Medical Policy: Compounded Medication-- Medical Foods			
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Specialty:	Anesthesiology, Pain Management	**Established Date:**	12/27/2011
Referral Number:	841499		

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 copacks 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 medical 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:**

1. Dendracin/Neurodendraxin (Blends of Methyl Salicylate, Benzocaine & Menthol and Capsaicin, Menthol & Methyl Salicylate respectively): Not recommended as all ingredients are OTC.

2. Topical Anti-Epilepsy Drugs: Not recommended. There is no evidence to support their use.

3. Topical Capsaicin: Recommended.

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

5. Topical Ketamine: Under study. Only recommended for neuropathic pain, for which all primary and secondary treatments have been exhausted.

6. Topical Ketoprofen: Not recommended. There are no high-quality studies to support its use.

7. Topical Lidocaine: Recommended for neuropathic pain.

8. Topical Muscle Relaxants: Not recommended. There is no peer-reviewed literature to support its use.

9. 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.

10. 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:**

1. Choline: Not recommended. There is inconclusive evidence to support its use.

2. GABAdone™ (Proprietary blend of Choline, Glutamic Acid, 5-Hydroxytryptophan, and GABA): Not recommended because of ingredients that are not recommended.

3. Gamma-aminobutyric acid (GABA): Recommended for epilepsy, spasticity, and tardive dyskinesia. There are no high-quality peer-reviewed studies to support use for insomnia.

4. Glutamic Acid: Not recommended. There is insufficient evidence to support its use.

5. 5-Hydroxytryptophan: Recommended for depression, anxiety disorders, fibromyalgia, obesity, and sleep disorders.

6. L-Serine: Not recommended. There is no indication for its use.

7. L-Arginine: Not recommended. There is no indication for its use in treating pain or inflammation.

8. Limbrel (flavocoxid/ arachidonic acid): Under study for treating arthritic pain in patients at risk of adverse effects from NSAIDs. Not yet recommended.

9. Sentra PM™ (Proprietary blend of choline, glutamate, and 5-hydroxytryptophan): Not recommended because of ingredients that are not recommended.

10. Theramine® (Proprietary blend of gamma-aminobutyric acid [GABA], choline, L-arginine, and L-serine): Not recommended because of ingredients that are not recommended.

11. Trepadone™ (Proprietary blend of L-arginine, L-glutamine, choline, L-serine and gammaaminobutyricacid [GABA]: Not recommended because of ingredients that are not recommended.

12. 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:**

1. Theracodophen-650 Convenience Pack (Hydrocodone 10 mg, Acetaminophen 650 mg, and Theramine);

2. Strazepam Convenience Pack (Temazepam 15 mg and Sentra PM);

3. Gabazolamine-0.5 Convenience Pack (Alprazolam 0.5 mg and GABAdone);

4. Gaboxetine Convenience Pack (Fluoxetine 10 mg and GABAdone);

5. Trazamine Convenience Pack (Tradazone 50 mg and Sentra PM);

6. Senophylline Convenience Pack (Theophylline 100 mg and Sentra PM);

7. Therapentin-60 (Gabapentin 200 mg and Theramine);

8. Prazolamine (Carisoprodol 350 mg and Theramine);

9. Sentradine (Ranitidine 150 mg and Sentra PM);

10. Therafeldamine (Piroxicam 20 mg and Theramine)

SUPPORTING DOCUMENTATION

ODG Pain (updated 06/13/17)- Online Version
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, -adrenergic receptor agonist, adenosine, cannabinoids, cholinergic receptor agonists, 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. Custom compounding and dispensing of combinations of medicines that have never been studied is not recommended, as there is no evidence to support their use and there is potential for harm. [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% dimithyl 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 DSMO 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. (Gurol, 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 not recommended in the U.S., as there are currently no FDA-approved versions of this product, but it is a first-line drug in Europe.
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 and gastrointestinal symptoms; NSAIDs, hypertension and cardiac disease & NSAIDs 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.
Criteria for use of Lidoderm patches:
(a) Recommended for a trial if there is evidence of localized pain that is consistent with a neuropathic etiology.
(b) There should be evidence of a trial of first-line neuropathy medications (tri-cyclic or SNRI anti-depressants or an AED such as gabapentin or Lyrica).
(c) This medication is not generally recommended for treatment of osteoarthritis or treatment of myofascial pain/trigger points.

