Medical Policy: Compounded Medication-- Medical Foods			
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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 businesses 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.

1. 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.

2. 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.

- **Private Label Non-Compounded Topical Medications:**

1. Dendracin/Neurodendraxin (Blends of Methyl Salicylate, Benzocaine & Menthol and Capsaicin, Menthol & Methyl Salicylate respectively): Private-label topical drugs are not recommended for any indication.

2. Topical Capsaicin: usually found in non-compounded over-the counter formulations, which are recommended. Private label formulations are not recommended.

3. Topical Salicylates: usually found in non-compounded over-the counter formulations, which are recommended. Private label formulations are not recommended.

4. 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.

- **Commonly Compounded Individual Medications:**

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

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

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

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

5. Topical Lidocaine: Recommended for neuropathic pain.

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

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 by MCG, Treatment Guidelines, Topicals, Private-Label for Pain, Last review/update date: Feb 12, 2021
Private-label topicals are independently manufactured over-the-counter products. They are generally prescribed for minor pain conditions. Common ingredients are those found in commercially available over-the-counter products (menthol, methyl salicylate, and capsaicin). The private-label products are not FDA-approved and not recommended on evidence-based guidelines. They are not clinically tested for safety or efficacy. Safety issues include reports of serious skin burns in products containing high doses of menthol and methyl salicylate.

ODG by MCG, Treatment Guidelines, Salicylate Topicals for Pain, Last review/update date: Feb 12, 2021
Recommended as an over-the-counter, non-compounded formulation as a trial for symptomatic pain relief.

ODG by MCG, Treatment Guidelines, Menthol Topical for Pain, Last review/update date: Feb 12, 2021
Recommended as an over-the-counter, non-compounded formulation as a trial for symptomatic pain relief.

ODG by MCG, Treatment Guidelines, Capsaicin, Topical (Chili Pepper/Cayenne Pepper) for Pain, Last review/update date: Feb 12, 2021
Not Recommended as a first-line treatment for chronic neuropathic pain or pain due to osteoarthritis. Recommended only as an option in patients who have not responded or are intolerant to other treatments.

Formulations:

Creams (over-the-counter): Capsaicin is generally available as an over-the-counter formulation. The 0.025% product is used as a treatment for osteoarthritis and a 0.075% formulation is primarily recommended for post-herpetic neuralgia, diabetic neuropathy, HIV-related neuropathy, and post-mastectomy/surgical neuropathic pain. Efficacy for other neuropathies is still under study.
Compounded: There have been no studies of a 0.0375% formulation (available as a compound) of capsaicin and there is no current indication that this increase over a 0.025% formulation would provide any further efficacy.
Private Label Topicals: Private label topicals containing differing combinations and doses of salicylates, menthol, capsaicin, and/or lidocaine are not recommended.
Patches: Qutenza (capsaicin) 8% patches This high dose formulation is approved by the FDA for treatment of postherpetic neuropathy. Efficacy for other painful neuropathies remains under study.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines and Massachusetts Treatment Guidelines do not address topical analgesics.

State of Colorado Department of Labor and Employment
RULE 17, EXHIBIT 9
Chronic Pain Disorder
Medical Treatment Guideline
Revised: 10/6/2017
Effective: 11/30/2017
G. Therapeutic Procedures - Non-Operative
10. Medications and Medical Management
k. Topical Drug Delivery:
i. Description: topical creams and patches may be an alternative treatment of localized musculoskeletal and neuropathic disorders. If ordered compounded topicals are reviewed by the payer, the payer must evaluate and approve or deny each ingredient separately.
ii. Indications: neuropathic pain for many agents; episodic use of NSAIDs and salicylates for joint pain or musculoskeletal disorders. All topical agents should be used with strict instructions for application as well as maximum number of applications per day to obtain the desired benefit and avoid potential toxicity.
iii. Dosing and Time to Therapeutic Effect: all topical agents should be prescribed with clear instructions for application and maximum number of applications per day to obtain the desired benefit and avoid potential toxicity. For most patients, the effects of long-term use are unknown. Thus, episodic use may be preferred for some agents.
iv. Side Effects: localized skin reactions may occur, depending on the medication agent used. v. Topical Agents:
A) Capsaicin: As of the time of this guideline writing, formulations of capsaicin have been FDA approved for management of pain associated with post-herpetic neuralgia. Capsaicin offers a safe and effective alternative to systemic NSAID therapy. Although it is quite safe, effective use of capsaicin is limited by the local stinging or burning sensation that typically dissipates with regular use, usually after the first 7 to 10 days of treatment. Patients should be advised to apply the cream on the affected area with a plastic glove or cotton applicator and to avoid inadvertent contact with eyes and mucous membranes. There is good evidence that low dose capsaicin (0.075%) applied 4 times per day will decrease pain up to 50%. There is strong evidence that a single application of 8% capsaicin is more effective than a control preparation of 0.04% capsaicin for up to 12 weeks. However, there may be a need for frequent application, and it is not known whether subsequent applications of capsaicin are likely to be as

