Complementary & Alternative

Volume 13, Issue 5

# Integrative Treatment Approaches for Juvenile Idiopathic Arthritis

Parents of children with JIA often turn to complementary and alternative approaches to handle their child's disease. Family values and resources play a critical role in determining which integrative therapies to recommend first. Therefore, forming a collaborative partnership with patients and their families is essential for avoiding "treatment fatigue" and improving overall success.

**CITE THIS ARTICLE**
Temple L. Integrative Treatment Approaches for Juvenile Idiopathic Arthritis. Pract Pain Manag. 2013;13(5).

**Jul 1, 2016**
**Leslie M. Temple, MD,** Assistant Professor of Family Medicine

Juvenile idiopathic arthritis (JIA), also known as juvenile rheumatoid arthritis, is a nonspecific type of arthritis appearing before the age of 16 years and lasting at least 6 weeks.[1,2] JIA is the most common chronic arthritis in children.[2] Two peaks of onset have been described at 2 to 4 and 6 to 12 years of age,[4] most often in Caucasian and female patients.[5] In 2011, the American College of Rheumatology (ACR) updated their recommendations for pharmaceutical management of patients with JIA to include the following treatments alone or in combination: non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoid injections, methotrexate (MTX), sulfasalazine, tumor necrosis factor alpha (TNF-α) inhibitors (ie, etanercept [Enbrel] and adalimumab [Humira]), leflunomide, abatacept (Orencia), anakinra (Kineret), and systemic glucocorticoids.[2]

Because of concerns of adverse events, the ACR recommends that NSAID and MTX safety monitoring consist of baseline serum creatinine levels, urinalysis, complete blood count, and liver function testing with repeat lab measurements over time. TNF-α inhibitors also require yearly

ON THIS PAGE

pharmaceuticals and natural health products (NHPs) are sparse, so if the clinician decides to use some natural products with the above medications, the lab studies can help with safety monitoring of novel combinations.

## Benefits/Risks of Pharmaceutical Therapy

Since most JIA patients will be on prescription medications to aleviate painful symptoms, it is important to understand the benefits and risks of treatments. In a double-blind placebo-controlled trial of early aggressive therapy, 85 patients with JIA were randomly assigned to two groups: 42 patients received a combination of MTX 0.5 mg/kg/week (maximum 40 mg) subcutaneously, etanercept 0.8 mg/kg/week (maximum 50 mg), and prednisolone 0.5 mg/kg/day (maximum 60 mg) tapered to 0 by 17 weeks; and 43 patients received MTX 0.5 mg/kg/week, etanercept-placebo, and prednisolone-placebo.

Results from the study found that a cohort of 85 JIA patients achieved clinically inactive disease status in 32% of patients by 6 months and in 66% by 12 months. Patients who were treated earlier during the course of the disease in both arms experienced a higher rate of JIA remission with these treatments. Despite the success of these treatments, both arms of the study reported severe to less severe adverse events, including significant transaminase elevations, peritonsillar abscess, worsened pre-existing herpes infection, pneumonia, psychotic episodes during steroid taper, and septic hip joints.[6] Concerns regarding malignancy and infection are also important to consider for patients taking a biologic agent.[7-10]

## Prognosis

Fifty percent or more of patients with JIA have the risk of ongoing arthritis as adults, which necessitates long-term support for those patients.[11,12] Despite MTX use in 66% and NSAID use in 88% of the children surveyed with polyarticular arthritis, many still experienced pain and reduced function, resulting in missed school and social activities. Higher levels of anxiety correlated with higher pain and function complaints, so adequate pain control should include mind–body approaches at promoting a sense of calm.[13]

## Integrative Rheumatology In JIA

The use of NHPs and complementary and alternative medicine (CAM) is common in JIA. Parental fear of medication side effects, pain relief, a desire to improve their child's well being, longer disease duration and multiple illnesses in the child, parental CAM use, and parental perception of whether medications are helping or not have all been found to drive pediatric CAM use in JIA.[14-17] To follow is a discussion of alternative therapies for JIA.

Clinicians have few guidelines on the judicious, safe, and effective use of NHPs and CAM

Clinicians have few guidelines on the judicious, safe, and effective use of NHPs and CAM modalities for improving JIA symptoms, with or without standard-of-care medications and exercise prescriptions. Clinical outcomes in JIA patients who used CAM and NHP therapies showed that outcomes were no better compared to non-users. However, CAM users were more adherent to conventional therapy compared to non-users.[18-20]

The most commonly used CAM therapies include dietary modification, NHPs, chiropractic care, relaxation techniques, homeopathy, prayer, massage, meditation, acupuncture, and naturopathy.[15-17, 21-23] This article will discuss the practical aspects of recommending a select group of these CAM therapies for the clinician managing the young patient with JIA. The following discussion provides a good sample of evidence-based recommendations, but does not include all possible therapies due to space constraints.