(d) An attempt to determine a neuropathic component of pain should be made if the plan is to apply this medication to areas of pain that are generally secondary to non-neuropathic mechanisms (such as the knee or isolated axial low back pain). One recognized method of testing is the use of the Neuropathic Pain Scale.
(e) The area for treatment should be designated as well as number of planned patches and duration for use (number of hours per day).
(f) A Trial of patch treatment is recommended for a short-term period (no more than four weeks).
(g) It is generally recommended that no other medication changes be made during the trial period.
(h) Outcomes should be reported at the end of the trial including improvements in pain and function, and decrease in the use of other medications. If improvements cannot be determined, the medication should be discontinued.
(i) Continued outcomes should be intermittently measured and if improvement does not continue, lidocaine patches should be discontinued.
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) Discussion about specific details of these studies are given in detail with references.
Second-line drugs such as capsaicin 8% patches had moderate to low effect sizes, but only low-quality evidence was available for lidocaine patches and the NNT could not be calculated. (Finnerup, 2015)
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)
The FDA has approved a lidocaine/ tetracaine cream (Pliaglis) for local analgesia. This is only indicated for superficial aesthetic procedures, such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. (FDA, 2013)
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: Not recommended except 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) See also Ketamine.
See also Salicylate topicals; & Glucosamine (and Chondroitin Sulfate).

ODG Pain (updated 06/13/17)- Online Version
Topical analgesics, compounded
See Topical analgesics, where it is explained that any compounded product that contains at least one drug (or drug class) that is not recommended is not recommended. The use of compounded agents requires knowledge of the specific analgesic effect of each agent and how it will be useful for the specific therapeutic goal required.

ODG Pain (updated 06/13/17)- Online Version
Medical food
Not recommended for chronic pain.
See specific Medical Food entries: Deplin (L-methylfolate); GABAdone; Sentra PM; Somnicin; Theramine; Trepadone; UltraClear & Limbrel. See also Compound drugs; Co-pack drugs; Physician-dispensed drugs; Repackaged drugs.
Medical foods are not recommended for treatment of chronic pain as they have not been shown to produce meaningful benefits or improvements in functional outcomes. The FDA defines a medical food 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." There are no quality studies demonstrating the benefit of medical foods in the treatment of chronic pain.
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 common supplements in available Medical Foods:
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, 2015) (Clinical Pharmacology, 2015)
Glutamic Acid: This is a precursor of gamma-aminobutyric acid (GABA). This supplement is used for treatment of gastric hydrochloric acid deficiency. Potential 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, 2015) (Lexi-Comp, 2015) (Clinical Pharmacology, 2015)
5-hydroxytryptophan: This is the intermediate metabolite between biosynthesis of L-tryptophan to serotonin. In alternative medicine it has been used for insomnia, obesity, aggressive behavior, eating disorders, fibromyalgia, chronic headaches and various pain disorders (postulated to inhibit inflammation). Current peer-reviewed evidence is inconclusive to support these claims. Other clinical applications for which inconclusive evidence has been found in terms of efficacy include as a treatment for anxiety. It is postulated as a treatment for depression, but a Cochrane Database Review found insufficient data to support efficacy and more extensive clinical trials are recommended