effective as the first application. There is some evidence that in patients who are being treated with capsaicin 8% patches, two methods of pre-treatment are equally effective in controlling application pain and in enabling patients to tolerate the patch: topical 4% lidocaine cream applied to the area for one hour before placement of the capsaicin patch and 50 mg oral tramadol taken 30 minutes before patch placement.
B) Clonidine: There is good evidence that topical clonidine gel 0.1% is likely to alleviate pain from diabetic peripheral neuropathy in patients who display a nociceptive response to the application of 0.1% capsaicin applied to the pretibial area. It is likely that patients who do not display a pain response to pretibial capsaicin are not likely to have a clinically meaningful analgesic response to clonidine gel. It is unknown if this screening test applies to other types of neuropathic pain. Clonidine gel may be used for neuropathic pain.
C) Ketamine and Tricyclics: Topical medications, such as the combination of ketamine and amitriptyline, have been proposed as an alternative treatment for neuropathic disorders including CRPS. A study using a 10% concentration showed no signs of systemic absorption. This low-quality study demonstrated decreased allodynia at 30 minutes for some CRPS patients. However, as of the time of this guideline writing, neither tricyclic nor ketamine topicals are FDA approved for topical use in neuropathic pain. Furthermore, there is good evidence that neither 2% topical amitriptyline nor 1% topical ketamine reduces neuropathic pain syndromes. Despite the lack of evidence, it is physiologically possible that topical tricyclics and a higher dose of ketamine could have some effect on neuropathic pain. Other less expensive topicals and compounds, including over-the counter, should be trialed before more expensive compounds are ordered. The use of topical tricyclics and/or ketamine should be limited to patients with neuritic and/or sympathetically mediated pain with documented supporting objective findings such as allodynia and/or hyperalgesia. Continued use of these agents beyond the initial prescription requires documentation of effectiveness, including functional improvement, and/or decreased use of other medications, particularly decreased use of opioids or other habituating medications.
D) Lidocaine: As of the time of this guideline writing, formulations of lidocaine (patch form) have been FDA approved for pain associated with post-herpetic neuralgia. Evidence is mixed for long-term use of lidocaine topically. Physicians should always take into account the blood level that may be achieved with topical use as toxic levels have been reported and there is variability and systemic absorption among individuals. There is good evidence that lidocaine 5% plasters, applied for up to 12 hours to the lower extremities of patients with post-herpetic neuralgia and diabetic painful neuropathy, is non-inferior to pregabalin for the same indications. The topical lidocaine is associated with significantly fewer drug-related adverse events over 4 weeks of observation. There is some evidence that a 5% lidocaine patch may be used as a secondary option for patients with focal neuropathic pain. A 30 to 50% pain reduction may be achieved in those who tolerate the patch. Up to three patches may be used simultaneously for 12 hours per day. It should be applied only to intact skin. Metered dose 8% pump sprays have also been used and usually require a three times per day reapplication. There is some evidence that the 8% sprays are effective for short-term, 2 week use. However, the effects of long-term use are unknown.
E) Topical Salicylates and Nonsalicylates: have been shown to be effective in relieving pain in acute musculoskeletal conditions and single joint osteoarthritis. Topical salicylate and nonsalicylates achieve tissue levels that are potentially therapeutic, at least with regard to COX inhibition. There is insufficient evidence to support the use of topical rubefacients containing salicylates for acute injuries or chronic conditions. They seem to be relatively well tolerated in the short term, based on limited data. The amount and quality of the available data mean that uncertainty remains about the effects of salicylate-containing rubefacients. There is good evidence that diclofenac gel (Voltaren, Solaraze) reduces pain and improves function in mild-to-moderate hand osteoarthritis. There is good evidence that topical diclofenac and ketoprofen are more effective than placebo preparations for purposes of relieving pain attributable to knee osteoarthritis. There is good evidence that topical NSAIDs probably reduce the risk of GI adverse effects by approximately 1/3 compared to oral NSAIDs. Topical diclofenac does not appear to affect the antiplatelet properties of aspirin unlike the oral version. The topical solution of 2% sodium diclofenac applied thrice a day is equal to 1.5% 4 times per day. Diclofenac gel has been FDA approved for acute pain due to minor strains, pains, and contusions and for relief of pain due to osteoarthritis of the joints amenable to topical treatment, such as those of the knees and hands (refer to the Division's Cumulative Trauma Conditions Medical Treatment Guideline). It is likely that other NSAIDs would also be effective topically. Thus, topical NSAIDs are permitted when patients show functional improvement. Other than local skin reactions, the side effects of therapy are minimal, although not non-existent. The usual contraindications to use of these compounds needs to be considered. Local skin reactions are rare and systemic effects are even less common. Their use in patients receiving warfarin therapy may result in alterations in bleeding time. Overall, the low level of systemic absorption can be advantageous. This allows the topical use of these medications when systemic administration is relatively contraindicated, such as is the case in patients with hypertension, cardiac failure, or renal insufficiency (refer to the Division's Cumulative Trauma Conditions Medical Treatment Guideline). Both topical salicylates and NSAIDs are appropriate for many chronic pain patients. However, in order to receive refills, patients should demonstrate increased function, decreased pain, or decreased need for oral medications.