### Anti-inflammatory Diet, Intestinal Permeability, and Autoimmune Disease

Increased intestinal permeability (IP) has been implicated in several autoimmune and inflammatory conditions like rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, celiac disease, type 1 diabetes, asthma, and inflammatory bowel disease.[24, 25] Mielants et al studied ileum biopsies of JIA patients and found a majority with histologic gut inflammation.[26, 27] Bacteria, antigenic fragments, and primed immune cells may migrate to joints from distant sites that originated in the "leaky gut," subsequently promoting synovitis.[28] More research is needed to firmly establish this relationship. Based on ongoing research on IP and its role in autoimmune disease, there is potential in mitigating diseases like JIA with therapies that can reduce gut permeability.

Testing for Intestinal Hyperpermeability

The lactulose/mannitol test may help diagnose IP.[29] Another possible non-invasive test for gut inflammation is the fecal calprotectin test, although more study is needed to validate its use.[30-32] The lactulose/mannitol and fecal calprotectin tests are available commercially, and are often bundled with other tests aimed at identifying parasites, candida, and pathogenic bacteria as causes of gut dysfunction. Testing for IP may be skipped unless the patient requests the tests or the clinician needs test data for better compliance with recommendations.

## The Elimination Diet

Certain food substances have been identified as negatively affecting the health of the small intestinal mucosa, whose functions include nutrient absorption, barrier function, metabolism, detoxification, immune modulation, and production of many biologically active compounds.[33] Some food substances have been implicated in the production of advanced glycation end products (AGEs) and glycated lipids (ALEs). The production of AGEs and ALEs form free radicals that can exacerbate IP through inflammation. Certain foods higher in AGEs and ALEs include fructose, casein (dairy), gluten (wheat, barley, rye), tea, coffee, diet soda, roasted peanuts, and soybean products.[34]

soybean products.

Elimination diets have been studied for autoimmune diseases like Crohn's disease, rheumatoid arthritis, and immunoglobulin E–mediated diseases like eosinophilic esophagitis. A vegan diet was studied in adult rheumatoid arthritis patients, showing that the respondents who adhered to the diet for 1 year had improvement in their symptoms compared to the control group. But, neither group achieved improvement on x-rays of the hands and feet after the intervention.[35] A small study of adults with rheumatoid arthritis showed symptom improvement with a 2-week exclusive elemental diet composed of commercially prepared amino acids, vitamins, minerals, and medium/long chain triglycerides.[36]

Recommendations for the very restrictive elemental or vegan diet are likely unrealistic and stressful burdens to uphold for most families unless the child and parent are motivated to remain compliant with these diets. Instead, there may be value to an empiric trial of a 6-food elimination diet (namely, cow's milk, soy, wheat, egg, peanut/tree nuts, and seafood)[37,38] for 4 to 6 weeks. Important nutrients like calcium and omega-3 fatty acids (fish oil is allowed) are supplemented during the elimination.

Elimination of refined sugar and nightshade vegetables may also be helpful in the dietary trial for patients with JIA. Nightshade vegetables include potatoes, tomatoes, peppers, and eggplant. Reintroduction of the child's most frequently eaten food is then added back one at a time, over a period of 3 to 4 days following the elimination diet. This challenge phase may elucidate specific food triggers if JIA or other symptoms worsen. Parents and the child should document symptoms in a journal to note their progress and identify trigger foods during reintroduction. Trigger foods would need to be avoided long term for best results.

Elimination diets run the risk of inducing stress in the parent and child, particularly if the child's favorite foods consist of trigger foods. For parents and children who are reluctant to change the diet, the author recommends saving the elimination diet trial for a time after the patient consistently has taken recommended NHPs, mind–body therapies, massage, exercise, or acupuncture for several months to prevent treatment fatigue.

An excellent educational review was written by David R. Seaman on an anti-inflammatory diet for patients with pain, and can serve as a guideline for dietary prescribing.[39]

## NHPs to Aid IP and JIA

### Turmeric

Curcumin is the yellow pigment found in the spice turmeric. Curcumin has antioxidant, anti-inflammatory, antibacterial, antifungal, antiviral, pro-apoptotic, and antiproliferative effects. TNF-α inhibition activity has been noted with curcumin, which may have a valuable role in reducing inflammation and intestinal permeability found in autoimmune diseases, including JIA.[40] Curcumin

inflammation and intestinal permeability found in autoimmune diseases, including JIA.[40] Curcumin combined with piperine (black pepper extract) may have enhanced bioavailability versus curcumin alone, which is poorly bioavailable. Safety studies have demonstrated doses as high as 15 g per day for 3 months were safe with no toxicity reported in adult subjects.[40] Few pediatric dosing studies have been performed, and in a small trial, a 2-g dose of curcumin twice daily was well tolerated by 11- to 18-year-old children with inflammatory bowel disease.[4] The average adult daily intake of turmeric in India is 2 to 2.5 g, which is equivalent to 60 to 100 mg of curcumin.[42]