before widespread clinical use is endorsed. Overall, general use is not recommended as alternative antidepressants are available which have been proven to be safe and studies of clinical usefulness are limited. 5-hydoxytryptophan may be most helpful when a patient is already taking an antidepressant, although this too requires further study. It should be used with caution in individuals using SSRI antidepressants due to possible serotonin syndrome. This product has been linked to a contaminant that causes a condition called eosinophilia-myalgia syndrome. The most common adverse effects are GI (nausea, vomiting and diarrhea). (Iovieno, 2011) (Turner, 2006) (Shaw, 2002) (Sarris, 2011) (De Benedittis, 1985) (Klarskov, 2003) (AltMedDex, 2015) (Lexi-Comp, 2015)
Gamma-aminobutyric acid (GABA): GABA is the derivative of glutamic acid and ornithine. It does not cross the blood-brain barrier so taking this orally does not increase brain levels. Therefore, taking the supplement will not replicate drugs that do work by a GABA-related mechanism. In complimentary medicine settings, this supplement has been used for treatment of depression, bipolar disorder, seizures, premenstrual dysphoric disorder, and anxiety, although there is no quality evidence that GABA supplements have any effect on these conditions. It has also been suggested that GABA can improve sleep quality and improve cognitive function, but there is no scientific evidence to support these claims. There is some preliminary evidence that GABA can reduce blood pressure, but further studies are needed to allow for a recommendation for general use. When used in Medical Foods such as Theramine, it is suggested that GABA dampens pain signals in the spinal cord and brain. All studies supporting these potential mechanisms of action were performed on animals, and as noted, the supplement does not cross the blood-brain barrier. (AltMedDex, 2015)
Histidine: This amino acid supplement is postulated to inhibit inflammation and is used as a supplement for the treatment of arthritis. It is a precursor to histamine. There is no indication in Micromedex, Clinical Pharmacology, or AltMedDex for the use of this supplement, although there were studies in the 1970's evaluating use in rheumatoid arthritis. The conclusion of the one randomized controlled trial on this subject (using L-histidine) was that histidine could not be advocated as a therapeutic agent in rheumatoid arthritis. (Pinals, 1977) Other suggested uses are for treatment of allergic disease, ulcers, and anemia caused by kidney failure.
Serine: There is no indication in Micromedex, Clinical Pharmacology, or AltMedDex for the use of this supplement. It is a precursor to D-serine and is proposed to work by increasing sensitivity to opioids.
L-Arginine: This amino acid supplement is not indicated in current references for pain or "inflammation." It is a precursor of nitric oxide, which exhibits activity as a vasodilator, platelet-aggregation inhibitor and modulator of immunological processes and epithelial permeability. Arginine has been studied for multiple conditions with the result that most are either ineffective or inconclusive. There is no peer-reviewed literature to support use for chronic pain or osteoarthritis. It is currently used as a growth hormone reserve indicator, as a treatment of metabolic alkalosis, and as a treatment for T-Cell function (as part of enteral nutrition),
Omega-3 fatty acids: See Omega-3-fatty acids.
Honey & cinnamon: Not recommended. See separate listing for Honey & cinnamon.
Limbrel (flavocoxid): Not recommended. See separate listing for Limbrel (flavocoxid/ arachidonic acid).
(AltMedDex, 2015) (CFSAN, 2015) (Clinical Pharmacology, 2015) (Lexi-Comp, 2015) (Micromedix, 2015)

ODG Pain (updated 06/13/17)- Online Version
Deplin (L-methylfolate)
Not recommended.
See also B vitamins & vitamin B complex & Medical food in this chapter.
Deplin (L-methylfolate) is a prescription medical food that contains L-methylfolate (vitamin B9) in doses of 7.5 mg or 15 mg. See Deplin & B vitamins for depression in the Mental Illness and Stress Chapter.

ODG Pain (updated 06/13/17)- Online Version
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, GABA, grape seed extract, griffonia extract, whey protein, valerian extract, ginkgo biloba and cocoa. It is intended to meet the nutritional requirements for sleep disorders and sleep disorders associated with insomnia. See Medical food, Choline, Glutamic Acid, 5-hydroxytryptophan, and Gamma-aminobutyric acid (GABA). In these entries, it is noted that there is no peer-reviewed research in humans to support the use of choline or glutamic acid for treatment of either anxiety or sleep disorder. There is inconclusive evidence for the use of 5-hydroxy tryptophan as a treatment for anxiety. GABA does not cross the blood-brain barrier so this supplement will not replace drugs that work in the brain by a GABA-related mechanism. There is no quality evidence to support use in anxiety.
Sleep disorders: Not recommended for this indication based on limited available research. There is one randomized, placebo-controlled trial of GABAdone for treatment of sleep disorder in 18 subjects in a 7-day study. There is no

analysis comparing the two groups. Improvement was noted in time to fall asleep-sleep latency. Hours slept improved in the treated group, but never reached the baseline level found in the placebo group (6.83 hours in the GABAdone group and 7.11 hours in the placebo group at day 7). The number of awakenings was associated with apneic events and decreased in the treated group. Again, there was no description of the baseline status of the subjects, including weight or history of sleep apnea. There were other numerous baseline differences for which statistical significance was not given (minutes awake during awakenings, restorative sleep and AM grogginess) or no description of baseline at all. The study was described as a "pilot" in the conclusion. (Shell, 2010)

ODG Pain (updated 06/13/17)- Online Version
Sentra PM
Not recommended.
See Medical food, Choline, Glutamic Acid, & 5-hydroxytryptophan.
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. It is a proprietary blend of choline bitartrate, glutamate, and 5-hydroxytryptophan, hawthorn berry, cocoa, gingko biloba, and acetyl L-carnitine.