F) Other Compounded Topical Agents: At the time of writing this guideline, no studies identified evidence for the effectiveness of compounded topical agents other than those recommended above. Therefore, other compounded topical agents are not generally recommended. In rare cases, they may be appropriate for patients who prefer a topical medication to chronic opioids or who have allergies or side effects from other more commonly used oral agents.
G) Prior authorization is required for all agents that have not been recommended above. Please refer to Rule 18-6(N), Prescription Strength Topical Compounds regarding requirements for reviewing, approving, denying, and refilling.

ODG by MCG
Last review/update date: Feb 12, 2021
Topical Analgesics, Compounded (Non-FDA Approved Formulations), for Pain
Body system: Pain
Treatment type: Medications
Formulary status: Y
Related Topics: See Compound Drugs for Pain for criteria for use. The following includes information about specific drugs which are compounded into non-FDA-approved formulations. If a prescription drug is required, commercially available, FDA-approved drugs for treatment of the disease process should be documented as trialed and failed prior to trials of compounded drugs. These commercially available, FDA-approved and over-the-counter formulations are found in the following ODG entries.
Capsaicin, Topical (Chili Pepper/Cayenne Pepper) for Pain
Diclofenac, Topical (Flector, Pennsaid, Voltaren Gel) for Pain
Flector Patch (Diclofenac Epolamine) for Pain
Lidocaine 5% Transdermal Patch (Lidoderm) for Pain
Pennsaid (Diclofenac Sodium Topical Solution) for Pain
Qutenza (High Concentration Capsaicin) 8% Patch for Pain
Topical NSAIDs for Pain
Voltaren Gel 1% (Diclofenac) for Pain
ZTLIDO (Lidocaine Topical Delivery System 1.8%) for Pain
Not Recommended (generally)
Not Recommended as a first-line treatment for chronic pain or osteoarthritis.
Evidence Summary
Overview:
Topical compounded analgesics in general are largely experimental in use with few randomized controlled trials to determine efficacy or safety. (1) (2) (EG 1) These agents are applied locally to painful areas with multiple proposed advantages: (1) bypass of first-pass metabolism with resultant faster onset of action); (2) low systemic absorption with higher concentration of the analgesic in the pain area, (3) lower to no levels of systemic effects and resultant toxicity; (4) absence of drug-drug interactions; (5) easier use of multiple drugs as they are combined into one vehicle. (3) (EG 2) 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, proteinoids, bradykinin, adenosine triphosphate, biogenic amines, and nerve growth factor). There is little to no research to support the use of many these agents, although ideally the clinicians involved should have knowledge of specific pharmacokinetic effects of each drug/agent used and how it will be useful for the specific therapeutic goal required.
[Note: Topical analgesics work locally underneath the skin where they are applied. The term transdermal analgesia is often used synonymously. The latter usually involves a delivery system such as a patch. Some transdermal systems allow for systemic delivery (ie, a fentanyl patch).]
Challenges with Use: When prescribed, there are multiple challenges with use. Overall, there is lack of research on appropriate topical delivery systems for many drugs that are compounded. This lack of research limits ability to provide treatment indications or guidelines. Equivalent and therapeutic topical doses are not established for the compounds and mechanism of action is often not established. Physicians may have little knowledge of active pharmaceutical ingredients of the compounded drugs in terms of proposed use, limiting appropriateness of prescribing. Once applied, systemic absorption is not determined. Finally, the limited studies available are generally short-term, so long-term effectiveness has not been established. Prescribers often omit any information about where the topical drug is to be applied or how often. With a lack of information about absorption, this can lead to either under- or over-dosing, and adverse systemic effects have been documented. Localized dermal reactions are common. (4) (EG 2)
Private Label Topicals: Private label topicals containing differing combinations and doses of salicylates, menthol,

