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In this issue…

The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

Apadaz™ (Immediate-release Benzhydrocodone and Acetaminophen)

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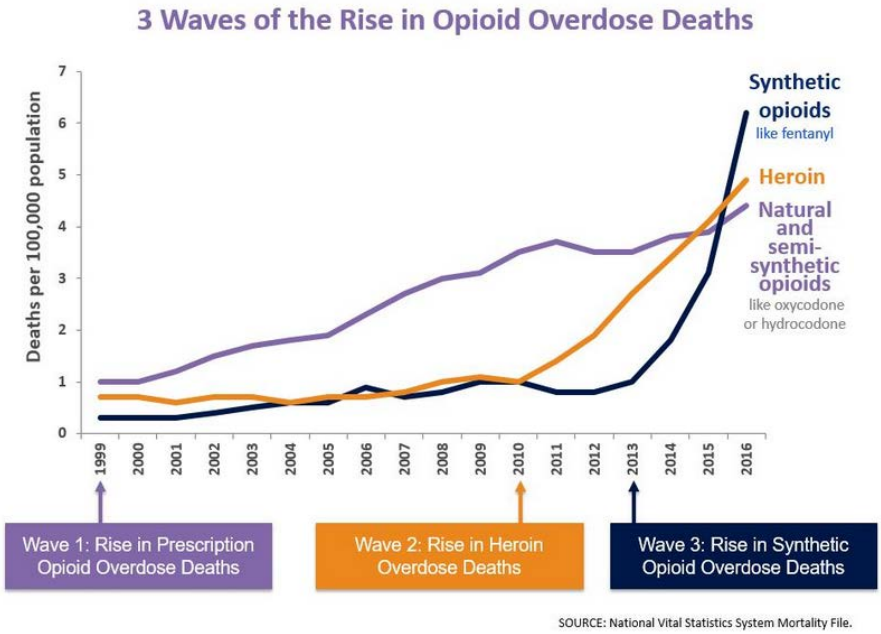
Background

The Centers for Disease Control and Prevention (CDC) estimate that opioids, prescription and illicit, led to the deaths of more than 42,000 Americans in 2016.[1] They estimate that 115 Americans die every day due to opioid overdose.[2] Figure 1 shows trends in opioid-related deaths over the past several decades, from which the CDC identified 3 distinct waves contributing to opioid overdose deaths. The CDC is addressing the epidemic by working with states to build prevention efforts, improving data quality tracking, supporting healthcare providers and systems, working with public safety officials, and encouraging consumers to make responsible decisions about opioids.

Figure 1. Opioid overdose trends.[2]



The Food and Drug Administration (FDA) also has a plan to reduce opioid-related deaths.[3] The FDA published its 2018 Strategic Policy Roadmap which highlights their focus on reducing opioid misuse and abuse. The Roadmap has 4 focus areas with 1 being to reduce the burden of addiction crises that are threatening American families.[4] To help reverse the epidemic while still ensuring adequate pain relief, the FDA developed the Opioids Action Plan.[5] The plan includes the following: expansion of use of advisory committees which allows for consultation with experts in the field, assurance that warnings and precautions are included in the labeling for immediate-release opioids, emphasis on the need for post-marketing studies to help determine long-term abuse and misuse risks with medications, proper use of risk evaluation and mitigation strategy (REMS) programs to help educate providers on safe prescribing habits, improvement in access to supportive treatment including overdose treatment, reassessment of the risks versus benefits with population health as a priority, and, finally, a focus on development of abuse-deterrent formulations. Table 1 describes common mechanisms of abuse deterrence.

Table 1. Common mechanisms of abuse deterrence.[6]

Mechanism	Characteristics
Physical/chemical barriers	Prevent chewing, crushing, cutting, grating, or grinding (physical) Impede extraction of opioids with common solvents (chemical)
Agonist/antagonist combinations	Addition of a sequestered or non-sequestered opioid antagonist
Aversion	Component(s) added that produce(s) an unpleasant effect after manipulation, after administration by alternate routes (e.g., mucous membrane irritant), or if used at doses higher than those indicated
Delivery systems	Long-acting injectable or depot formulations that are difficult to manipulate
Prodrugs or new molecular entities	Require chemical or enzymatic transformation in vivo to active drug; may have inherent pharmacodynamic or pharmacokinetic properties that lower abuse potential
Combination of technologies	Contain ≥2 of the other defined technologies
Novel approaches	Technologies that are not characterized by 1 of the defined categories (e.g., technology that provides protection against multiple-pill overdose)

The FDA requires 3 categories of testing for approval of an abuse-deterrent opioid.[6] The first category involves physical manipulation or in vitro testing using various household tools and solvents to crush, grate, mill, or grind the medication to determine how difficult it is to defeat the abuse-deterrent properties. The second category involves pharmacokinetic studies to test the medication while intact and also after being manipulated, compared to an appropriate control. The last category includes trials evaluating the clinical abuse potential. These trials are typically randomized, double-blind, crossover studies involving both placebo and active controls. Table 2 describes typical endpoints for these studies. Though Drug Liking scores, or measures of the rewarding effects of drugs, are traditionally the primary outcomes of these studies, it should be noted that the FDA requires more than statistically improved differences in these scores to approve a drug as abuse-deterrent. It is thought that the FDA also requires statistically significant reductions in the Take Drug Again scores, or measures of how likely patients would be to take the drug again, regarding the oral and nasal routes.[7]

Table 2. Typical endpoints assessed in category 3 testing.[6]