### Glutamine

The most abundant amino acid in the body, glutamine, has several beneficial effects on gut epithelium through antioxidant, anti-inflammatory, and intestinal cell protective mechanisms. This generally well-tolerated compound has been shown to reduce IP in ischemia/reperfusion injury,[43] critically ill patients,[44] malnourished children,[45] and low birth weight children with allergies.[46] Glutamine dose varies in studies of children with several chronic diseases, trauma, burns, and cancer from 0.25 g/kg/day to 0.7 g/kg/day for infants and children.[47] An average dose of 0.5 g/kg/day may be reasonable for children. More research is needed to determine clearer guidelines on safety and efficacy of glutamine use in children.

### Probiotics

Probiotics are bacterial strains known to have beneficial effects on intestinal mucosa and gut immunity. They may also have a role in reducing IP with respect to autoimmune disease.[48,49] Evidence for using probiotics in rheumatologic disease is currently sparse, with little guidance on optimal strains or dosing in adult or pediatric rheumatology. A general rule of thumb based on data from the 2011 Johnston Cochrane analysis of probiotics for antibiotic-associated pediatric diarrhea is to prescribe 5 billion colony-forming units (CFU) or more per day.[50] The best blend of strains is unclear, but *Lactobacillus rhamnosus* and *Saccharomyces boulardii* were the most commonly studied strains in the meta-analysis, and the dose range went as high as 40 billion CFU per day with few adverse effects in healthy individuals.[50] Some studies looked at *Lactobacillus* and *Bifidobacterium* species to improve symptoms, with mixed results seen in pediatric arthritis.[51,52] While generally well tolerated and safe in healthy individuals, probiotics should be avoided in patients with severe pancreatitis, immunosuppression, or the critically ill due to concerns about harm.[53,54]

## Calcium and Vitamin D Supplementation

Calcium intake of 1,000 mg per day for 4 to 8 year olds and 1,300 mg per day for 9 to 18 year olds through food and supplementation is important for children with JIA to promote bone growth and density. Patients with JIA are at risk for osteoporosis given their exposure to systemic steroids and the reduction of physical activity during pain flares.[55-57]

### Vitamin D

At present, no clear evidence exists to support a link between vitamin D levels and JIA.[58] [25]-hydroxy vitamin D testing can identify children with vitamin D deficiency and, if identified, should be treated with supplemented vitamin D2 or D3, vitamin D rich food like fish and eggs (unless the patient is allergic to these foods), and judicious exposure to sunlight. Vitamin D's role in bone mineralization and immune modulating effects are especially important for a growing child. A daily vitamin D2 or D3 dose of 2,000 international units is likely safe,[59] although guidance on specific dosing and length of treatment is unclear. The "optimal" 25-hydroxy vitamin D level is also a matter of controversy, but normal levels are defined as greater than 50 nmol/L (or 20 ng/mL). 25-hydroxy vitamin D levels less than 25 nmol/L (or 10 ng/mL) are considered a severe deficiency.[60] Clinicians should definitely aim for vitamin D 25-hydroxy levels higher than 20 ng/mL, and strive for levels in the 40 to 50 ng/mL range.

## Traditional Chinese Medicine

### Acupuncture

IP, or "leaky gut," is considered a complex and difficult-to-treat entity in traditional Chinese medicine (TCM). This entity would be referred to as a "knotty" disease, which includes conditions like allergies, autoimmune disease, and intestinal dysbiosis. In the TCM paradigm, "knotty diseases" come from complex imbalances of qi, or "life force," which may include spleen qi vacuity, damp heat, liver qi stagnation, and other conditions beyond the scope of this article.[61]

Acupuncture, herbs, movement, and nutrition comprise the main treatments used in TCM. Acupuncture has been studied the most, with very low side effects documented in children and adults. The most common side effect of pediatric acupuncture is puncture site redness. Although significant side effects can occur, like organ puncture, this is extremely rare.[62] The 2005 Casimiro Cochrane review showed inconclusive evidence of acupuncture's effects on rheumatoid arthritis,[63]but other meta-analyses noted statistically significant improvement in neck,[64] back,[65] and shoulder[66] pain with acupuncture versus sham controls.[67] Based on acupuncture's excellent safety profile, the therapeutic relationship between practitioner and patient, and current evidence from related conditions, acupuncture is a useful treatment to advise to patients with JIA if the family can afford the treatments. Treatments are typically once weekly, and the author suggests a baseline of 10 treatments before assessing efficacy and continuation of the therapy.

