of insomnia. Adverse reactions associated with treatment include hypertension, increased heart rate and anxiety. Dose reductions are indicated for a creatinine clearance > 60 ml/min. ([AltMedDex, 2008](#)) In this low quality RCT, with no description for the actual sleep disorder, an amino acid preparation containing both GABA and 5-hydroxytryptophan reduced time to fall asleep, decreased sleep latency, increased the duration of sleep, and improved quality of sleep. ([Shell, 2009](#))

*L-Serine*: There is no indication in *Micromedex*, *Clinical Pharmacology*, or *AltMedDex*® for the use of this product.

*L-Arginine*: This medication is not indicated in current references for pain or “inflammation.” It is indicated to detoxify urine. Other indications include in use for angina, atherosclerosis, coronary artery disease, hypertension, migraines, obesity, and metabolic syndrome. (AltMedDex, 2008) (CFSAN, 2008) (Clinical Pharmacology, 2008) (Lexi-Comp, 2008) (Micromedex, 2008)

*Honey & cinnamon*: Recommended as an option for arthritis pain, even though the evidence is low quality, it is promising, and there is minimal down side. An unpublished study found that within a week of treatment with a mixture of one-tablespoon honey and half-teaspoon cinnamon powder before breakfast, 73 patients out of the 200 people treated were totally relieved of pain within a month, and almost all patients who could not walk because of arthritis started walking without significant pain. (Fotopoulou, 2008)

*Limbrel (flavocoxid)*: Under study as an option for arthritis in patients at risk of adverse effects from NSAIDs. Limbrel is a botanical medical food, made from root and bark extracts from plants. It contains flavocoxid, a blend of two flavonoids (baicalin and catechins). It is thought to inhibit the conversion of arachidonic acid to both prostaglandins and leukotrienes.

Evidence for use: (The following studies were sponsored by Primus Pharmaceuticals, the manufacturer of the product.) The initial pilot study tested flavocoxid 500 mg BID against naproxen 500 mg BID. In the one-month onset of action trial there was no statistical difference in signs and symptoms of knee osteoarthritis, or between the groups in any of the outcome variables of discomfort or global disease activity ( $P \leq 0.001$ ). (Levy, 2009) Adverse effects were similar. A 12-week study was then conducted (double-blind, controlled). Non-inferiority margin values were not published, nor were P values for non-inferiority. Both groups showed improvement at 6 weeks with further improvement at 12 weeks, with no statistically significant differences in efficacy. (Levy, 2010) A post-hoc subset analysis was then conducted. The statistical method used to address post-hoc methodology was not explained. Twelve subsets were compared in a study group of 220 subjects. With the understanding that this type of analysis increases the risk of finding a statistical difference by chance, trends favoring flavocoxid occurred in older subjects ( $> 60$  years), males and in subjects with milder disease. (Levy, 2010b) A post-marketing study of 60 days duration was performed to determine the overall efficacy and gastrointestinal tolerability of flavocoxid. This was an open-label study of 1005 patients with no control group. Approximately a third of patients had had to interrupt previous NSAID use and/or discontinue due to a GI issues. Almost half of the patients taking NSAIDs were also using gastroprotective medication. Multiple improved outcomes were noted at the completion of the study. Unlike the previous subset analysis, those individuals with more clinically severe osteoarthritis responded better than those with milder disease. Upper GI tolerability was improved in patients who had symptoms with use of NSAIDs and the use of gastroprotective medications was decreased. (Pillai, 2010)

Adverse effects with use: Flavocoxid (Limbrel) has been linked to liver toxicity, which is a mild to moderate mixed hepatocellular-cholestatic hepatitis that arises 1 to 3 months after starting the medication. This appears to be a limited effect (occurring in about 0.012% of patients) as per current postmarketing surveillance. Hypersensitivity is thought to be the mechanism. There is also one case report of hypersensitivity pneumonia reported as a meeting abstract. Current post-marketing data reports that there are 12 confirmed cases and 5 unconfirmed cases of this complication. (Chalasan, 2012) (Youssef, 2010) (Limbrel Post-Marketing Surveillance Report, March 2012)

Monitoring: The package insert recommends initial testing of liver function within two months of initiating therapy. (Limbrel Package Insert)

Regulation with use: Medical foods do not require formal premarketing studies of safety and efficacy. As this product is made with botanical ingredients, variation can occur in concentration of substances. (Chalasanani, 2012)

Note: Limbrel is not included on the ODG Drug Formulary because it is not a drug. If Limbrel were covered on the Formulary, it would be an N drug, because it is not recommended as a first-line drug, but only after first-line drugs have been trialed and found to produce adverse effects or a history of adverse effects with use is obtained.

