American Academy of Pain Medicine
and
Integrative Healthcare Symposium
Walter Alexander

American Academy of Pain Medicine
The 32nd Annual Meeting of the American Academy of Pain Medicine brought together approximately 1,000 clinicians and other professionals in Palm Springs, California, from February 18 to 21. Meeting highlights included sessions on the abuse potential of benzhydrocodone; a low-cost opioid taper program; and an abuse-deterrent formulation of hydrocodone.

Oral Abuse Potential of Benzhydrocodone, a Novel Prodrug of Hydrocodone
• Sven Guenther, PhD, Executive Vice President of Research and Development, KemPharm, Inc., Coralville, Iowa

A novel prodrug of hydrocodone in combination with acetaminophen (KP201/APAP) leads to lower hydrocodone exposure and as a consequence may have reduced abuse potential and overdose risk. In the prodrug benzhydrocodone, hydrocodone is chemically bound to benzoic acid, according to Dr. Guenther. After oral administration, release of hydrocodone through breaking of the covalent bond occurs most rapidly and efficiently in the intestinal tract. KP201 has shown decreased bioavailability at abuse levels after oral intake and after insufflation (snorting).

KemPharm conducted a single-center, randomized, double-blind, active- and placebo-controlled clinical trial among non-addicted recreational opioid users. The study (KP201.A01) was designed to compare abuse liability and relative bioavailability and safety of oral KP201/APAP (6.67 mg/325 mg per tablet) compared with oral hydrocodone bitartrate with acetaminophen (HB/APAP) (7.5 mg/325 mg per tablet). Opioid combination products containing HB are the second-most commonly prescribed drugs in the U.S.¹ Dr. Guenther said.

Subjects received seven individual treatments separated by washout periods, including a placebo period and periods with low, mid, and high doses of each agent. There were 62 completers (mean age, 29.1 years) out of 151 enrolled subjects.

Analysis showed that with up to four tablets, KP201/APAP mean plasma hydrocodone concentrations (single oral dose) were bioequivalent to HB/APAP, a currently marketed hydrocodone combination product. “That means you have the same analgesia, the same efficacy and safety profile when you take KP201/APAP orally as intended,” Dr. Guenther said. At 12 tablets, however, cumulative hydrocodone exposures at intervals between one and 24 hours post-dose (AUC0–1 through AUC0–24) were reduced by about 15.8% to 4.8% (P = 0.0102–0.0324) for KP201/APAP. In addition, peak hydrocodone exposure (Cmax) was reduced by about 10.0% (P = 0.0333) and 11.5% (P = 0.0134) following oral doses of eight and 12 tablets of KP201/APAP, respectively, when compared to equivalent doses of HB/APAP.

Furthermore, at mid-dose (eight tablets), reductions of 20% or more in Cmax and AUC0–1 (measures of hydrocodone exposure) were observed in approximately 39% and 38% of the subjects, respectively, for KP201/APAP versus HB/APAP. At the high dose (12 tablets), approximately 25% and 34% of the subjects had a reduction of at least 20% in Cmax and AUC0–1, respectively, when comparing KP201/APAP with HB/APAP.

The lower exposure, Dr. Guenther said, may potentially reduce the risk of oral overdose in this large patient population. “Also, it might buy you some extra time with someone who took too many pills,” he said.

In an earlier trial (KP201.A03) of insufflated KP201 (as active pharmaceutical ingredient powder without APAP), the reduction in peak hydrocodone exposure was about 36% compared with HB (also dosed without APAP). The cumulative exposure differences were even greater at early time points, with reductions ranging from about 95% to 56% from five minutes through two hours post-dose. Time to peak hydrocodone exposure (Tmax) was significantly delayed for KP201 versus HB (1.75 hours versus 0.50 hours). Both speed of onset and magnitude of effect correlate, Dr. Guenther noted, with behavior reward. The intranasal trial showed significantly lower drug liking and pupil dilation and greater difficulty for snorting with KP201 than with HB.

“The greater advantage for KP201/APAP,” Dr. Guenther said in an interview, “is in its deterrent characteristics among abusers who take hydrocodone products intranasally.” Adolescents are more likely than adults to abuse hydrocodone intranasally. They often also know how to extract APAP from hydrocodone/APAP formulations. If they “snort” extracted KP201, however, they inhale the inactive prodrug and actually get much less hydrocodone. “This might prevent them from escalating their euphoric experience—and hopefully, they lose interest,” Dr. Guenther said.