capsaicin, and/or lidocaine are not recommended.
Specific Drugs
Capsaicin:
Compounded formulations are not recommended over current low dose over-the-counter capsaicin products that are available (as 0.025% and 0.07% doses). For instance, there are currently no studies to support any advantage of a 0.0375% compounded capsaicin formulation in terms of efficacy over the 0.025% product. Capsaicin is also available in a high dose concentration patch (Qutenza 8% patch). The latter is FDA-approved for postherpetic neuropathy. See Capsaicin, Topical (Chili Pepper/Cayenne Pepper) for Pain; Qutenza (High Concentration Capsaicin) 8% Patch for Pain.
Non-steroidal anti-inflammatory agents (NSAIDs):
Compounded topical formulations are not recommended. See Topical NSAIDs for Pain for further information, including FDA-approved products
Overview:
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. Proposed advantages include administration directly at the site of pain, avoidance of first-pass metabolism, reduced systemic exposure (with resultant lower risk of systemic adverse effects), ability to use in patients unable to tolerate oral NSAIDs, avoidance of drug-drug interactions, and patient preference (with potential for increased compliance). 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. (5) (EG 1) Topically applied NSAIDs appear to reach the synovial fluid of joints, although the mechanism for delivery remains unclear. (6) (7)
Pharmacokinetics and systemic availability:
Absorption and penetration through the skin depends on the active medication, formulation (ie, 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. (8) (5) (6) (EG 1)
Adverse effects of topical NSAIDs in general:
Topical NSAIDs have a high safety margin with fewer severe gastrointestinal adverse effects. Adverse drug events of topical NSAIDs 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. (9) (EG 1) The use of oral NSAIDs concomitantly with topical agents is not recommended. (10) (EG 1) . See also NSAIDs for Pain, Gastrointestinal Symptoms; NSAIDs for Pain, Hypertension and Cardiac Disease; NSAIDs for Pain, 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.
Compounded formulations:
There is little research available in terms of bioavailability and objective clinical endpoints for these agents. (8) (EG 1)
Ketoprofen:
This agent is not currently FDA approved for a topical application. It has an extremely high incidence of photocontact dermatitis and photosensitization reactions. (11) (12) (13) (14) (15) (16) (EG 2) 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. (17) (EG 2) Absorption of the drug depends on the base it is delivered in. (18) . 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. (19) (EG 2) 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. (20) (EG 1) . See also Ketoprofen, Topical for Pain 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. (21) (16) (EG 2) Numerous adverse effects are noted with systemic delivery of piroxicam including elevated hepatic enzymes in 1-10% in patients who receive the drug.
Flurbiprofen:
Not recommended. There is no FDA-approved topical formulation of this drug. Flurbiprofen exposure has been found to be toxic to cats by casual exposure. (22)
Meloxicam:
Not recommended. There is no FDA-approved topical formulation of this drug. Meloxicam has not been used by a major pharmaceutical company for topical delivery through the skin as the drug has limited permeability through the skin layer.
Topical Anesthetics: Lidocaine, bupivacaine, and mepivacaine
Lidocaine, compounded:
Not recommended as a compounded formulation. There are two prescription formulations of topical lidocaine: lidocaine patch 5% (Lidoderm and generic); ZTLIDO (lidocaine topical delivery system 1.8%). Both of these are FDA-approved for treatment of pain associated with postherpetic neuralgia. Numerous over-the-counter formulations are available including a 4% patch. See Lidocaine 5% Transdermal Patch (Lidoderm) for Pain; ZTLIDO (Lidocaine Topical Delivery System 1.8%) for Pain
Lidocaine 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.
Bupivacaine and mepivacaine: The use of either of these drugs for topical compound use is not supported by evidence research and should be considered as experimental. (4) (EG 2) There are no FDA-approved topical formulations of either of these drugs. Bupivacaine has been suggested as a topical, as it has a prolonged duration of action over lidocaine.
Muscle Relaxants
Baclofen:
Not recommended. Baclofen produces its analgesic effects by acting on GABA B receptors in the periphery, spinal cord, and brain. (2) (EG 1)
There is currently one Phase III study of Baclofen-Amitriptyline-Ketamine gel in cancer patients for treatment of chemotherapy-induced peripheral neuropathy. There is a retrospective study of a compound with ketamine 10%, baclofen 2%, gabapentin 6%, amitriptyline 4%, bupivacaine 2% and clonidine 0.2% with decreased pain scores and equal effectiveness in diabetic neuropathy, neuropathic pain and other pain states. The combination was considered a possible useful modality for pain therapy. (23) (EG 2) A case series has also evaluated a combination of diclofenac, ibuprofen, baclofen, cyclobenzaprine, bupivacaine, gabapentin, and pentoxifylline for radicular pain. Additional studies were recommended. (24) (EG 2)
Cyclobenzaprine:
Not recommended. A peripheral action of cyclobenzaprine is unlikely (ie, it is only thought to act centrally). (2) (EG 1) In animal studies, systemically administered cyclobenzaprine (10 mcg/kg) but not topically administered attenuated nociceptive pain. (25) (EG 2)
Other muscle relaxants:
There is no evidence for use of any other muscle relaxant as a topical product.
Anticonvulsants
The exact mechanism of action of these drugs used peripherally is not known.
Gabapentin:
Not recommended. There is no peer-reviewed literature in humans to support use. Animal studies have examined different concentrations (1%, 5%, and 10%) in Lipoderm at different pre-treatment times (30 minutes, 1 hour, and 4 hours). Minimal skin and deeper tissue levels were found following 4-hour pre-treatment. (26) (EG 2) There is some suggestion, based on animal studies that topical gabapentin may produce local antinociception. (27) (EG 2)
Other antiepilepsy drugs:
There is no evidence for use of any other antiepilepsy drug as a topical product.
General Anesthetic Agents/N-Methyl-D-Aspartate-Receptor Antagonists
Ketamine:
Not recommended. There is no FDA-approved topical formulation of this drug. Topical ketamine has only been studied in open label and case studies for use for CRPS I and post-herpetic neuralgia and both have shown encouraging results. There is no exact recommendation for percentage of drug delivery. The exact mechanism of