#### GABAdone™

Not recommended. GABAdone™ is a medical food from Physician Therapeutics, Los Angeles, CA, that is a proprietary blend of Choline Bitartrate, Glutamic Acid, 5-Hydroxytryptophan, and GABA. It is intended to meet the nutritional requirements for inducing sleep, promoting restorative sleep and reducing snoring in patients who are experiencing anxiety related to sleep disorders. (Shell, 2009)

#### Sentra PM™

Sentra PM™ is a medical food from Targeted Medical Pharma Inc., Los Angeles, CA, intended for use in management of sleep disorders associated with depression, that is a proprietary blend of choline bitartrate, glutamate, and 5-hydroxytryptophan. See Choline, Glutamic Acid, & 5-hydroxytryptophan.

#### Theramine®

Not recommended. Theramine® is a medical food from Physician Therapeutics, Los Angeles, CA, that is a proprietary blend of gamma-aminobutyric acid [GABA] and choline bitartrate, L-arginine, and L-serine. It is intended for use in the management of pain syndromes that include acute pain, chronic pain, fibromyalgia, neuropathic pain, and inflammatory pain. See Medical food, Gamma-aminobutyric acid (GABA), where it says, “There is no high quality peer-reviewed literature that suggests that GABA is indicated”; Choline, where it says, “There is no known medical need for choline supplementation”; L-Arginine, where it says, “This medication is not indicated in current references for pain or inflammation”; & L-Serine, where it says, “There is no indication for the use of this product.” In this manufacturer study comparing Theramine to naproxen, Theramine appeared to be effective in relieving back pain without causing any significant side effects. (Shell, 2012) Until there are higher quality studies of the ingredients in Theramine, it remains not recommended.

#### Trepadone™

Trepadone™ is a medical food from Targeted Medical Pharma Inc., Los Angeles, CA, that is a proprietary blend of L-arginine, L-glutamine, choline bitartrate, L-serine and gammaaminobutyric acid [GABA]. It is intended for use in the management of joint disorders associated with pain and inflammation. See Medical food, L-Arginine, Glutamic Acid, Choline, L-Serine, and Gamma-aminobutyric acid (GABA).

#### UltraClear

UltraClear is a medical food from Metagenics, Inc., San Clemente, CA, intended to nutritionally support the management of chronic fatigue syndrome.

#### Deplin®

Deplin® (L-methylfolate) is a prescription medical food from Pan American Laboratories, Inc., Covington, LA, for the dietary management of suboptimal folate, a naturally occurring B vitamin, in

depressed patients. L-methylfolate is not an antidepressant, but may make antidepressants work better by correcting folate levels in the brain. See Folate (for depressive disorders) in the Mental Illness & Stress Chapter. See also Vitamin B

## **CO-PACK DRUGS**

Co-packs are convenience packaging of a medical food product and a generic drug into a single package that requires a prescription. The labeler may create a new NDC for the co-pack. While the generic drug is FDA-approved, the co-pack of a medical food and FDA-approved drug is not unless the manufacturer obtains FDA approval for the product as a new drug. There are no high quality medical studies to evaluate co-packs on patient outcomes, so this is not addressed in ODG.

## **FOLATE (For Depressive Disorders)**

Under study. The limited available evidence suggests folate may have a potential role as a supplement to other treatment for depression. It is currently unclear if this is the case both for people with normal folate levels, and for those with folate deficiency. (Taylor, 2004) Some studies have shown that folic acid may be a simple method of greatly improving the antidepressant action of fluoxetine and other antidepressants (Coppen, 2002) but another metaanalysis concludes that none of the CAM studies show evidence of efficacy in depression according to the hierarchy of evidence. (Thachil, 2006) Multiple studies show that a low dietary intake of folate may be a risk factor for severe depression. (Tolmunen, 2004) (Papakostas, 2004) (Lerner, 2006) A trial of oral doses of both folic acid (800 microg daily) and vitamin B12 (1 mg daily) may be tried to improve treatment outcome in depression, with continuation depending on results. (Coppen, 2005) (Thachil, 2006)

## **VITAMIN B**

Not recommended. Vitamin B is frequently used for treating peripheral neuropathy but its efficacy is not clear. A recent meta-analysis concluded that there are only limited data in randomized trials testing the efficacy of vitamin B for treating peripheral neuropathy and the evidence is insufficient to determine whether vitamin B is beneficial or harmful. In the comparison of vitamin B with placebo, there was no significant short-term benefit in pain intensity while there is a small significant benefit in vibration detection from oral benfotiamine, a derivative of thiamine. In comparing different doses of vitamin B complex, there was some evidence that higher doses resulted in a significant short-term reduction in pain and improvement in paraesthesiae, in a composite outcome combining pain, temperature and vibration, and in a composite outcome combining pain, numbness and paraesthesiae. There was some evidence that vitamin B is less efficacious than alpha-lipoic acid, cilostazol or cytidine triphosphate in the short-term improvement of clinical and nerve conduction study outcomes. Vitamin B is generally well-tolerated. (Ang-Cochrane, 2008)

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