Types of outcomes	Description	VAS interpretation
Balance of positive and negative	Drug Liking assessed at multiple time points after drug administration	Bipolar; 100-point scale; 0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking
Global	Overall Drug Liking typically assessed 12 and 24 hours after drug administration Take Drug Again typically assessed 12 and 24 hours after drug administration	Bipolar; 100-point scale; 0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking Bipolar; 100-point scale; 0 = strong disliking; 50 = neither like nor dislike; 100 = strong liking
Positive (good effects, high)	Drug Effects Questionnaire assessed at multiple times after drug administration	Unipolar; 100-point scale; 0 = not at all; 100 = extremely
Negative (bad effects, nausea, sleepiness)	Drug Effects Questionnaire assessed at multiple times after drug administration	Unipolar; 100-point scale; 0 = not at all; 100 = extremely
Nasal effects	Ease of snorting; pleasantness of snorting or specific symptoms such as burning or facial pains	Bipolar; 100-point scale; 0 = very difficult/very unpleasant; 50 = neither easy or difficult/ neither pleasant nor unpleasant; 100 = very easy/very pleasant; or 0-5 numeric rating scale
Objective (pupillometry)	Change in pupil diameter assessed at multiple points after drug administration	N/A

N/A=not applicable; VAS=visual analog scale

Immediate-release opioids are thought to be more commonly diverted and abused than extended-release formulations.[7] They are also challenging to make abuse-deterrent because they are designed to work quickly. At the time of development of benzhydrocodone/acetaminophen (APAP), the only approved abuse-deterrent opioids were extended-release formulations. This posed a unique niche for drug developers to enter the market place. Table 3 shows the FDA's decisions regarding abuse-deterrent opioids as of April 2017.

Table 3. Abuse-deterrent opioids.[7]

Recent Advisory Committee meetings considering approval of AD formulation opioids (September 2015-April 2017)				
Product	**Sponsor**	**Release profile and active moiety**	**Description of product**	**Summary of vote (FDA decision)**
Avridi™	Purdue Pharma L.P.	IR oxycodone	Tablet formulation with gelling and aversive agents	23-1 against approval (not approved)
Xtampza® ER	Collegium Pharmaceutical, INC.	ER oxycodone	Microsphere-in-capsule formulation	23-0 in favor of approval (approved with nasal and IV AD labeling)
Apadaz™	KemPharm, Inc.	IR benzhydrocodone /APAP	Prodrug of hydrocodone with APAP	16-4 in favor of approval; 18-2 against labeling as AD product (not approved as AD product)
Vantrela™ ER	Teva Pharmaceutical Industries Ltd.	ER hydrocodone	Triple-layer polymer formulation	14-3 in favor of approval; 14-3 in favor of oral AD labeling; 14-3 in favor of nasal AD labeling; 16-1 in favor of IV AD labeling (approved with oral, nasal, and IV AD labeling)
Troxyca® ER	Pfizer, Inc.	ER oxycodone	Agonist/antagonist formulation with sequestered naltrexone	9-6 in favor of approval and IV AD labeling; 9-6 against oral AD labeling; 11-4 in favor of nasal AD labeling (approved with oral, nasal, and IV AD labeling)
Arymo™ (ER)	Egalet Corporation	ER morphine	Polymer matrix tablet technology utilizing injection molding	18-1 in favor of approval and nasal and IV AD labeling; 16-3 in favor of oral AD labeling (approved with IV AD labeling)
RoxyBond™	Inspirion Delivery Sciences, LLC	IR oxycodone	Tablet formulation with physical and chemical barriers	19-0 with 1 abstention in favor of approval; 19-1 in favor of nasal AD labeling; 16-4 in favor of IV AD labeling (approved with nasal and IV AD labeling)

AD=abuse-deterrent; APAP=acetaminophen; ER=extended-release; FDA=Food and Drug Administration; IR=immediate-release; IV=intravenous

Benzhydrocodone/APAP

Benzhydrocodone/APAP is a schedule II controlled substance comprised of a combination of immediate-release benzhydrocodone and APAP and was approved in February 2018.[8] The product is unique in that it is the only prodrug for an immediate-release opioid currently approved in the United States. It is indicated to treat acute pain severe enough for opioid therapy and inadequately controlled with non-opioid analgesics and is approved for a maximum duration of 14 days. Benzhydrocodone/APAP is manufactured by KemPharm. The medication was studied with hopes of gaining approval as an abuse-deterrent formulation, but the FDA did not grant approval for that indication.[7]

Clinical pharmacology

Benzhydrocodone is a prodrug of hydrocodone.[8] Hydrocodone is a full opioid agonist, selective for the mu-opioid receptor. As the dose increases, the selectivity decreases which can lead to adverse effects. APAP is a non-opioid, non-salicylate analgesic. The precise mechanism of action for APAP is unknown.

Dosing

Initial

The manufacturer recommends dosing benzhydrocodone/APAP as 1-2 tablets orally every 4-6 hours as needed for pain with a maximum of 12 tablets per day.[8]

Conversion

When switching from hydrocodone/APAP to benzhydrocodone/APAP, the manufacturer suggests that a 7.5 mg/325 mg dose of hydrocodone/APAP should be substituted with 6.12 mg/325 mg of benzhydrocodone/APAP.[8]

Titration

It is recommended for patients to always keep an open line of communication with their healthcare provider as any increases in pain should be further assessed before increasing the dose.[8] The risk of side effects should always be considered before increasing the dose. Use of this product and others containing APAP should not exceed an APAP dose greater than 4000 mg/day.

Discontinuation

For patients who are physically dependent on benzhydrocodone/APAP, it is recommended to never abruptly discontinue the product, but rather to decrease the dose by 25-50% every 2-4 days to minimize the risk of withdrawal.[8] If symptoms of withdrawal occur, it is recommended to resume therapy at the previous dose and then start a slower taper.

Renal impairment

As the hydrocodone component is eliminated primarily via the kidneys, the manufacturer recommends use of a low initial dose and slow titration in patients with renal impairment.[8] Patients with renal impairment may have higher plasma concentrations of hydrocodone compared to those with normal renal function, increasing the risk of adverse effects including respiratory depression.

Hepatic impairment

The effect of hepatic impairment on the clearance of benzhydrocodone/APAP has not been fully determined.[8] It is recommended to initiate therapy using low doses and monitor for any side effects or worsening liver function before increasing the dose.