action remains undetermined. It has been suggested that the effects of ketamine for pain treatment are most likely due to actions in the brain rather than in the periphery. (28) (29) (30) (31) (2) (EG 1) There are two studies of combination of topical 2% amitriptyline and 1% ketamine. The open label study showed a reduction in neuropathic pain. A follow-up, double-blind, randomized, placebo-controlled study did not replicate the results. (29) (32) (EG 1)
Antidepressants
Current research indicates that analgesic effects of antidepressants are due to actions in the central nervous system rather than peripherally. (2) (EG 1)
Amitriptyline:
Not recommended. There are no FDA-approved topical formulations of this drug. The topical application of amitriptyline in several concentrations for a variety of localized neuropathic pain syndromes has been tested, with ambiguous results, regarding not only the efficacy but also the site of action when given as a single drug. Controlled clinical trials reveal that topical amitriptyline is not effective in treating neuropathic pain. The uncontrolled clinical trials do support efficacy of topical amitriptyline. Higher concentrations (ie, 10%) may be more effective in pain relief, but this appears to be related to systemic effects. A double-blind, randomized, placebo-controlled study of a combination of compounded topical amitriptyline 2% and ketamine 1% did not find a reduction in neuropathic pain. (33) (34) (4) (29) (32) (EG 1)
Doxepin:
Not recommended. There are two low level studies published in the early 2000s that suggested evidence of Doxepin for treatment of chronic neuropathic pain and CRPS. None have been published since this time. (35) (36) (4) (EG 1)
Alpha2 Adrenergic Agents
Clonidine: Not recommended. This drug is generally approved orally for hypertension. The efficacy of 0.1% topical clonidine application has been evaluated in cases of diabetic peripheral neuropathy, providing a possible contribution to pain relief with no systemic absorption, with a medium level of evidence. Additional trials are needed to assess topical clonidine in other neuropathic pain conditions and to determine how patients who have a chance to respond to the drug should be selected for treatment. (4) (37) (EG 1) . See also Salicylate Topicals for Pain; Glucosamine (and Chondroitin Sulfate) for Pain.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address medical food.