### Massage

Daily massage for 15 minutes by a parent for 30 days showed decreased levels of anxiety, serum cortisol, pain, and morning stiffness in juvenile rheumatoid arthritis patients compared to progressive muscle relaxation. Massage consisted of two phases in a sequence typically followed by massage therapists. For the first phase, the child was placed in a supine position, and oil was applied to allow smooth, continuous stroking movements of the face, stomach, legs, feet, and

applied to allow smooth, centripetal stroking movements of the face, stomach, legs, feet, and arms. The child is then placed in a prone position, and the parent gently massages the back, shoulders, neck, and feet.[68]

### Exercise

Exercising 3 times per week for 12 weeks with free weights, core exercises, and jumping rope can improve leg strength, bone health, and mental health without increasing pain scores in JIA patients.[69] Prescribing exercise and activity in a fun, positive way (ie, walking the dog twice daily) may be more effective than prescribing it as "physical therapy," which implies a sick role.[70] Regular physical activity may also help regulate sleep patterns, anxiety, and promote an overall sense of well being, all of which are important for reducing chronic pain from JIA.

### Sleep

Chronic pain and sleep problems may feed upon one another. The need for restorative sleep is critical to managing pain, quelling anxiety, and improving health. Good sleep hygiene is imperative and includes avoidance of late-day caffeine, large meals just before bedtime, television, video games, Internet chats and surfing, and other mentally stimulating activities at bedtime that interfere with falling and staying asleep.[71,72]

## Mind–Body Approaches

Cognitive behavioral therapy helps patients recognize negative or incorrect thoughts and teaches one to respond to difficult situations like pain in a more effective way. Some of the tools used to deal with mental and physical challenges include progressive muscle relaxation, guided imagery, and meditative breathing, which may reduce pain intensity and improve function for patients with JIA.[73,74]

## Putting it All Together: Avoiding "CAM Treatment Fatigue"

It is important to balance integrative therapy recommendations with the individual's level of interest, motivation, resources, and school/family support to maximize successful compliance and to observe changes or side effects from treatments. Trying too many recommendations at the same time often overwhelms and frustrates parents and children, so a stepwise approach with initial assessments over a 2- to 3-month span of time may be appropriate with more frequent visits or phone calls if necessary (Figure 1). Open communication with the patient's rheumatologist and primary care physician regarding the care plan is also essential.