KP201 has been granted priority review by the Food and Drug Administration and has a PDUFA date in June 2016.

Boots on the Ground in Opioid Tapering:
A Low-Cost, Medically Supervised Opioid Taper Program for Community-Dwelling Patients
• Richard L. Stieg, MD, MHS, Aurora, Colorado, and Beth D. Darnall, PhD, Associate Clinical Professor, Stanford University School of Medicine, Stanford, California

A low-cost, 16-week opioid tapering program administered by a private physician and two assistants led to opioid reductions...
of 25% to 100% in 75% of patients, without significant changes in pain or psychosocial outcomes.

The program was developed by Dr. Steig, a neurologist and addiction specialist with extensive experience supervising pain clinics in academic and nonacademic settings. Dr. Steig, in an interview, first cited the drastic reduction in available multidisciplinary pain clinics over the last 25 years, and then three additional stimuli for his creation of the program: He read a book by Dr. Darnall (who led the present study) that impressed him deeply; he was planning on retiring from his practice; and he was looking for a new way to help people taper down or completely eliminate opioids in a cost-effective way.

Dr. Steig invited 119 patients to participate in a voluntary opioid taper program with two orientation sessions (groups of eight to 12 patients). At the talks, he notified them of his intent to retire and described the free program (except for the copays for their four monthly visits). “I told them that access to opioids was getting tougher and tougher, that insurance companies were bowing out of paying, and that doctors were declining to prescribe them—all good reasons to taper down,” Dr. Steig said.

Patients’ mean age was 47 years, with a mean of seven years on opioids, mean pain scores of 5.9 (on a 0–10 scale), and mean Morphine Equivalent Daily Doses of 244. The 48 patients who enrolled in the program each received a free copy of the book and a slow, individualized taper schedule. In the event of withdrawal symptoms, they were given pharmacological support (nonbenzodiazepine). Dr. Steig said that he had intended to provide psychosocial support as part of the program, but insurance coverage could not be secured for that component.

A surprising finding beyond the high success rate was that neither the baseline dose nor the duration of opioid use correlated with success. Analysis revealed significant improvement at 16 weeks among the 34 completers (13 remain in progress; one discontinued) in absolute change in opioid dose ($P = 0.002$) and in pain catastrophizing ($P = 0.01$), a measure of exaggerated mental and emotional response to pain. While 50% of the group reduced their opioids by 50%, 30% reduced them by 75% to 100%, and about 75% reduced doses by 25% to 100%. Dr. Steig noted that many of the subjects have continued to taper their doses after the 16-week study period.

“Success was totally dependent on self-motivation except for the little bit of coercion I provided in telling them I was retiring and that their health plan might cut them off. That’s the essence,” Dr. Steig said.

A strong trend ($P = 0.055$) was observed showing that opioid reductions were related to pain reduction, Dr. Darnall said in an interview. While more patients are needed in the ongoing study to lend greater statistical power, “the preliminary story is that people who taper opioids appear to have reductions in pain.” Pain catastrophizing at four months was also greatly reduced, she said. “The voluntary nature of the taper likely confers a high degree of controllability. In the end, two of our most important findings may be:

1. Offer a taper pathway. Many patients will accept it.
2. Make it voluntary and supportive so they know they are in control. It will reduce stress, and they are more likely to succeed.”

Efficacy and Safety of Hydrocodone Extended-Release Tablets Formulated With an Abuse-Deterrent Technology Platform for the Treatment Of Moderate-to-Severe Pain in Patients With Chronic Low Back Pain

- Richard Malamut, MD, Head of the Pain Therapeutic Area for Teva Pharmaceutical Industries, Frazer, Pennsylvania

In a phase 3 trial assessing efficacy and safety, patients with histories of moderate-to-severe chronic low back pain for three months or longer receiving an oral hydrocodone bitartrate extended-release (ER) tablet formulated with CIMA abuse-deterrent technology experienced more effective alleviation of pain compared with placebo with a safety profile consistent with other opioids. The formulation (CEP-33237, Teva) resists tampering (e.g., crushing, chewing, dissolving in alcohol or water) that leads to rapid release of hydrocodone (dose dumping) and increased toxicity and side effects.

Patients entering the study were already receiving analgesia and had pain that was not well controlled, with average pain intensity (API) scores averaging above eight of 10. Subjects required around-the-clock treatment. An open-label titration period identified an optimal pain-relief dose without unacceptable adverse events.