ODG by MCG
Last review/update date: Feb 12, 2021
Medical Food for Pain
Body system: Pain
Treatment type: Medications, Other
Related Topics: Compound Drugs for Pain
Co-Pack Drugs for Pain
Deplin (L-Methylfolate) for Pain
GABAdone for Pain
Limbrel (Flavocoxid) for Pain
Physician-Dispensed Drugs for Pain
Repackaged Drugs for Pain
Sentra PM for Pain
Somnicin for Pain
Theramine for Pain
Trepadone for Pain
UltraClear for Pain
Not Recommended (generally)
Not recommended for chronic pain.
Evidence Summary
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. (1) (EG 2)

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. (2) (3) (EG 2)

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. (2) (4) (3) (EG 2)

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). (5) (6) (7) (8) (9) (10) (2) (4) (EG 1)

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. (2) (EG 2)

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. (11) (EG 1) 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 (EPA/DHA) for Pain.

Honey & cinnamon: Not recommended. See separate listing for Honey and Cinnamon for Pain.

Limbrel (flavocoxid): Not recommended. See separate listing for Limbrel (Flavocoxid) for Pain (flavocoxid/ arachidonic acid). (2) (1) (3) (4) (12) (EG 2)

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Deplin.

ODG by MCG
Last review/update date: Feb 12, 2021
Deplin (L-Methylfolate) for Mental Illness and Stress
Body system: Mental Illness and Stress
Treatment type: Medications
Not Recommended (generally)
Not recommended.
Evidence Summary
Deplin is a prescription medical food that contains L-methylfolate (vitamin B9) in doses of 7.5 mg or 15 mg. There are no head-to-head studies comparing folic acid supplementation versus L-methylfolate in terms of augmenting antidepressant therapy for depression. Studies are equivocal as to the efficacy of such supplementation, including in terms of whether other B vitamins are added to treatment. Two poster studies were presented on Deplin in 2011 at the European Congress of Psychiatry. The first was a controlled study that compared patients who were resistant to SSRI antidepressants into three groups. (Deplin 7.5 mg for 30 days and then 15 mg/day for 30 days; Placebo for 30 days and then Deplin 7.5 mg for 30 days; Placebo for 60 days). All supplementation was as an adjunct to therapy. There was no difference in outcomes between the three groups. The second study evaluated patients with SSRI resistant depression in two groups with supplementation again used as an adjunct (Deplin 15 mg for 60 days or Placebo). Statistical differences were seen in reduction of the HAM-D score. The results of these posters were ultimately published. (1) (EG 1) All patients who completed the studies were offered an open-label treatment option with SSRI and L-methylfolate. The results emphasize 13 patients who achieved remission in the original studies. At 12 months, 53.8% of patients sustained full remission. Future research was recommended. (Jain R, et al, College of Psychiatric and Neurological Pharmacists Annual Meeting, 2012, Tampa, FL, April and May 2012) See also B Vitamins for Depression (Vitamin B6, Folic Acid/Folate, Vitamin B12), Mental Illness and Stress (vitamin B6, folic acid/folate, vitamin B12).
Additional Research: An automated telephone survey was made of patients who took three months of either Deplin 7.5mg or 15 mg. There was no control group. Outcomes were measured in part with the PHQ-9. Those with a lower baseline score had higher remission rates. This study was funded by the manufacturer. Many of the P scores were reported as 0.000. The significance of this is not known. (2) (EG 2) See also the Deplin (L-Methylfolate) for Pain.

ODG by MCG
Last review/update date: Feb 12, 2021
Deplin (L-Methylfolate) for Pain
Body system: Pain
Treatment type: Medications
Related Topics: See also B Vitamins and Vitamin B Complex for Pain & Medical Food for Pain in this chapter. See Deplin (L-Methylfolate) for Mental Illness and Stress and B Vitamins for Depression (Vitamin B6, Folic Acid/Folate, Vitamin B12), Mental Illness and Stress in the Mental Illness and Stress Chapter.
Not Recommended (generally)
Not recommended.
Evidence Summary
Deplin (L-methylfolate) is a prescription medical food that contains L-methylfolate (vitamin B9) in doses of 7.5 mg or 15 mg.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address GABAdone.