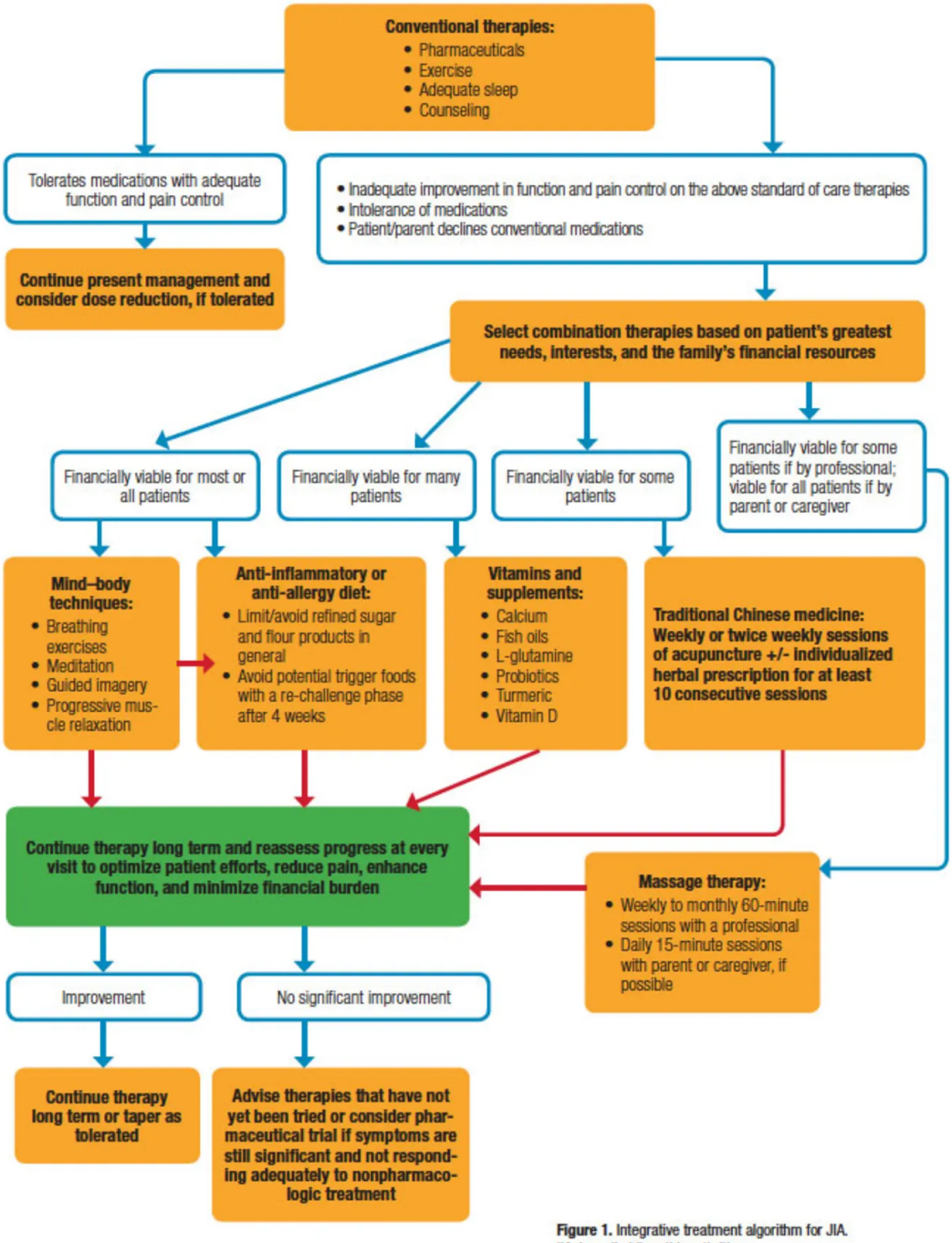


**Figure 1.** Integrative treatment algorithm for JIA.
JIA, juvenile idiopathic arthritis

## Individualized Treatment Plans

Patient values and resources play a critical role in determining which integrative therapies to recommend first, since many therapies are an out-of-pocket expense. For instance, some patients are more interested in exploring acupuncture before changing their diet. Other patients may be motivated to take vitamins and herbs before employing mind–body therapies. Other patients can only afford to try breathing and meditation with some diet changes. Given the myriad potential treatment options, forming a collaborative partnership with patients and their families is a beneficial therapy in and of itself.

REFERENCES

**Notes:** This article was originally published June 14, 2013 and most recently updated July 1, 2016.

Opioids

Volume 13, Issue 5

# How Changing Hydrocodone Scheduling Will Affect Pain Management

Since the FDA changed hydrocodone combination products from a schedule III controlled substance to a schedule II, pain practitioners and their patients need to know their options.

**CITE THIS ARTICLE**
Donovan K, Fudin J. How Changing Hydrocodone Scheduling Will Affect Pain Management. Pract Pain Manag. 2013;13(5).

**May 19, 2015**
**Kyle J Donovan, PharmD**
**Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB,** Clinical Pharmacy Specialist in Pain Management

The FDA has now officially rescheduled hydrocodone combination products from schedule III controlled substances to schedule II. After a decade of limited momentum, a request came before the FDA advisory committee in 2008, with a decision to keep hydrocodone combination products as schedule III.[1] On January 25, 2013, after 5 years, this came to the forefront again, with an FDA advisory committee voting 19 to 10 to reschedule hydrocodone combination products from III to II.[2]

After a scientific review, FDA made the recommendation that DEA take this step in December 2013. "We concluded that hydrocodone combination products meet the criteria for control under Schedule II of the Controlled Substances Act, and we believe DEA's new rule will help limit the

Schedule II of the Controlled Substances Act, and we believe DEA's new rule will help limit the risks of these potentially addictive but important pain-relieving products," noted Douglas C.

Throckmorton, MD, Deputy Center Director for Regulatory Programs in FDA's Center for Drug Evaluation and Research.[3]Prescription opioid contributed to over 16,000 overdose deaths in the United States.[4]

According to the FDA, here are some of the key changes that will occur with the reclassification of hydrocodone from a Schedule III drug to a Schedule II drug:

- If a patient needs additional medication, the prescriber must issue a new prescription. Phone–in refills for these products are no longer allowed.
- In emergencies, small supplies can be authorized until a new prescription can be provided for the patient.
- Patients will still have access to reasonable quantities of medication, generally up to a 30-day supply.
- If a patient needs additional medication, the prescriber must issue a new prescription. Phone–in refills for these products are no longer allowed.
- In emergencies, small supplies can be authorized until a new prescription can be provided for the patient.
- Patients will still have access to reasonable quantities of medication, generally up to a 30-day supply.