Dosage form/strength

Benzhydrocodone/APAP only comes in 1 strength: 6.12 mg of benzhydrocodone with 325 mg of APAP.[8] The product is an immediate-release tablet that is white and imprinted with “KP201” on 1 side.

Storage/disposal

Benzhydrocodone/APAP should be stored at 20-25 degrees Celsius (68-77 degrees Fahrenheit).[8] Unused tablets should be flushed down the toilet.[9] Alternatively, patients wishing to dispose of the medication are encouraged to contact the Drug Enforcement Administration (DEA) to find an authorized collection site.

Safety

Contraindications

Benzhydrocodone/APAP is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma when unmonitored or when resuscitative equipment is not readily available, known or suspected gastrointestinal obstruction (including paralytic ileus), and known hypersensitivity to any component of the product.[8]

Warnings/precautions

Benzhydrocodone/APAP has boxed warnings for the following: addiction, abuse, and misuse; life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; cytochrome P450 (CYP) 3A4 interactions; hepatotoxicity; and risk of concomitant use with benzodiazepines and other central nervous system (CNS) depressants.[8]

Additional warnings include respiratory depression in patients with chronic pulmonary disease, or elderly, cachectic, or debilitated patients.[8] It is recommended to closely monitor these patients upon initiation of therapy and with any increases in the dosage.

Opioid use has been associated with adrenal insufficiency.[8] If adrenal insufficiency is suspected, it is recommended to wean the patient from the opioid, treat adrenal insufficiency with corticosteroids, and to try a different opioid, if needed, for future pain management.

Benzhydrocodone/APAP can cause severe hypotension.[8] The risk appears to be increased with concurrent use of anesthetics or phenothiazines. Use of benzhydrocodone/APAP should be avoided in patients with circulatory shock.

APAP has been associated with serious skin reactions, including Stevens-Johnson Syndrome and toxic epidermal necrolysis.[8] The product should be discontinued at the first sign of a skin rash or hypersensitivity.

It is not recommended to use benzhydrocodone/APAP in patients with increased intracranial pressure, brain tumors, head injuries, or impaired consciousness as these conditions could be worsened with respiratory depression and impair the clinical course of the patient.[8]

Benzhydrocodone/APAP may increase the risk of seizures in patients who have a history of a seizure disorder or who are in clinical situations that could predispose them to seizures.[8] It is recommended to monitor these patients for seizure activity while they are taking benzhydrocodone/APAP.

It is recommended to avoid concurrent use of mixed opioid agonists/antagonists or use with partial agonists to avoid precipitating withdrawal signs and symptoms.[8] When discontinuing therapy, the drug dosage should be tapered gradually; discontinuation should not be abrupt.

Patients should be counseled to avoid operating heavy machinery and driving cars until they are familiar with how they will react to benzhydrocodone/APAP as it can cause mental impairment.[8]

Adverse reactions

As is typical with most opioid analgesics, benzhydrocodone/APAP can cause drowsiness, nausea, vomiting, constipation, dizziness, and headache.[8] Post-marketing evidence has shown associations with serotonin syndrome, adrenal insufficiency, androgen deficiency, and anaphylaxis.

Drug Interactions

Hydrocodone concentrations can be increased when benzhydrocodone/APAP is taken concomitantly with CYP3A4 or 2D6 *inhibitors* such as erythromycin, ketoconazole, and ritonavir.[8] It is recommended to decrease the dose of benzhydrocodone/APAP temporarily while the patient is taking the interacting medication and to monitor closely for signs of respiratory depression. If the interacting therapy is completed or discontinued, it is recommended to consider increasing the dose of benzhydrocodone/APAP temporarily and to monitor patients for symptoms of withdrawal.

Dose increases of benzhydrocodone/APAP may be necessary with concurrent use of CYP3A4 *inducers* such as rifampin, carbamazepine, and phenytoin.[8] Patients should be monitored for symptoms of withdrawal. If the interacting therapy is completed or discontinued, it is recommended to monitor patients for signs of respiratory depression.

Benzhydrocodone/APAP should not be used with additional CNS depressants such as alcohol, sedatives/hypnotics, and muscle relaxants.[8] If they must be used together, it is recommended to reduce the doses and duration to the minimum necessary. Patients should be monitored for signs of hypotension, respiratory depression, and sedation.

It is not recommended to use benzhydrocodone with selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, tricyclic antidepressants, triptans, serotonin receptor antagonists, medications that affect the serotonin neurotransmitter system (e.g., trazodone and tramadol), or monoamine oxidase inhibitors, due to an increased risk of serotonin syndrome.[8] If they must be used together, monitor patients for symptoms of serotonin syndrome.

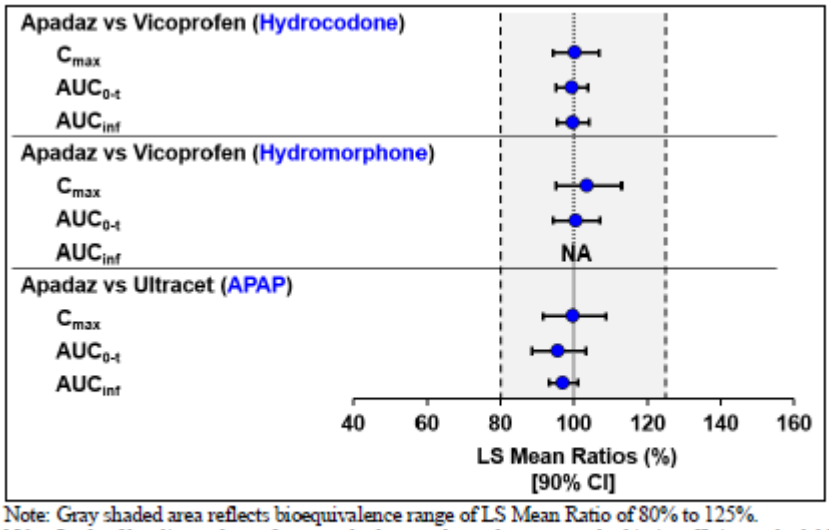
Benzhydrocodone/APAP can reduce the efficacy of diuretics due to increased production of antidiuretic hormone.[8] It is recommended to increase the dose of the diuretic as needed.

