THE JOURNAL OF FAMILY PRACTICE

Richard R. Watkins, MD, MS; Tracy L. Lemonovich, MD
Division of Infectious Diseases, Akron General Medical Center, Ohio (Dr. Watkins); Division of Infectious Diseases and HIV Medicine, University Hospitals Case Medical Center, Cleveland (Dr. Lemonovich)

rwatkins@agmc.org

The authors reported no potential conflict of interest relevant to this article.

Is *C difficile* to blame for your patient's diarrhea?

Once viewed almost exclusively as a nosocomial infection, *C difficile* is increasingly common in outpatient settings, making it imperative that FPs be proficient in detection and treatment.

PRACTICE RECOMMENDATIONS

› *A* C difficile *diagnosis should be made by one of several widely available testing protocols, including a 2-step method using the common antigen assay to determine whether* C difficile *is present, followed by an enzyme immunoassay for toxins A and B to improve specificity.* (B)

› *Oral metronidazole should be used for initial treatment of mild to moderate* C difficile *infection, and oral vancomycin and possibly intravenous metronidazole for severe cases.* (A)

› *Metronidazole should not be used after an initial recurrence or for long-term therapy because of the risk of neurotoxicity.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE▶ Mary S, an 82-year-old patient you recently treated for bronchitis with a 3-day course of levofloxacin, calls your office complaining of diarrhea and abdominal cramps. She describes the diarrhea as nonbloody and particularly foul smelling and asks if she can take loperamide for her symptoms.

If Mary S were your patient, what would you tell her?

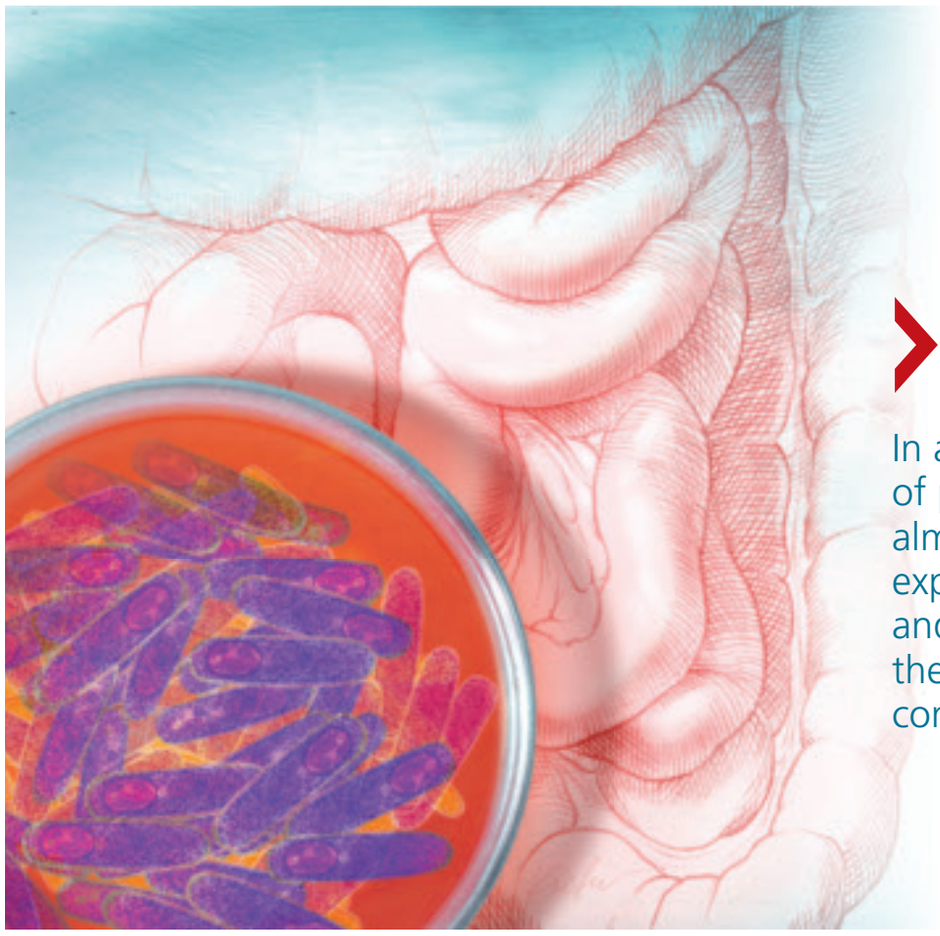
The incidence of *Clostridium difficile* infection (CDI) has been on the rise since 2000, when a common epidemic strain began circulating in North America.[1] Although hospitalization or residency in a long-term care facility remains a classic risk factor for CDI, physicians in outpatient settings are increasingly likely to see patients with community-acquired CDI.