ODG by MCG
Last review/update date: Mar 31, 2021
GABAdone for Pain
Body system: Pain
Treatment type: Medications
Related Topics: See Medical Food for Pain

Not Recommended (generally)
Not recommended because there is no quality evidence to support use in pain, anxiety, or sleep disorders.
Evidence Summary
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; however, 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.
Sleep disorders: Not recommended for this indication based on limited available research, including a small single randomized, placebo-controlled pilot trial of GABAdone for treatment of sleep disorder (18 subjects, 7-day study). There was no analysis comparing the two groups, where 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 GABAdone, 7.11 hours placebo). The number of awakenings was more associated with apneic events and decreased in the treated group, but there was no description of the baseline status of the subjects, including weight or history of sleep apnea. (1) (EG 1)
GABA is a derivative of glutamic acid and ornithine, which does not cross the blood-brain barrier, so oral intake could not increase brain levels. Therefore, taking the supplement will not replicate drugs that do work by a GABA-related mechanism. It has been suggested that GABA can improve sleep quality and improve cognitive function, but there is no scientific evidence to support these claims. (2) (EG 2) Medical foods, or nutraceuticals', have widespread inconsistencies and contradictions in the many published definitions, demonstrating wholesale uncertainty about what they actually are. There are no internationally agreed definitions of 'nutraceuticals', 'functional foods', or of similar terms like 'health foods', or of terms related to herbal products, further compounding the confusion. These are all vague, nondiscriminatory, unhelpful terms; the evidence suggests that they should be abandoned in favor of more precise terms. The term 'dietary supplement', widely used to designate formulations also called 'nutraceuticals', would be better restricted to individual compounds used to treat or prevent deficiencies. (3) (EG 2)

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Sentra PM.

ODG by MCG
Last review/update date: Feb 12, 2021
Sentra PM for Mental Illness and Stress
Body system: Mental Illness and Stress
Treatment type: Medications
Related Topics: See also Sentra PM for Pain in the Pain Chapter.
Not Recommended (generally)
Not recommended for insomnia. Preliminary results are promising, from a single study sponsored by the manufacturer, but independent unbiased studies are necessary for a recommendation.
Evidence Summary
Sentra is a medical food from Targeted Medical Pharma (aka Physician Therapeutics), Los Angeles, CA, intended for use in management of sleep disorders, that is a proprietary blend of choline bitartrate, glutamate, and 5-hydroxytryptophan. In a RCT published in a pay-to-publish journal, and written by employees of the marketer of Sentra PM, the authors concluded that Sentra PM can improve the quality of sleep, the response to trazodone as a sleep medication and parasympathetic autonomic nervous system activity. (1) (EG 1) See also Insomnia Treatment for Mental Illness and Stress, where it says there is limited evidence to support trazodone for insomnia, but it may be an option in patients with coexisting depression.

ODG by MCG
Last review/update date: Feb 12, 2021
Sentra PM for Pain
Body system: Pain
Treatment type: Medications
Not Recommended (generally)
Not recommended.
Evidence Summary
See Medical Food for Pain, 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.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Somnicin.

ODG by MCG
Last review/update date: Feb 12, 2021
Somnicin for Pain
Body system: Pain
Treatment type: Medications, Other
Not Recommended (generally)
Not recommended.
Evidence Summary
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 for Pain. 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. (1) (2) (3) (EG 2)
For oxitriptan and 5-hydroxytriptophan, see Medical Food for Pain. 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. (1) (2) (3) (EG 2)
This can be purchased over-the-counter.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Theramine.

ODG by MCG
Last review/update date: Feb 12, 2021
Theramine for Pain
Body system: Pain
Treatment type: Medications
Not Recommended (generally)
Not recommended for the treatment of chronic pain.
Evidence Summary
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. (1) (EG 2) See Medical Food for Pain. 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. (2) (EG 1) 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. (3) (EG 1)

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Trepadone.

ODG by MCG
Last review/update date: Feb 12, 2021
Trepadone for Pain
Body system: Pain
Treatment type: Medications
Not Recommended (generally)
Not recommended. Trepadone is a medical food that is suggested for use in the management of joint disorders associated with pain and inflammation.
Evidence Summary
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 for Pain. 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 (EPA/DHA) for Pain. 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.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address UltraClear.

ODG by MCG
Last review/update date: Mar 31, 2021
UltraClear for Pain
Body system: Pain
Treatment type: Complementary/Alternative Medicine, Medications
Not Recommended (generally)
Not recommended.
Evidence Summary
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.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address Limbrel.