ODG Pain (updated 06/13/17)- Online Version
Somnicin
Not recommended.
Somnicin, a nutritional supplement, contains melatonin, magnesium oxide, oxitriptan (the L form of 5-hydroxytryptophan), 5-hydroxytryptophan, tryptophan and Vitamin B6 (pyridoxine). It is postulated as a treatment for insomnia, anxiety and depression. Melatonin appears to reduce sleep onset latency and is used for delayed sleep phase syndrome. This is considered a circadian abnormality. It is also used to treat rapid eye movement sleep disorders. It is not a hypnotic and treatment for chronic insomnia is inconclusive. It is available over-the-counter. See Melatonin. Magnesium oxide uses for which there is evidence favoring efficacy include the following: (1) as a treatment for magnesium deficiency; (2) as a treatment for upset stomach and acid indigestion. There is no indication for magnesium oxide as a treatment for sleep disorders of any kind. (Micromedex, 2015) (Lexi Comp, 2015) (Clinical Pharmacology, 2015)
For oxitriptan and 5-hydroxytriptophan, see Medical foods. Inconclusive evidence has been found for treatment for anxiety. There is some suggestion that 5-hydroxytryptophan can be used for treatment of depression, but at this point, this is only recommended for patients who are unable to take conventional antidepressants. With respect to Vitamin B 6 (pyridoxine), this vitamin is FDA-labeled for treatment of pyridoxine deficiency, certain metabolic disorders, prevention of drug-induced neurotoxicity, and for the treatment of neuritis due to pyridoxine deficiency that is not drug-induced. There is no indication for treatment for any sleep disorder. (Micromedex, 2015) (Lexi Comp, 2015) (Clinical Pharmacology, 2015) This can be purchased over-the-counter.

ODG Pain (updated 06/13/17)- Online Version
Theramine
Not recommended for the treatment of chronic pain.
Theramine is a medical food that contains 5-hydroxytrytophan 95%, choline bitartrate, L-arginine, histidine, L-glutamine, L-serine, gamma-aminobutyric acid (GABA), whey protein concentrates, grape seed extract 85%, cinnamon, and cocoa (theobromine 6%). It is intended for use in the management of pain syndromes that include acute pain, chronic pain, fibromyalgia, neuropathic pain, and inflammatory pain. The proposed mechanism of action is that it increases the production of serotonin, nitric oxide, histamine, and gamma-aminobutyric acid by providing these precursors. (Micromedex, 2015) See Medical food. Under this entry discussions of the various components of this product are given. The entries for 5-hydorxytryptophan, choline bitartrate, L-arginine, histidine, L-glutamine, L-serine and GABA are given and all indicate there is no role for these supplements as treatment for chronic pain. Current studies: A study funded by the manufacturer of this formulation looked at a comparison of Theramine to naproxen alone with a third arm using both as a comparison. The study of 129 patients was conducted at 12 commercial sites. The patients given naproxen were only given 250 mg/day in one dose. The recommended dose of naproxen for moderate pain is 250 mg every 6-8 hours as needed. The recommended dose for osteoarthritis is 250-500 mg twice a day, and this can be increased to 1500 mg/day for limited periods of up to 6 months if required. Based on the subtherapeutic dose of naproxen this study does not allow for an accurate comparison of this drug to Theramine alone. A third arm utilized two Theramine and one 250 mg naproxen a day. The study population was largely heterogeneous, with no etiologies of back pain given, and back pain was of duration of < 6 weeks. Patients with surgery in the previous 6 months or those with neurological impairment were excluded, as were patients who had taken an opiate analgesic for greater than 5 days in the month before screening. The naproxen group alone remained unchanged after 28 days using psychometric testing (Oswestry disability index and Roland-Morris Pain