Recently updated guidelines from the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America define CDI as the presence of diarrhea (≥3 unformed stools in 24 hours) and either a positive stool test for toxigenic *C difficile* or its toxins or colonoscopic or histopathologic findings demonstrating pseudomembranous colitis.[2] That said, the clinical features of CDI are nonspecific and many patients do not fit the classic profile. So diagnosing CDI requires a high index of suspicion.

The text and tables that follow detail some surprising things about who is likely to develop CDI and which treatment options to employ (and, in some cases, avoid).

Is it CDI? Looking beyond the obvious

Antibiotic use and advanced age, like hospitalization, are classic risk factors for CDI.[3] Diarrhea typically begins during or shortly after a course of antibiotics, but may develop as long as 8 weeks after treatment is completed. While any antibiotic, including metronidazole, can precipitate CDI, clindamycin,



In a recent study of patients with CDI, almost half had no exposure to antibiotics and 20% of the cases were community-acquired.

cephalosporins, extended-spectrum penicillins, and quinolones are most frequently implicated.[4] Epidemiologic studies have suggested an association between gastric acid-reducing agents—primarily proton-pump inhibitors—and CDI.[4-7] But this link remains controversial, as other investigations have not found a clear relationship.[8]

In addition to diarrhea, approximately 28% of patients with CDI develop a fever (as high as 104°F); 50% develop leukocytosis (up to 50,000 cells/mcL); and 22% develop abdominal pain, usually localized to the lower quadrants.[9] These symptoms, however, are not specific to *C difficile*, and could be due to a different enteric pathogen, intra-abdominal sepsis, inflammatory bowel disease, or adverse effects of medication, among other causes.[9]

Markers for severe CDI include age >70 years, leukocyte count >20,000 cells/mcL, albumin level <2.5 g/dL, small-bowel obstruction or ileus, and a computed tomography (CT) scan showing colorectal inflammation.[10] Severe CDI can lead to toxic megacolon, bowel perforation, sepsis, and even death.

IMAGE © CRAIG KIEFER

In addition to considering CDI in patients with nonspecific symptoms, it is important to include it in the differential diagnosis of patients who do not fit the classic profile. In a recent study of patients with CDI at 4 Veterans Affairs facilities, almost half (49%) of those studied had no exposure to antimicrobial drugs. The researchers further found that the median age of patients with CDI was 61 years—younger than that found in previous studies—and that 20% of the cases were community-acquired.[11]

Consider CDI in children, too. Risk factors for CDI in pediatric patients include disruption of the normal microflora of the gastrointestinal tract, compromised immune status, poor diet, underlying health conditions, concurrent infections, and cancer.[12]

Diagnostic testing: Consider a 2-step assay

Patients with symptoms suggestive of CDI should undergo laboratory testing to confirm the diagnosis. **TABLE 1** lists the tests that are widely available in the United States.[3] Only

liquid stools should be tested and just one sample should be sent to the lab, as multiple samples do not increase the diagnostic yield.[13] In addition, tests should be used only for diagnosis, and not as a "test of cure." This is because patients can shed *C difficile* toxin and spores for several weeks after completing treatment, and there are wide variations in the sensitivity of toxin assays.