Efficacy

Bioequivalence

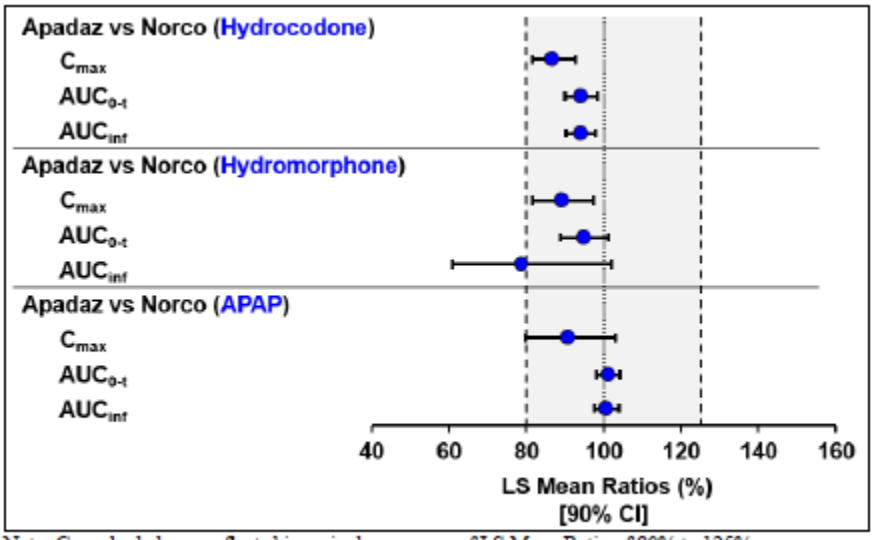
Benzhydrocodone/APAP met bioequivalence standards when compared to other immediate-release hydrocodone- and APAP-containing products.[8] See Figure 2 and Figure 3 for results of the comparison between benzhydrocodone/APAP and Vicoprofen®, Ultracet®, and Norco®.[10] Based on these data, the FDA approved the product for acute pain severe enough for opioid therapy and inadequately controlled with non-opioid analgesics with a maximum duration of 14 days.

Figure 2. Bioequivalence between benzhydrocodone/APAP and Vicoprofen® or Ultracet®.[10]



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.
NA = Lack of log-linear decay for many hydromorphone datasets resulted in insufficient calculable AUC_{inf} values.
As a result, the 90% CI does not provide a reliable estimate for bioequivalence.

Figure 3. Bioequivalence between benzhydrocodone/APAP and Norco®.[10]



Note: Gray shaded area reflects bioequivalence range of LS Mean Ratio of 80% to 125%.

Abuse deterrence

Initially, benzhydrocodone/APAP was studied in vitro to assess the ability of different methods to extract and convert benzhydrocodone to hydrocodone for abuse by inhalation (smoking) or by the intravenous route.[8] The ease of extracting benzhydrocodone was similar to the ease of extracting hydrocodone from non-abuse-deterrent formulations of hydrocodone/APAP.

Secondarily, the oral abuse potential of benzhydrocodone/APAP was also investigated in a single-center, randomized, double-blind, crossover trial.[8] Recreational opioid users received the following treatments: 4, 8, and 12 tablets of benzhydrocodone/APAP (each containing 6.12 mg benzhydrocodone and 325 mg APAP), 4, 8, and 12 tablets of hydrocodone/APAP (each containing 4.54 mg hydrocodone and 325 mg APAP), and placebo. The primary endpoint was maximal score (E_{max}) for Drug Liking; E_{max} for Take Drug Again was a secondary endpoint. Seventy-one subjects were randomized; 62 completed the study. No statistically significant

differences were observed between benzhydrocodone/APAP and hydrocodone/APAP in the rate and extent of exposure (i.e., the maximum concentration and area under the curve measurements, respectively). There were also no statistically significant differences between products in the Drug Liking E_{max} or the Take Drug Again E_{max}. Therefore, benzhydrocodone/APAP was not expected to deter abuse via the oral route.

The intranasal abuse potential of benzhydrocodone/APAP was studied in a single-center, randomized, double-blind, double-dummy, 2-part trial.[8] There were 5 treatment arms, including intranasal crushed and oral benzhydrocodone/APAP (2 of the 6.12 mg benzhydrocodone/325 mg APAP tablets), intranasal and crushed oral hydrocodone/APAP (2 of the 4.54 mg hydrocodone/325 mg APAP tablets), and intranasal placebo powder. The primary endpoint was E_{max} for Drug Liking; E_{max} for Take Drug Again was a secondary endpoint. The results are shown in the Table 4. The Drug Liking and the Take Drug Again scores showed some improvement with benzhydrocodone/APAP, but the differences were not statistically significant. These findings do not support abuse deterrence by the intranasal route of administration.

Table 4. Intranasal benzhydrocodone/APAP versus hydrocodone/APAP and placebo.[8]

VAS Scale (100 point) Intranasal (n=42)	Benzhydrocodone/APAP Crushed	Hydrocodone/APAP Crushed	Placebo
Drug Liking*			
Mean (SE)	75.9 (2.3)	79 (2.7)	53 (1.2)
Median (Range)	74 (50-100)	80 (50-100)	51 (50-85)
High**			
Mean (SE)	61.8 (4.6)	59.1 (5.1)	8.8 (3.8)
Median (Range)	68.5 (0-100)	67.5 (0-100)	0 (0-100)
Take Drug Again*			
Mean (SE)	69.5 (3.9)	74.5 (3.9)	48.2 (2.2)
Median (Range)	68 (0-100)	81.5 (0-100)	50 (0-100)

APAP=acetaminophen; SE=standard error; VAS=visual analog scale
*Bipolar scale (0 = maximum response, 50 = neutral response, 100 = maximum positive response)
**Unipolar (0 = maximum negative response, 100 = maximum positive response)

Based on the results of the in vitro studies and oral and intranasal human abuse potential studies, the FDA did not grant approval of benzhydrocodone/APAP as an abuse-deterrent formulation.[8]

Summary

Benzhydrocodone/APAP is a new formulation of a short-acting opioid in combination with APAP that was developed with the intention to reduce abuse and misuse, but the results of several clinical trials did not support its efficacy as an abuse-deterrent product.[8] There are limited data to support a clinical advantage of this drug vs. other short-acting opioids. Also, given that it is branded, the cost of benzhydrocodone/APAP will likely be more than those of similar generic drugs. For now, the product represents an additional option for short-acting opioids.