- See more at: http://blogs.fda.gov/fdavoice/index.php/2014/10/re-scheduling-prescription-hydrocodone-combination-drug-products-an-important-step-toward-controlling-misuse-and-abuse/#sthash.y24tdnVy.dpuf

## Products Affected

All available combination hydrocodone products will be affected by the change. A list of medications with the amount of hydrocodone and the combination medications is listed in Table 1.[5-9]

| Table 1. Hydrocodone Products | | |
|---|---|---|
| **Hydrocodone With Acetaminophen** | | |
| **Brand** | **Hydrocodone bitartrate, mg** | **Acetaminophen, mg** |
| **Lorcet** | 10 | 650 |
| **Lorcet Plus** | 7.5 | 650 |
| **Vicodin HP** | 10 | 660 |
| **Xodol** | 5, 7.5, 10 | 300 |
| **Vicodin ES** | 7.5 | 300 |
| **Norco** | 5, 7.5, 10 | 325 |
| **Lortab** | 5, 7.5, 10 | 500 |
| **Maxidone** | 10 | 750 |
| **Zamicet** | 10/15 mL | 325/15 mL |
| **Hycet** | 7.5/15 mL | 325/15 mL |
| **Hydrocodone solution** | 7.5/15 mL and 10/15 mL | 325/15 mL |
| | 7.5/15 mL | 500/15 mL |
| **Hydrocodone With Ibuprofen** | | |
| **Brand** | **Hydrocodone Bitartrate, mg** | **Ibuprofen, mg** |
| **Reprexain** | 2.5, 5,10 | 200 |
| **Vicoprofen** | 7.5 | 200 |
| **Hydrocodone With Homatropine** | | |
| **Brand** | **Hydrocodone Bitartrate, mg** | **Homatropine, mg** |
| **Hydrocodone-homatropin tablet** | 5 | 1.5 |
| **Hydrocodone-homatropin syrup** | 5/5 mL | 1.5/5 mL |

Based on references 5-9.

## Alternatives to Consider

The use of **non-steroidal anti-inflammatory drugs** (NSAIDs) for treatment of acute or chronic pain can provide a viable alternative to hydrocodone, but increasing usage of these agents comes with increased risks of gastrointestinal (GI) bleeds, gastroesophageal reflux disease, and fatalities (due to bleeding and renal toxicity). Given these limitations, NSAIDs may be used more appropriately to treat mild-to-moderate somatic pain and should not be considered the panacea to replace hydrocodone. As with opioids, different patients may or may not respond to the various available NSAIDs, and efficacy with one does not guarantee response or failure of another. This may lead to a lengthy period of subtherapeutic analgesia while clinicians attempt to find the NSAID that works best for the patient.

For patients who experience GI side effects from NSAIDs, treatment with antacids, $H^2$ receptor blockers, or proton pump inhibitors (PPIs) is recommended. In certain cases, switching the NSAID to one that is more cyclo-oxygenase (COX)-2 specific, such as celecoxib (Celebrex), etodolac, or

meloxicam, may be necessary.[IV] For chronic NSAID use, concomitant therapy with a PPI may be indicated for gastric ulcer prophylaxis. NSAIDs should be avoided in patients who have a history of gastric/duodenal ulcers, blood dyscrasias, anticoagulation therapy, cardiovascular disease, diabetes mellitus, hypertension, concomitant use of nephrotoxic medications, or renal impairment.

**Tramadol** is another option to consider for the treatment of acute or chronic pain. It comes in several formulations including tramadol 50 mg, tramadol/acetaminophen 37.5 mg/325 mg, and tramadol extended-release (ER) 100 mg, 200 mg, and 300 mg. The maximum recommended daily dose of tramadol is up to 400 mg per day, depending on the formulation. The medication and its metabolite desmethyltramadol work as agonists at the μ opioid receptor. In addition, they cause serotonin and norepinephrine reuptake inhibition, the latter of which contributes to the analgesic effect. It is important to note that the μ-receptor binding affinity of tramadol is 6,000 times less than that of morphine, so the opioid agonist activity only provides minimal benefit.[11] It is metabolized primarily by cytochrome P450 (CYP) 2D6 (desmethyltramadol) and CYP3A4, but there are five important metabolites.[12] Inhibitors or inducers of this medication may affect the analgesic and toxicity profile of this drug, the most concerning of which are serotonin syndrome and seizure. Both of these potential toxicities could be enhanced by concomitant serotonin-type antidepressants across all chemical and therapeutic classes, lithium, and several other drug classes that may affect serotonin (certain antipsychotics, triptans, etc). As with NSAIDs, tramadol has pharmacology that can result in a significant rise in blood pressure. Finally, compared to other "opioid agonists," tramadol is one of the most constipating agents.

**Acetaminophen with codeine** is a schedule III option for the treatment of acute pain. This medication is inferior to hydrocodone, however, because it has significant variability in action with respect to absorption and activation. Codeine requires metabolism to morphine to achieve analgesia; this is accomplished by the CYP2D6 isoenzyme, which is necessary for the conversion on first-pass metabolism through the gut. Another issue is that patients with different polymorphisms could be fast and slow metabolizers of codeine, depending on their ability to make CYP2D6. Fast metabolizers end up experiencing a lot of analgesia for the dose received and may have side effects because of this; slow metabolizers, on the other hand, may not experience any benefit from the codeine because conversion to the active form is absent or negligible. Also, certain medications commonly induce or inhibit CYP2D6 isoenzymes. The selective serotonin reuptake inhibitors, in particular, have varying potency to inhibit CYP2D6, thereby preventing the conversion of codeine to its active analgesic form of morphine.