In total, 371 patients (mean age, 51.8 years; 49% male) achieved an analgesic dose of hydrocodone ER (30 mg to 90 mg every 12 hours) and were randomized to a 12-week, double-blind, placebo-controlled, randomized-withdrawal treatment period. The primary endpoint was change from baseline to week 12 in the weekly average of daily worst pain intensity (WPI) scores on an 11-point scale.

In the withdrawal period (among patients randomized to placebo), “pain intensity started to inch up,” Dr. Malamut said in an interview. The least squares mean change in WPI from baseline at week 12 was significantly higher with placebo compared with hydrocodone ER ($0.55 [0.14] versus –0.03 [0.12], $P < 0.001$). The percentage of patients with an API increase of 30% or more from baseline and an API score of 5 or greater at week 12 was significantly lower in the hydrocodone ER group (13%) than in the placebo group (19%) ($P = 0.029$). The percentage of patients with loss of efficacy (i.e., discontinuation for lack of efficacy [a secondary efficacy measure]) was lower with hydrocodone ER (23%) than placebo (30%): hazard ratio, 0.68; 95% confidence interval, 0.45–1.01; $P = 0.059$.

Rescue medications (hydrocodone immediate release), allowed in both groups, were used at the same level in both groups.

Common adverse events with hydrocodone ER during double-blind treatment were constipation (14%) and nausea (10%). No clinically meaningful differences in pure tone audiometry were observed between the two groups.

Dr. Malamut also noted that in a separate presentation of study data, study drug loss and diversion rates were low, supporting the potential abuse-deterrent properties of this formulation. “These results confirm that hydrocodone, even with the abuse-deterrent characteristics and the ER formulation, functions as an analgesic,” he said.
Increased growth and weight gain. Reduced gut microbiome used subtherapeutic doses of antibiotics in animals to induce infections.5 Clostridium difficile predispose individuals to and other enteric infections. 

Dr. Mullin’s message for pharmacists, delivered in an interview after his presentation, was straightforward advocacy for a bottom-up therapeutic strategy rather than a top-down “strike first with your heaviest weapons” approach to getting acute disease states under control. His rationale is that agents and diets that perturb the gut microbiome can incur a heavy price, leading to diabetes, obesity, nonalcoholic fatty liver disease, dementia, and cardiovascular disease.

Dr. Mullin cited a meta-analysis of studies of small intestine bacterial overgrowth (SIBO).4 In it, eight of 11 studies showed increases in SIBO risk with PPI use, with an overall odds ratio of 2.282 (range, 0.577–39.087; P = 0.008). PPIs, he said, delay small intestine transit. “Our community acknowledges that PPIs are overprescribed. The point is that they should not be first-line therapy. They should be last resort or short term and increases an ecosystem’s efficiency and productivity while making it less functionally susceptible to external stressors, he pointed out that gut microbiome diversity helps with barrier integrity and with training the immune system, and overall has a great impact on health and well-being. Factors contributing to dysbiosis of the gut microbiota include host genetics, lifestyle (e.g., diet, stress), reduced early colonization (e.g., hospital birth, altered microbe exposure), and medical practices (e.g., vaccination, antibiotics, excessive hygiene). Two phyla (mainly anaerobic) of bacteria have been linked to obesity, the firmicutes positively and the bacteroidetes negatively—presumably through effects on metabolism—with animal studies demonstrating induced obesity with transplanted firmicutes.3

With respect to his two specific pharmacological targets—the overuse of proton pump inhibitors (PPIs) and antibiotics—Dr. Mullin cited a meta-analysis of studies of small intestine bacterial overgrowth (SIBO).4 In it, eight of 11 studies showed increases in SIBO risk with PPI use, with an overall odds ratio of 2.282 (range, 0.577–39.087; P = 0.008). PPIs, he said, delay small intestine transit. “Our community acknowledges that PPIs are overprescribed. The point is that they should not be first-line therapy. They should be last resort or short term and not chronic, just like steroids. We overkill diseases with heavy medications to get them under control and then people can’t withdraw or substitute because they have become physiologically dependent,” Dr. Mullin said.