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Increasing Use of Kratom: A Pharmacist's Quick Guide

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Recently, the use of a substance called kratom has gained media attention, as evidenced by press announcements or reports from the Food and Drug Administration (FDA) and the Drug Enforcement Administration (DEA).[1] As the opioid crisis has encouraged pain management away from opioids, other products which are less known and potentially dangerous have become widely available. A July 2016 report by the Centers for Disease Control and Prevention identified that calls to poison centers concerning kratom exposure increased 10-fold from 26 in 2010 to 263 in 2015.[2]

Kratom (*Mitragyna speciosa*) is an herb with psychoactive opioid compounds that is indigenous to Thailand and Southeast Asia.[3,4] At low doses, kratom acts as a stimulant, while at high doses it acts as an analgesic. At high doses it has the potential to elicit a euphoric response which increases its abuse potential. The dose-dependent effects of kratom are understood as the following:[5,6]

Dose	Effects	Adverse Effects
1 – 5 grams	Mild stimulant effects	Nausea, vomiting, loss of appetite, loss of muscle coordination, increased urination, dizziness
>5 – 15 grams	Analgesia	≥8 grams: tachycardia, constipation, sedation, changes in blood pressure, sweating, dry mouth
>15 grams	Sedation	Respiratory depression, aggression, hallucinations, insomnia, seizures, hypothyroidism

"Typical opioids," such as morphine and codeine, are derived from *Papaver* and produce effects of analgesia by agonism at the mu-opioid receptor.[5] In recent years, due to the abuse potential of typical opioids, efforts in finding analgesics that offer pain relief with fewer adverse effects and less abuse potential have led to the increased use of drugs such as buprenorphine, tapentadol, and tramadol. Drugs such as these have been termed "atypical opioids" as they produce a weaker effect on opioid receptors and may have effects on

additional receptors via multiple mechanisms.[7] Kratom is difficult to classify as its chemistry and basic pharmacology reveal that it acts as an opioid but also has subsidiary non-opioid effects.[5]

Currently there is much controversy over the clinical benefits of kratom and the potential risks such as abuse potential. The FDA, DEA, and Congress have had difficulty deciphering the many viewpoints concerning this drug.[8] Ultimately, there are no current FDA-approved therapeutic or medical uses of kratom.[9]

In November 2017, the FDA Commissioner issued a public health advisory related to concerns regarding risks associated with the use of kratom.[9] This plant-based product has been wrongfully touted as a safe substance and is actively being marketed for treatment of pain, anxiety, and depression. The FDA warning was issued based on increasing reports of emergency room visits and hospitalizations due to kratom use and withdrawal.[10] In May 2018, the FDA sent warning letters to 3 marketers and distributors of kratom products in the United States for illegally selling unapproved kratom-containing drug products with unproven claims about their effectiveness in the treatment of opioid addiction and withdrawal.[11] Overdose from kratom can cause seizures, psychosis, coma, hallucination, paranoia, severe emesis, respiratory depression or even death. It is clear that kratom is associated with many adverse effects and currently it remains unclear on how to treat overdose or withdrawal.[12]

Increased availability of kratom has led to a surge in demand for this product; therefore, healthcare providers must understand the potential harm of using this drug.[4] The ability to address the concerns and dangers using remedies lacking evidence is imperative as many patients may be misled into believing these potential alternatives are safe and effective for treating pain.[9]

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Safety Update – Clarithromycin

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Background

Clarithromycin was approved by the Food and Drug Administration (FDA) in 1991 for treatment of bronchitis, *Helicobacter pylori*, disseminated mycobacterial infections, community-acquired pneumonia, sinusitis, as well as skin and skin structure infections.[1] The FDA recently issued a warning to prescribers which stated to "[use] caution before prescribing the antibiotic clarithromycin (Biaxin®) to patients with heart disease because of a potential increased risk of heart problems or death that can occur years later."[2] This drug safety communication was issued based on a review of a large clinical trial known as CLARICOR and a 10-year follow-up study of CLARICOR subjects. The CLARICOR trial, published in 2005, investigated the effects of short-term clarithromycin treatment on mortality and cardiovascular morbidity in patients with stable coronary heart disease.[3] The primary endpoint of this study was a composite of all-cause mortality, myocardial infarction, or unstable angina pectoris, and the secondary endpoint was a composite of cardiovascular mortality, myocardial infarction, or unstable angina pectoris. A total of 4373 patients were randomized to receive 2 weeks of the antibiotic (dosed at 500 mg/day) or placebo, then were subsequently followed for 3 years. No significant difference was observed between groups in the primary outcome (hazard ratio [HR] = 1.15, 95% confidence interval [CI] 0.99-1.34) or secondary outcome (HR = 1.17, 95% CI 0.98-1.40); however, all-cause mortality was significantly higher in the clarithromycin group (HR = 1.27, 95% CI 1.03-1.54). Additionally, cardiovascular mortality was significantly higher in the clarithromycin group (HR = 1.45, 95% CI 1.09-1.92).

Safety Update

A 10-year follow-up study of subjects enrolled in the CLARICOR trial was performed to assess long-term survival rates.[4] Data were obtained from the National Register of Causes of Death, a Danish public register. Of note, the demographics between the study and control group were no longer comparable after year 3, so an adjusted P value was calculated, as seen below in Table 1.