Index) but this could be explained by the subtherapeutic dose of the drug provided. The group with the most improvement was that receiving both Theramine and naproxen. Unfortunately, actual raw values are not provided to assess the results (only % change from baseline is provided). Other criticism of the study is that there is little information on patient adherence or how patients were recruited. Based on the exclusion criteria alone, this study is not readily applicable to a majority of chronic non-malignant workers' compensation pain patients. (Shell, 2012) A second study was again published by this group in 2014 that addressed neurotransmitter deficiency. In this study, the arm using low dose ibuprofen (400 mg daily) is now indicated as a basic proxy to placebo. The standard dose of this drug for moderate pain is 400 mg q 4-6 hours. The dose for osteoarthritis is 400-800 mg 3-4 times a day. This study was performed on 122 patients at 8 clinical sites. Pain was again heterogeneous, and in this study lasted for greater than 6 weeks, although the exact duration of pain was not given. Patients must have used analgesics (at least 10 days in the month before the study), although this could not include opiate analgesics for 5 days in the month before screening. Other exclusion criteria were similar to the 2012 study. Plasma amino acids rose in the Theramine group and it was suggested that this increase was a reason for decreased pain and increased function. Again, values are only given in percent change. A final summary is that treating metabolism-based nutritional deficiencies of pain syndromes could possibly allow for reduction of NSAID use without affecting therapeutic efficacy. Once again, the design of this study limits applicability to a majority of chronic non-malignant workers' compensation patients. (Shell, 2014)

ODG Pain (updated 06/13/17)- Online Version
Trepadone
Not recommended. Trepadone is a medical food that is suggested for use in the management of joint disorders associated with pain and inflammation.
It is a proprietary blend of L-arginine, L-glutamine, L-histidine, choline bitartrate, 5-hydroxytryptophan, L-serine, gamma-aminobutyric acid, grape seed extract, cinnamon bark, cocoa, omega-3 fatty acids, histidine, whey protein hydrolysate, glucosamine, chondroitin and cocoa. See Medical food. Under this entry discussions of the various components of this product are given. The entries for 5-hydorxytryptophan, choline bitartrate, L-arginine, histidine, L-glutamine, L-serine and GABA all indicate there is no role for these supplements as treatment for chronic pain. See also Omega-3 fatty acids. Current literature suggests omega-3 fatty acids for treatment of certain cardiovascular and lipid conditions, treatment of rheumatoid arthritis, and for selected patients for depression (primarily those who are unable to take conventional antidepressants). There is insufficient evidence to support use for osteoarthritis or for neuropathic pain.

ODG Pain (updated 06/13/17)- Online Version
UltraClear
Not recommended.
Metagenics, Inc., San Clemente, CA, markets several UltraClear products. In August 2013 the FDA sent this company a warning letter indicating that none of their products were Medical Foods, as advertised by the manufacturer. The following statements were made in terms of the products. (1) UltraClear, UltraClear Plus, and UltraClear Plus pH: While labeled as intended for treatment for chronic fatigue syndrome, there was no evidence to support the need for any specific nutrient for this condition; (2) UltraClear RENEW: While labeled as a treatment for fibromyalgia, there was no evidence of any nutrient need for this condition; (3) All other UltraClear products had similar warnings. There is then another warning that these products were being promoted for conditions that caused them to be defined as drugs. Specific disease conditions included chronic fatigue syndrome and fibromyalgia.

ODG Pain (updated 06/13/17)- Online Version
Limbrel (flavocoxid)
Not recommended based on additional evidence of adverse effects. (Panduranga, 2013) (ACP, 2012) (Reichenbach, 2012)
It had been 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 (P0.001). (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. (Chalasani, 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. (Chalasani, 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.

ODG Pain (updated 06/13/17)- Online Version
Co-pack drugs
Not generally recommended as there are no high-quality studies to demonstrate improved patient outcomes.
See also Compound drugs; Medical foods; Physician-dispensed drugs; Repackaged drugs.
Co-packs are convenience packaging of a medical food product and a generic drug into a single package that requires a prescription. They may also include convenience packaging of multiple medications, even in the absence of medical foods. There is no evidence to support the medical necessity of co-packs as there are no high-quality medical studies to evaluate co-packs on patient outcomes. Labelers 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. See specific entries for each ingredient in ODG.