A recent study documented adverse gut microbiome changes in PPI users versus nonusers consistent with changes that presumably through effects on metabolism—with animal studies demonstrating induced obesity with transplanted firmicutes.3

For more than 50 years, the meat industry has effectively used subtherapeutic doses of antibiotics in animals to induce increased growth and weight gain. Reduced gut microbiome diversity in humans is a likely effect of ingested antibiotics on top of prescribed antibiotics, with extended consequences. Recovery of gut biodiversity after a week’s course of clindamycin, a regimen commonly prescribed for dental procedures, Dr. Mullin said, may take up to two years.6 Furthermore, it has been proposed that subtherapeutic levels of antibiotics lead to increased adiposity through increased production and uptake of short-chain fatty acids. One study showed that repeated exposure to broad-spectrum antibiotics at ages zero to 23 months is associated with early childhood obesity.7 That risk is potentially modified through more narrow antibiotic selection. Altered gut microbiota promote obesity and insulin resistance through reduced fatty-acid oxidation in muscles, increased triglyceride incorporation and inflammation in adipose tissue, and increases in short-chain fatty acids and inflammation in the liver. Another study showed Helicobacter pylori eradication to be associated with body-mass index increases.8

Dr. Mullin cited studies showing the antiobesity effects of probiotic supplementation, including reduced body weight, lowered visceral and subcutaneous fat area, and improved serum glucose and homocysteine levels.9

While many questions remain around optimal probiotic use (e.g., dosages, schedule, mixtures, human or synthetic, oral or injectable, fecal bacteriotherapy) and prebiotic use, Dr. Mullin said, the majority of studies showing benefits for C. difficile and antibiotic-associated diarrhea have been conducted with Saccharomyces boulardii.

Diet, he said, must also be emphasized, with avoidance of high-fat and sugary foods during antibiotic administration. The substitution of artificial sweeteners, however, promotes gut dysbiosis and may induce glucose intolerance.10

How can patients be tapered off PPIs? The answers are not formulaic. “You can’t just say you can replace them with zinc or Tagamet. Answers will be individualized, and the process may be long and complicated,” Dr. Mullin said. “But you can start with Tums and, of course, lifestyle. The big obstacle is that people do not want to lose weight or cut down on their cigarettes or caffeine or alcohol. They want to live the magic bullet lie.”

Healing Depression and Integrative Depression Care

Dr. Mullin cited studies showing the antiobesity effects of probiotic supplementation, including reduced body weight, lowered visceral and subcutaneous fat area, and improved serum glucose and homocysteine levels.9

While many questions remain around optimal probiotic use (e.g., dosages, schedule, mixtures, human or synthetic, oral or injectable, fecal bacteriotherapy) and prebiotic use, Dr. Mullin said, the majority of studies showing benefits for C. difficile and antibiotic-associated diarrhea have been conducted with Saccharomyces boulardii.

Diet, he said, must also be emphasized, with avoidance of high-fat and sugary foods during antibiotic administration. The substitution of artificial sweeteners, however, promotes gut dysbiosis and may induce glucose intolerance.10

How can patients be tapered off PPIs? The answers are not formulaic. “You can’t just say you can replace them with zinc or Tagamet. Answers will be individualized, and the process may be long and complicated,” Dr. Mullin said. “But you can start with Tums and, of course, lifestyle. The big obstacle is that people do not want to lose weight or cut down on their cigarettes or caffeine or alcohol. They want to live the magic bullet lie.”

Dr. Mullin cited studies showing the antiobesity effects of probiotic supplementation, including reduced body weight, lowered visceral and subcutaneous fat area, and improved serum glucose and homocysteine levels.9

While many questions remain around optimal probiotic use (e.g., dosages, schedule, mixtures, human or synthetic, oral or injectable, fecal bacteriotherapy) and prebiotic use, Dr. Mullin said, the majority of studies showing benefits for C. difficile and antibiotic-associated diarrhea have been conducted with Saccharomyces boulardii.

Diet, he said, must also be emphasized, with avoidance of high-fat and sugary foods during antibiotic administration. The substitution of artificial sweeteners, however, promotes gut dysbiosis and may induce glucose intolerance.10

How can patients be tapered off PPIs? The answers are not formulaic. “You can’t just say you can replace them with zinc or Tagamet. Answers will be individualized, and the process may be long and complicated,” Dr. Mullin said. “But you can start with Tums and, of course, lifestyle. The big obstacle is that people do not want to lose weight or cut down on their cigarettes or caffeine or alcohol. They want to live the magic bullet lie.”