ODG by MCG
Last review/update date: Feb 12, 2021
Limbrel (Flavocoxid) for Pain
Body system: Pain
Treatment type: Medications
Not Recommended (generally)
Not recommended based on additional evidence of adverse effects. (1) (2) (3) (EG 2) .
Evidence Summary
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). (4) (EG 1) 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. (5) (EG 1) 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. (6) (EG 1) 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. (7) (EG 2)
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 post marketing 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. (8) (9) (EG 2) (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. (8) (EG 2)
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.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guidelines, Massachusetts Treatment Guidelines, and State of Colorado Department of Labor and Employment do not address co-pack drugs.

ODG by MCG
Last review/update date: Feb 12, 2021
Co-Pack Drugs for Pain
Body system: Pain

Treatment type: Medications
Other
Not generally recommended as there are no high-quality studies to demonstrate improved patient outcomes.
Evidence Summary
See also Compound Drugs for Pain; Medical Food for Pain; Physician-Dispensed Drugs for Pain; Repackaged Drugs for Pain.
Co-packs are convenience packaging of a Medical Food for Pain 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.

Massachusetts Treatment Guidelines does not address B vitamins.

California Medical Treatment Utilization Schedule (MTUS)/ACOEM Practice Guideline
Chronic Pain (MTUS Effective Date December 1, 2017)
Chronic Persistent Pain
Diagnostic and Treatment Recommendations
Allied Health Interventions
Vitamins for Chronic Persistent Pain
Not Recommended.
Vitamins are not recommended for treatment of chronic pain if there are no documented deficiencies or other nutritional deficit states.
Strength of Evidence Not Recommended, Insufficient Evidence (I)
Level of Confidence Low
Rationale: There is no quality evidence of efficacy for the use of vitamins to treat chronic pain disorders. There are indications for use with documented nutritional deficiencies. There are three quality studies with conflicting evidence on the prevention of CRPS among those with fractures treated with vitamin C.[292] Whether this finding is applicable to working-age adults is unclear.
Vitamins are not invasive, have low adverse effects (aside from high dose fat soluble vitamins), are low to moderate cost cumulatively, but in the absence of quality evidence of efficacy, they are not recommended.
Evidence: There are high- and moderate-quality RCTs incorporated into this analysis. There are no quality studies evaluating vitamins for the treatment of chronic persistent pain syndrome.

State of Colorado Department of Labor and Employment
RULE 17, EXHIBIT 9
Chronic Pain Disorder
Medical Treatment Guideline
Revised: 10/6/2017
Effective: 11/30/2017
F. Initial Evaluation & Diagnostic Procedures
4. Laboratory Testing
h. Vitamin B12 levels may be appropriate for some patients.

ODG by MCG
Last review/update date: Feb 12, 2021
B Vitamins and Vitamin B Complex for Pain
Body system: Pain
Treatment type: Other
Related Topics: See B Vitamins for Depression (Vitamin B6, Folic Acid/Folate, Vitamin B12), Mental Illness and Stress in the Mental Illness and Stress Chapter.
Not Recommended (generally)
Not recommended for the treatment of chronic pain unless this is associated with documented vitamin deficiency.
Evidence Summary
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. (1) (EG 1)
Vitamin B deficiency could influence memory function, cognitive impairment and dementia. In particular, vitamins B1, B3, B6, B9 and B12 are essential for neuronal function and deficiencies have been linked to depression, contributing to the complexity of depressive symptoms. (2) (EG 2) A meta-analysis of 4 RCTs on herpetic neuralgia concluded, that compared with placebo, Vitamin B12 administration exhibited a significant decrease in pain scores (4/100), resulting in improved quality of life and significantly decreased analgesics use. (3) (EG 1)

ODG by MCG
Last review/update date: Feb 12, 2021
B Vitamins for Depression (Vitamin B6, Folic Acid/Folate, Vitamin B12), Mental Illness and Stress
Body system: Mental Illness and Stress
Treatment type: Medications
Related Topics: See also B Vitamins and Vitamin B Complex for Pain in the Pain Chapter.
Conditionally Recommended
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.
ODG Criteria
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). (1) (2) (EG 1)
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).
Evidence Summary
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. (3) (4) (EG 1) Other recent studies examining the role of folic acid and vitamin B12 found little evidence for potentiation of antidepressant medicine with this adjunct treatment. (5) (EG 1) 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. (6) (7) (EG 2)
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). (8) (EG 1)
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. (9) (10) (11) (12) (13) (EG 1) 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. (10) (EG 1) Furthermore, a meta-analysis of these studies indicated that there was no difference between folic acid and placebo. (14) (EG 1)
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) for Mental Illness and Stress (L-methylfolate) in this chapter.

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