Table 1. All-cause mortality and cardiovascular mortality findings from the 10-year follow-up of CLARICOR.[4]

Outcomes	0-3 years after randomization				3-6 years after randomization				6-10 years after randomization			
	HR (95% CI)	P values (fully adjusted)[a]	Deaths		HR (95% CI)	P values (fully adjusted)[a]	Deaths		HR (95% CI)	P values (fully adjusted)[a]	Deaths	
			C	Pl			C	Pl			C	Pl
All-cause mortality	1.26 (1.04-1.53)	0.017 (0.04)	237	192	1.13 (0.95-1.34)	0.18 (0.12)	260	240	1.00 (0.87-1.15)	0.99 (0.31)	369	383
Non-CV mortality	1.10 (0.83-1.45)	0.52 (0.40)	102	95	0.94 (0.74-1.20)	0.94 (0.47)	134	134	1.08 (0.81-1.32)	0.43 (0.77)	206	197
CV mortality	1.42 (1.09-1.84)	0.008 (0.053)	135[b]	97	1.24 (0.96-1.60)	0.11 (0.06)	126	106	0.91 (0.74-1.13)	0.39 (0.14)	163	186
CV mortality at hospital	0.92 (0.59-1.44)	0.73 (0.51)	37	41	1.23 (0.89-1.70)	0.22 (0.20)	80	68	1.20 (0.91-1.60)	0.20 (0.31)	104	90
CV mortality outside hospital	1.76 (1.27-2.45)	0.001 (0.006)	97	56	1.26 (0.82-1.93)	0.30 (0.14)	46	38	0.64 (0.46-0.88)	0.006 (0.002)	59	96

C=clarithromycin; CI=confidence interval; CV=cardiovascular; HR=hazard ratio; Pl=placebo

[a] P values were adjusted for stratification variables and for all variables; values in parentheses are from a fully-adjusted analysis (adjusting for all entry variables, not just stratification variables)

[b] One death could not be classified

The results indicate that short-term survival (years 0-3 post-randomization) favored the placebo group, with an overall HR of 1.26 (95% CI 1.04-1.53).[4] When looking into the secondary endpoints among patients who had received clarithromycin, cardiovascular mortality outside of the hospital was significantly higher in the short-term (years 0-3, HR = 1.76, 95% CI 1.27-2.45) but lower in the long-term (years 6-10, HR = 0.64, 95% CI 0.46-0.88).

The investigators discussed the correlation between the use of statin-type drugs at the beginning of the study period and survival.[4] Statin use at entry of CLARICOR was associated with a protective effect in the short-term. For those not taking a statin drug at entry, the risk of cardiovascular death outside of the hospital in years 0-3 was increased (HR = 2.36, 95% CI 1.60-3.50); in contrast, the risk of cardiovascular death among patients taking a statin at study entry was lower (HR = 0.75, 95% CI 0.38-1.47). Though the latter data were not statistically significant, it would appear to be clinically significant given the endpoint of death. An HR was not calculated for cardiovascular death at the 10-year mark, but the absolute number of deaths of patients in the study group was higher in the non-statin-at-entry group versus the statin-at-entry group (148 vs. 54, respectively).

Limitations

There were several limitations to the CLARICOR trial and its 10-year follow-up study.[3,4] A major weakness is the investigators' failure to collect or account for the use of additional courses of clarithromycin, or other drugs which may hasten death, during the follow-up period.[4] It is certainly plausible that over the course of 10 years, patients in the placebo group may have been prescribed the study drug. Death dates and causes were obtained through public records, but the participants were not surveyed to obtain updated demographic data.[4] Additionally, the trial was conducted in a single country outside of the United States.[3]

Strengths

The large sample size of CLARICOR (n=4373) and few losses to follow-up (26 during 10 years) are major strengths.[3,4] The baseline demographics and risk factors were comparable between groups at the start of the CLARICOR trial.[3] Additionally, use of double-blinding and randomization leads to reduced bias.

Implications in Pharmacy Practice

Investigators calculated the number-needed-to-treat at year 10 for an additional harmful outcome as 35 patients for all-cause mortality and 52 patients for cardiovascular mortality outside of the hospital.[4] Clarithromycin currently remains a first-line treatment choice in conditions such as *H. pylori*[5] and community acquired pneumonia.[6] All co-morbidities and concomitant medications should be considered when creating a patient-centered treatment plan. The FDA's safety warning should be considered, and benefits and risks of clarithromycin should be weighed before prescribing it to any patient, particularly patients with heart disease. Pharmacists should advise patients with heart disease of potential signs and symptoms of cardiovascular problems when dispensing clarithromycin.

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New Treatment Consideration: Lurasidone (Latuda®) for Pediatric Bipolar Disorder

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Introduction

Bipolar disorder, previously referred to as manic-depressive illness, is characterized as extreme changes in mood including emotional highs (hypomania or mania) and lows (depression).[1] Pediatric bipolar disorder significantly affects psychosocial development and increases the risk of substance abuse, legal issues and suicide, necessitating treatment. The estimated lifetime prevalence of bipolar disorder in children and adolescents is less than 3%.[2] It is quite rare for children or adolescents to be diagnosed with bipolar disorder. The mean age at onset of the first manic, hypomanic or major depressive episode is approximately 18 years for bipolar I disorder and mid-20s for bipolar II disorder.[1] However, there is evidence of patients diagnosed with bipolar disorder prior to 15 years of age.[3] The manic symptoms associated with bipolar disorder mirror those of attention deficit hyperactivity disorder (ADHD) and disruptive mood dysregulation disorder (DMDD).[1]

Therefore, children may be incorrectly diagnosed with ADHD or DMDD first, then diagnosed with bipolar disorder after experiencing a depressive episode later in life.