Healing Depression and Integrative Depression Care

Dr. Mullin cited studies showing the antiobesity effects of probiotic supplementation, including reduced body weight, lowered visceral and subcutaneous fat area, and improved serum glucose and homocysteine levels.9

While many questions remain around optimal probiotic use (e.g., dosages, schedule, mixtures, human or synthetic, oral or injectable, fecal bacteriotherapy) and prebiotic use, Dr. Mullin said, the majority of studies showing benefits for C. difficile and antibiotic-associated diarrhea have been conducted with Saccharomyces boulardii.

Diet, he said, must also be emphasized, with avoidance of high-fat and sugary foods during antibiotic administration. The substitution of artificial sweeteners, however, promotes gut dysbiosis and may induce glucose intolerance.10

How can patients be tapered off PPIs? The answers are not formulaic. “You can’t just say you can replace them with zinc or Tagamet. Answers will be individualized, and the process may be long and complicated,” Dr. Mullin said. “But you can start with Tums and, of course, lifestyle. The big obstacle is that people do not want to lose weight or cut down on their cigarettes or caffeine or alcohol. They want to live the magic bullet lie.”
Acetylcholine can show up in memory problems with impaired creative and/or math function.

No single approach is likely to be effective, but a totality of measures addressing issues of sleep, stress, diet, inflammation, and exercise, adding hydrotherapy, detoxification, and supplements, can be very powerful, Dr. Bongiorno said.

Deciding whether to take a conventional or integrative approach rests on the answers to several important questions. If the patient is at risk for self-harm or harming others, conventional therapies should be given first with natural remedies as adjuncts. The same is true if the patient cannot take care of herself, himself, or family. Natural therapies can be selected if the patient falls outside the first two categories and is willing. Pregnancy and breastfeeding call for case-by-case evaluation.

When a patient is already on pharmacological treatment for depression, natural treatments can be initiated and, as they take effect, the former can be tapered.

Dr. Bongiorno suggested very complete laboratory tests, including the standard assays plus others for folic acid, methyltetrahydrofolate reductase, carnitine, serum mercury, celiac disease, urine kryptopyrroles, environmental metals, SIBO, and leaky gut. Saliva testing, he said, is more accurate for assessing cortisol levels than is serum testing.

The lab tests will give insight into choosing among the endless variety of supplements to meet repletion needs. Pointing out that supplements are at the bottom of the list of strategies, he said that they probably are not going to be effective “if you are not working on sleep and all the others.”

Sleep disturbances are common precursors to depression onset or recurrence. Research has shown that 70% of sleep apnea patients have depression,

and 30% of patients with insomnia are depressed. Helpful supplements include melatonin (including prolonged release), tryptophan, valerian, casein decapeptide, magnesium glycinate/threonate, and phosphatidylserine.

Treatment resistance with conventional antidepressants may be overcome when deficiencies revealed in lab tests are addressed with supplemental folic acid, testosterone, estrogen, thyroid hormone, zinc, vitamin B12, and creatine. Dr. Bongiorno cited a study showing full responses to antidepressant medications when B12 levels were higher (439.1 pmol/L) versus nonresponders (347.2 pmol/L) and partial responders (396.0 pmol/L) and another showing enhanced responses to escitalopram by week 2 among women with major depression who received creatine (5 g) versus placebo. Augmentation of antidepressant response has been shown for omega-3 fatty acids, as well.

The basic “three you need” supplements for depression, Dr. Bongiorno said, are multiple vitamin, fish oil (2 g per day), and probiotics (lactobacillus/bifidus) for 30 days. Other supplements with research supporting their efficacy in depression include chromium, rhodiola, berberine (which inhibits monoamine oxidase-A), and curcumin. Response rates with the combination of curcumin and fluoxetine were higher (77.8%) than with either agent alone (fluoxetine, 64.7%; curcumin, 62.5%) in major depressive disorder. An Australian meta-analysis of six studies of saffron (Crocus sativus) (15 to 30 mg once daily) revealed large treatment effects.

Dr. Bongiorno’s favorite supports for neurotransmitters include tyrosine, macuna, SAMe, 5-HTP, and Apocynum venetum (Rafuma leaf extract).

Dr. Bongiorno noted that research from 2005 revealed that 15% of 315 depression patients preferred medication alone, 24% preferred psychotherapy alone, and 60% preferred both. “Those who received a preferred treatment experienced more rapid improvements.” He concluded with Hippocrates’ fifth-century recommendations: a vegetable diet, physical movement, water therapy, and St. John’s wort.

REFERENCES