**Buprenorphine** is a viable schedule III option for the management of chronic pain. It works as a partial agonist on the μ-1 receptor and as an antagonist on κ receptors. The FDA recognizes the buprenorphine patch (Butrans) for treatment of moderate-to-severe chronic pain. The patch is not recommended if the patient is receiving 80 mg of oral morphine equivalents due to risk of opioid withdrawal. Conversions from morphine equivalent to the Butrans patch may be found within the package insert.[13] The patch is refillable and requires once weekly changes. After steady state is reached, it provides linear consistent serum levels, unlike any immediate-release opioids such as hydrocodone.[14]

**Pentazocine** is another schedule III choice that can be used to provide patients with moderate

**Pentazocine** is another schedule III choice that may be used to provide patients with analgesia; however, we warn against this option for various reasons. Pentazocine has agonist activity at the κ receptor and partial agonist activity at the μ receptor. This prescription is formulated in a tablet with naloxone or acetaminophen but not pentazocine alone, and it is available as injection. Naloxone was added to the formulation decades ago to prevent abuse by dissolving the product and injecting it. Pentazocine is a racemic mixture of dextro- and levopentazocine, each causing its own unique set of side effects. Levopentazocine is known to cause analgesia and side effects that are common among the opioid class, including nausea, constipation, and respiratory depression. Dextropentazocine is known for causing hallucinations, delusions, and panic.[15] In addition, penatazocine may increase systolic blood pressure. This may lead to an increase in cardiac load, with adverse cardiovascular events.[16] It is for these reasons that pentazocine has fallen out of favor for the treatment of pain.

**Acetaminophen** as a single agent is yet another alternative that may be considered for the treatment of pain. The exact mechanism of action for acetaminophen has not been elucidated, although studies suggest that the COX-3 enzyme may have a role in its analgesic effects.[17] The use of acetaminophen generally is regarded as safe, although there is a risk of liver toxicity at high doses, as well as potential drug interactions with drugs metabolized via the liver. Patients and prescribers need to be cognizant that combining several products containing acetaminophen is an avoidable liability. This risk is compounded when patients self medicate with over-the-counter sleep aids and cough and cold products that may contain acetaminophen, leading to an unintentional overdose.[18] Nephrotic syndrome is a risk following chronic acetaminophen use over many years.[19] Acetaminophen is available in several strengths from pediatric to adult formulations that can be used depending on the patients' need for pain relief. It also is available in several dosage forms, including tablet, capsule, gelcap, oral liquid, injection, and suppository forms. Following a 2009 FDA panel decision, the maximum amount of acetaminophen in products is 3,000 mg per day.[20,21]

## Federal Law

As it stands, hydrocodone combination products are considered Schedule II medications, by Drug Enforcement Administration (DEA) definition, have a higher abuse potential than scheduled III agents.[22]

Schedule II prescriptions include, but are not limited to, fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. A schedule II prescription needs to be dated and signed on the date prescribed. Schedule II prescriptions may need to be filled within a certain period of time, depending on the state. If the state has no specific law on the subject, then the supremacy clause takes effect, meaning that a schedule II prescription has no "fill by" date. If this is not the case and the prescription is sufficiently old, the pharmacist should call the prescriber to ensure that the patient still requires the prescription before filling it.[23-29]

Emergency schedule II prescriptions may be telephoned or faxed to a pharmacy. There is no maximum limit on the quantity that may be called into a pharmacy under federal law. The

maximum limit on the quantity that may be called into a pharmacy under federal law. The prescriber may call in an amount that is sufficient to treat the emergency. The prescriber must then provide a signed prescription within 7 days of the emergency prescription. If mailed, it must be postmarked within these 7 days of the emergency prescription. If no cover is received within 7 days of the emergency prescription, then it is the pharmacist's duty to report this to the DEA Diversion Field Office. Failure to do so may result in the pharmacist's emergency fill privileges for Schedule II prescriptions being revoked.

If a pharmacist does not dispense the full quantity of a schedule II prescription, the balance must be filled within 72 hours. Failure to complete the partially filled prescription within 72 hours forfeits the balance of the controlled substance prescription. If this happens, the pharmacist should notify the prescriber that the patient was unable to attain the full amount of the prescription. Partial fills may be appropriate and are an acceptable option for patients in a long-term care facility (LTCF) or for terminally ill patients. The pharmacists should note the reason for partial prescription fill on the prescription.