Depressive episodes of unipolar depression and bipolar disorder often present similarly.[1] One study reported that nearly 70% of adult patients with bipolar disorder were evaluated by a mean of 4 physicians before receiving the correct diagnosis of bipolar disorder.[3] While there are specific diagnostic criteria for bipolar disorder in adults, there are no clear diagnostic criteria available for pediatric bipolar disorder.[1] It is crucial that diagnosticians collect a thorough patient history, as adolescent and young adult patients may inadvertently be diagnosed with unipolar depression. Any previous symptoms of mania may support a diagnosis of bipolar disorder, even if the patient only had 1 manic episode. There are several screening tools that have been used to assess symptoms of bipolar disorder in both pediatric and adult patients. The Mood Disorder Questionnaire (MDQ) is a tool used to identify previous manic symptoms; it consists of 13 yes/no questions derived from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for bipolar disorder, and clinical experience.[4] In addition to the MDQ screening tool, the Patient Health Questionnaire-9 (PHQ-9) assessment identifies the presence of a depressive episode. These screening tools can assist a clinician in determining a diagnosis of bipolar disorder.

Current Guideline Recommendations

Given the increasing prevalence of pediatric bipolar disorder, the burden of illness and the high suicide rate, there is an urgent need to improve treatment outcomes.[2] A guideline identified for treatment of children and adolescents with bipolar disorder in the United States was published in 2005.[5] This guideline, sponsored by the Child and Adolescent Bipolar Foundation (CABF), recommends monotherapy with conventional mood stabilizers including lithium or divalproex, or second generation antipsychotics (SGAs) including olanzapine, quetiapine, and risperidone as first-line treatment. Lithium is a Food and Drug Administration (FDA)-approved mood stabilizer for adolescents greater than 12 years of age, and while it is effective, monotherapy with lithium has been associated with rapid time to relapse. Some pediatric patients may respond to mood stabilizers, but there is growing evidence that SGAs work rapidly, and are at least as effective, if not more effective, than classic mood stabilizers for treatment of acute manic and depressive episodes.[6,7] The CABF guideline does not provide a treatment algorithm for depressive episodes associated with bipolar disorder, known as bipolar depression, as there were no prospective studies in children and adolescents at the time of writing.[5] Based on adult data, the panel recommends lithium for bipolar depression in children and adolescents. Selective serotonin reuptake inhibitors (SSRIs) and other antidepressants should only be recommended adjunctively to a mood stabilizer, as monotherapy can result in antidepressant-induced mania. The panel asserts that prospective clinical trials are needed as recommendations in this guideline are based on retrospective analyses, anecdotal reports, and expert consensus.

Second Generation Antipsychotics

As a class, SGAs are known to cause cardiometabolic adverse effects, including hypertriglyceridemia, hypercholesterolemia, hyperglycemia, and weight gain (with increased waist circumference).[8] As a result, patients with severe mental illness (including schizophrenia and bipolar disorder) receiving antipsychotic therapy have morbidity and mortality rates that are 2 to 3 times higher than those of the general population.[9] The potential for weight gain and development of diabetes is of great concern when using SGAs in pediatric patients with bipolar disorder, specifically the first-line agents of olanzapine and quetiapine.[5,8,10,11] Risperidone,

another first-line agent, is strongly associated with prolactin elevation, which can negatively affect menstruation in adolescent females, and cause gynecomastia in males, due to its high affinity and strong binding profile at dopamine receptors.[5,8,12]

Unlike other antipsychotics in its class, lurasidone (Latuda®) has not been associated with clinically significant prolactin elevation or weight gain, and it may be less sedating, making it a more favorable SGA for treatment of bipolar depression.[8,13]

Efficacy of Lurasidone in Pediatric Bipolar Disorder

Lurasidone is an SGA that was approved in March 2018 for the treatment of bipolar depression in pediatric patients 10 to 17 years of age.[14] The FDA approved this indication based on the results of a randomized controlled trial, sponsored by Sunovian Pharmaceuticals, which was the first prospective study to evaluate the efficacy and safety of an antipsychotic for treatment of bipolar depression in children and adolescents.[15]

Delbello et al conducted a 6-week, randomized, double-blind, placebo-controlled, parallel-group, intent-to-treat trial evaluating the efficacy and safety of lurasidone.[15] Patients included in this trial were aged 10 to 17 years who had been diagnosed with bipolar disorder I and experiencing a depressive episode lasting 1 to 12 months. Patients were required to have a Children's Depression Rating Scale-revised (CDRS-R) total score ≥45 and a Young Mania Rating Scale (YMRS) score ≤15. The CDRS-R is a 17-item scale that was adapted from the Hamilton Depression Rating Scale (HAM-D) and has become the rating scale of choice when assessing depressive symptoms in children and adolescent patients with depressive episodes.[16] A total score ≥40 on the CDRS-R scale (total score range of 17 to 113) indicates depression, while a score ≤28 denotes remission of depressive symptoms. YMRS is an 11-item rating scale (total score range of 0 to 60) used to assess severity of manic symptoms associated with bipolar disorder.[17] Exclusion criteria included a diagnosis of schizophrenia, psychotic disorder, substance use disorder, intellectual disability, autism spectrum disorder and CDRS-R total score >85.[15]

Patients were randomized to receive either lurasidone 20 mg daily for 7 days followed by flexible dosing (range of 20 to 80 mg/day) or placebo for 6 weeks.[15] Doses were administered in the evening with food (at least 350 calories). Anticholinergic therapy was allowed as needed for treatment of extrapyramidal symptoms (EPS), as was propranolol for treatment of akathisia. Concomitant benzodiazepine therapy was also allowed for intolerable anxiety or agitation. The primary endpoint was mean change in CDRS-R total score from baseline to week 6. The key secondary endpoint was mean change from baseline to week 6 in the Clinical Global Impression-Bipolar Severity (CGI-BP-S) assessment. The CGI-BP-S rates depression severity on a 7-point scale. Treatment response was defined as a ≥50% reduction in CDRS-R total score. Treatment remission was defined as a composite of CDRS-R total score ≤28, YMRS total score ≤8 and CGI-BP-S total score ≤3.