ODG Pain (updated 06/13/17)- Online Version
B vitamins & vitamin B complex
Not recommended for the treatment of chronic pain unless this is associated with documented vitamin deficiency.
See B vitamins for depression in the Mental Illness and Stress Chapter.
There are multiple B vitamins with specific symptoms due to deficiency: (1) vitamin B1 (thiamine) - beriberi; (2) vitamin B2 (riboflavin); (3) vitamin B3 (niacin or nicotinic acid) - pellagra; (4) vitamin B5 (pantothenic acid); (5) vitamin B6 (pyridoxine); (6) vitamin B7 (biotin); (7) vitamin B9 (folic acid) - megaloblastic anemia; (8) vitamin B12 (various cobalamins) - pernicious anemia, myelopathy, neuropathy, dementia, subacute combined degeneration of the spine, and decreased cognition. Treatment of vitamin B12 deficiency is generally parenteral. Vitamin B Complex contains the above 8 vitamins plus para-aminobenzoic acid, inositol, and choline. It 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 (diabetic and alcoholic). Evidence was insufficient to determine whether specific B vitamins or B complex for these conditions was beneficial or harmful. (Ang-Cochrane, 2008)

ODG Mental Illness and Stress (updated 04/25/17)- Online Version
Recommended as an option for special populations for long-term management of depression as an adjunct to antidepressant therapy, in particular if there is a deficiency. One theory for the potential benefit is that high plasma homocysteine has been consistently associated with depression, and treatment with certain B vitamins reduces its concentration.
See also B vitamins & vitamin B complex in the Pain Chapter.

Criteria for use of B vitamins for depression:
If a clinician chooses to start vitamin B supplementation to antidepressant therapy, a recommended starting point is a trial of
- Oral folic acid (800 mcg/day)
- Vitamin B12 (1 mg daily). (Coppen, 2005) (Thachil, 2006)
An added consideration is to obtain baseline lab values for both, as deficiency alone of either can be confused with depression and cognitive decline (particularly of B12).
Recent research: A recent randomized controlled trial (evaluating use of vitamin B6, folic acid and vitamin B12 in combination) and subsequent meta-analysis (evaluating folic acid and vitamin B12 in combination) indicated that these various B vitamins used as a supplement to antidepressant therapy do not appear to decrease the severity of depressive symptoms over a period of several weeks (short-term) in people with depressive disorder. The analysis did suggest that use over a long-term period enhances and sustains antidepressant response. (Almeida, 2015) (Almeida, 2014) Other recent studies examining the role of folic acid and vitamin B12 found little evidence for potentiation of antidepressant medicine with this adjunct treatment. (Christensen, 2011) Future randomized placebo-controlled trials are suggested to investigate use for improving response to antidepressants. There is insufficient evidence to recommend the use of B vitamins as a monotherapy for depression. (Sengl, 2014) (Nahas, 2011)
Vitamin B12 as a single supplement to antidepressants: Patients with low normal B12 levels were randomized to receive antidepressants alone or antidepressants plus B12 injections (the treatment arm). HAM-D score was significantly improved in the treatment group (100% showed at least 20% reduction vs. 69% in the group that received antidepressants only). (Syed, 2013)
Folic acid as a single supplement to antidepressants: The results of randomized controlled trials have been mixed regarding the effectiveness of folic acid as an adjunct to antidepressant therapy. (Baolu, 2009) (Bedson, 2014) (Coppen, 2000) (Resler, 2008) (Venkatasubramanian, 2013) However, the largest of these studies, a double-blinded randomized controlled trial that included 475 participants and compared the use of folic acid alone as an adjunct to antidepressant medication over 12 weeks, showed no clinical effectiveness in augmentation. The authors suggested that their findings undermined treatment guidelines that advocated the use of folic acid for treating depression, and suggested future trials of methylfolate to augment antidepressant medications. (Bedson, 2014) Furthermore, a meta-analysis of these studies indicated that there was no difference between folic acid and placebo. (Sarris, 2016)
Folic acid vs. L-methylfolate: There are no head-to-head trials comparing these two for adjunct treatment with antidepressants.
L-methylfolate: See Deplin (L-methylfolate) in this chapter.

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