A facsimile prescription may be sent to a pharmacy for filling. If this is done to expedite filling, a signed prescription must be brought in by the patient. If this is done as an emergency supply, the prescriber needs to provide a cover within 7 days. A cover is not needed if the prescription is for use in home infusion, in an LTCF, or for hospice care, as certified under Medicare under Title XVII. Schedule II may not be transferred or refilled.[30]

## Hydrocodone Liability

Although combination hydrocodone products just became Schedule II, hydrocodone monotherapy (Zohydro) has always been a schedule II medication.[31] The original distinction was drawn between the combination formulation and the pure drug for two reasons. First, it was believed that if you were to combine hydrocodone with these other medications, then the amount of hydrocodone that would be needed to achieve a therapeutic effect would be less, due to synergy. Acetaminophen or other ingredients such as ibuprofen would lead to a decreased dose needed for analgesia,[32] and chlorpheniramine and decongestants would lead to a lower dose needed for use as an antitussive. This could, in turn, lead to a lowered risk for experiencing euphoria and also may discourage misuse because of "undesirable" side effects from the adjuvant agent.

The second reason hydrocodone combinations were initially scheduled lower is because it was believed that the secondary medication, such as belladonna alkaloids, would cause dysphoric reactions at higher dosages, thus making it less appealing to abuse.[33] This could cause significant and possibly dangerous toxicities at higher dosages and should, theoretically, lead to less abuse or misuse. However, while this deterrent may work for someone who is opioid-naïve, or someone who is compliant with hydrocodone, it may not be a deterrent for someone with a history of substance abuse. People with a past history of alcohol, prescription, or illicit substance abuse or misuse may use these formulations at higher dosages despite the toxicities that occur secondary to their use. In fact, what is thought to be an "undesirable" side effect for the legitimate user might be quite "desirable" for the abuser. In the authors' experience, some abusers have indicated that

be quite "desirable" for the abuser. In the authors' experience, some abusers have indicated that

they derived pleasure from the sedating antihistamines and/or atropine alkaloids combined with these products.

In 2009, Wilsey et al reported that hydrocodone/acetaminophen 30 mg/975 mg (equivalent to 3 Norco 10 mg) had the same abuse liability as morphine extended-release (ER) 15 mg.[34] In 2003, Zacny et al reported no significant difference between hydrocodone/homatropine 20 mg/6 mg and morphine 40 mg in terms of abuse liability.[34] Both of these medications also were shown to have similar incidences of the unpleasant effects. More recently, Wightman et al showed that hydrocodone/acetaminophen 20 mg/1,000 mg (equivalent to taking 2 Lortab 10 mg) had a similar rate of "likability" as morphine 40 mg.[34] In another study, Walsh et al examined high-dose hydrocodone, oxycodone, and hydromorphone as single agents.[31] The investigators found that there was no significant difference in abuse liability with hydrocodone 45 mg, oxycodone 40 mg, and hydromorphone 25 mg. With an abuse liability similar to other schedule II medications, it begs the question of whether or not hydrocodone was properly scheduled in the first place or if some of the schedule II medications could just as easily be treated as schedule IIIs. They concluded that the equianalgesic dosing for an opioid medication is not a good measure of abuse liability.[35]

## New York State Led the Way

As of February 23, 2013, hydrocodone combination products in New York State (NYS) became schedule II controlled substances. Based on discussions with colleagues in NYS, it appears that hydrocodone sales have dropped off slightly at the time. Moreover, an interesting outcome is that many patients previously receiving hydrocodone with acetaminophen are now receiving codeine with acetaminophen instead. These prescriptions are generally for more than 100 tablets per month and have multiple refills on them, which was largely unseen prior to the schedule change.

In the authors' opinion, this law has resulted in replacing hydrocodone with an option that is inferior therapeutically due to reduced efficacy, worse side effect profile, higher incidence of drug interactions, and greater toxicity. The standard of care suggests that extended release analgesics be used when chronic opioid therapy is required. The place for a medication like hydrocodone should, therefore, most commonly be in the treatment of acute pain or incidental pain in chronic patients; this is not the case, because hydrocodone prescriptions are commonly written to be filled monthly. Many patients in NYS still seem to receive their hydrocodone each month, only now they have an extra trip to the doctor's office to pick up the prescription, or must rely on the hard copy prescription being mailed at least until such time that electronic ordering is allowable by federal regulation. The effect of rescheduling hydrocodone in NYS remains to be seen. Perhaps the federal government could use the results of a retrospective analysis tracking outcomes from rescheduling hydrocodone in NYS to make a more informed decision about changing hydrocodone schedule status nationally. But, for now, there is no scientific evidence to support or dispute the rescheduling of hydrocodone.