A total of 347 patients were randomized to treatment in this study; of these, 175 received at least 1 dose of lurasidone and 172 received placebo.[15] No significant differences in baseline demographics were detected between the groups. Approximately 20% of patients in both groups had a comorbid ADHD diagnosis, which may confound the results as the presentation of ADHD and bipolar disorder is very similar in young patients.[1,15] No clinically significant differences were found for the percent of patients receiving as needed treatment with benzodiazepines or sedative hypnotics between the lurasidone and placebo groups.

Findings for the primary and key secondary endpoints are shown in Table 1.

Table 1. Primary and secondary efficacy measures.[15]

Outcomes	Lurasidone (n=173)	Placebo (n=170)	Treatment difference (95% CI)
CDRS-R total score			
Baseline mean (SD)	59.2 (8.24)	58.6 (8.26)	n/a
LS mean change (SE)	-21.0 (1.06)	-15.3 (1.08)	-5.7 (-8.4 to -3.0)
CGI-BP-S depression score			
Baseline mean (SD)	4.6 (0.65)	4.5 (0.57)	n/a
LS mean change (SE)	-1.49 (0.085)	-1.05 (0.087)	-0.44 (-0.66 to -0.22)

CDRS-R=Children's Depression Rating Scale-revised; CGI-BP-S=Clinical Global Impression-Bipolar Severity; CI=confidence interval; LS=least squares; n/a=not applicable; SD=standard deviation; SE=standard error

There was a statistically and clinically significant difference between lurasidone and placebo in mean change in CDRS-R total score from baseline to week 6.[15] A statistically significant difference was also observed between groups in mean change in CGI-BP-S scores; however, this difference may not be clinically significant as the change was quite small.

The percent of patients meeting criteria for treatment response was significantly greater in those treated with lurasidone compared to placebo following 6 weeks (59.5% versus 36.5%; $p<0.0001$; number needed to treat [NNT]=5).[15] However, the percent of patients who achieved remission following 6 weeks of treatment did not significantly differ between the lurasidone and placebo groups (26.0% versus 18.8%; $p=0.082$).

Safety of Lurasidone in Pediatric Bipolar Disorder

In addition to efficacy, DelBello et al investigated the safety and tolerability of lurasidone in children and adolescents, measured by adverse event monitoring through physical examinations, vital signs, laboratory tests, and electrocardiograms (ECG).[15] Movement disorders were assessed with the Simpson-Angus Rating Scale (SARS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS). SARS is a 10-item scale (total score range of 0 to 40) used to evaluate severity of EPS with antipsychotic use.[18] BARS assesses the severity of antipsychotic-induced akathisia (0=absent, 1=questionable, 2=mild akathisia, 3=moderate akathisia, 4=marked akathisia, 5=severe akathisia).[19] AIMS is a 12-item scale that measures presence and severity of tardive dyskinesia (TD).[20] A rating score ≥2 is evidence of TD.

Sixty-four percent (64.0%) of patients treated with lurasidone and 51.7% of patients treated with placebo reported ≥1 adverse event.[15] The most frequent adverse events associated with lurasidone therapy were nausea (16.0% vs. 5.8% in placebo, number need to harm [NNH]=10) and somnolence (11.4% vs. 5.8% in placebo, NNH=18). EPS-related adverse events, except for akathisia, occurred more frequently in the lurasidone group (2.3% in lurasidone group vs. 1.7% in placebo group). Notably, akathisia occurred more frequently in the placebo group compared to those receiving treatment with lurasidone (3.5% in placebo group vs. 2.9% in lurasidone group). However, more patients receiving lurasidone treatment received anticholinergic medications for the treatment of EPS (1.2% lurasidone vs. 0.6% placebo). There were no clinically meaningful changes from baseline to week 6 for the SARS, BARS and AIMS rating scales. There were also no clinically significant differences in cardiometabolic adverse effects between lurasidone and placebo (see Table 2). The overall discontinuation rate for lurasidone was 8%, which appears quite low, but considering this was a 6-week

trial, higher discontinuation rates may be seen with longer use as cardiometabolic adverse events tend to be duration dependent.[8,9,13,15]

Table 2. Adverse effects of lurasidone compared to placebo.[15]

Change from Baseline to Week 6	Lurasidone	Placebo
Weight (kg)		
Number of subjects	162	157
Baseline mean	56.58	57.02
LS mean (SE) change	+0.74 (0.15)	+0.44 (0.15)
Fasting glucose (mg/dL)		
Number of subjects	145	145
Baseline mean (SD)	90.1 (10.4)	90.6 (9.3)
Median change (95% CI)	0.0 (-1.0 to 1.0)	0.0 (-2.0 to 1.0)
Prolactin, male (ng/mL)		
Number of subjects	82	79
Baseline mean (SD)	7.9 (6.4)	7.2 (5.2)
Median change (95% CI)	+0.8 (0.0 to 1.8)	+0.5 (-0.2 to 0.9)
Prolactin, female (ng/mL)		
Number of subjects	83	78
Baseline mean (SD)	16.3 (25.4)	12.3 (11.0)
Median change (95% CI)	+2.5 (0.1 to 4.1)	+0.6 (-0.2 to 1.6)

CI=confidence interval; LS=least squares; SD=standard deviation; SE=standard error

Conclusion

Lurasidone is an SGA that was recently FDA-approved for the treatment of depressive episodes in children and adolescents diagnosed with pediatric bipolar disorder.[14] Unlike other SGAs that have been recommended as first-line treatment options, lurasidone has not been shown to cause significant cardiometabolic adverse effects.[5,8,13,15] It should be noted that head-to-head studies evaluating the efficacy and safety of lurasidone compared to other SGAs have not yet been conducted. Previously published guidelines and recommendations have been based on retrospective analyses, anecdotal reports, and expert consensus.[5] One prospective, randomized controlled trial, to date, has demonstrated the efficacy and safety of lurasidone in the treatment of children and adolescents 10 to 17 years of age with bipolar depression, leading to its FDA approval in this population.[14,15]

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