Infants <1 year old have high rates of asymptomatic toxigenic strains of *C difficile,* and until 2008, recommendations from SHEA discouraged testing the stools of such young patients. Because of the difficulty in differentiating incidental colonization from true CDI in this patient population, the authors of a recent review suggested using more than one diagnostic approach when testing children <1 year of age.[14]

We advocate a 2-step assay—that is, testing for both glutamate dehydrogenase (GDH)—an antigen common to all strains of *C difficile*—and *C difficile* toxins A and B. The common antigen test is sensitive, but may detect carriers who do not have active disease. The enzyme immunoassay (EIA) for toxins A and B helps to improve specificity. Therefore, positive results of both tests would be considered a positive finding, negative results of both tests would be considered a negative finding, and one positive result with one negative result would require another test for toxin detection.[3]

The reverse-transcriptase polymerase chain reaction (RT-PCR) assay, which detects the toxin B gene of *C difficile,* is the newest test for CDI. The RT-PCR assay detects only toxigenic strains of *C difficile,* and all toxigenic strains produce toxin B, making it more specific than testing for the common antigen. The RT-PCR assay also has better sensitivity than the cytotoxin assay, which also tests for toxin B. The major limitation of the RT-PCR assay is the frequency of false-positive results in hospitalized patients with a high incidence of *C difficile* colonization.[3]

Routine laboratory studies, including a complete blood count with differential and a complete metabolic panel, are often useful to ascertain the presence and degree of leukocytosis, dehydration, and other metabolic abnormalities and to test for hypoalbuminemia. Fecal leukocytes can be seen in colitis and may be useful in select cases.

Imaging studies such as radiography, CT, and endoscopy have largely been superseded by lab testing for CDI. Plain radiographs are usually normal in patients with CDI, unless the patient has an ileus or toxic megacolon. CT is useful, however, in suspected cases of fulminant CDI or toxic megacolon, and may reveal colonic-wall thickening, pericolonic stranding, or ascites.[9] Colonoscopy is preferred over sigmoidoscopy because up to one-third of patients with pseudomembranous colitis will have involvement of the right colon only.[9] However, this test carries the risk of perforation in patients with fulminant colitis. .

Treatment: What to consider, what to avoid

Of the 2 antibiotics most commonly used to treat CDI—metronidazole and vancomycin—only the latter has been approved by the US Food and Drug Administration for this indication. Nevertheless, metronidazole is generally recommended as first-line therapy and has the advantage of being much less expensive than vancomycin. However, an RCT found that oral vancomycin was superior to metronidazole in patients with severe disease.[15] The time to resolution of diarrhea may be shorter with oral vancomycin than with metronidazole, as well.[16]

Recent guidelines suggest that clinicians consider 3 factors in deciding how to treat a first episode of CDI: the patient's age, peak white blood cell count, and peak serum creatinine level.[2] **TABLE 2** presents an overview of treatment recommendations for both an initial episode of CDI and recurrences.

Treat severe CDI without delay. For patients with suspected severe CDI, treatment should be started empirically, without waiting for test results. Avoid antiperistaltic agents, which can obscure symptoms and precipitate toxic megacolon.[2] Discontinue an antibiotic, if the patient is taking one, as soon as possible after the original infection has been adequately treated. If other infections need to be treated concurrently, we recommend that the course of treatment for CDI be

TABLE 1
Lab tests for *C difficile* infection

Test	Substance detected	Time needed	Sensitivity	Specificity
Cytotoxin	Toxin B	1-3 d	95%	90%-95%
Toxin culture	Toxigenic *C difficile*†	3-5 d	>95%	80%-90%
EIA toxin A or A/B	Toxin A or A/B	Hours	75%-80%	97%-98%
EIA GDH*	*C difficile*	Hours	95%-100%	70%-80%
EIA GDH* and toxin A/B	*C difficile* and *C difficile* toxin	Hours	95%-100%	97%-98%
RT-PCR	Toxigenic *C difficile*†	Hours	>98%	80%-99%

*GDH is the common *C difficile* antigen.
†All toxigenic strains produce toxin B.
EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; RT-PCR, reverse-transcriptase polymerase chain reaction.
Adapted from: Bartlett JG. *Infect Control Hosp Epidemiol.* 2010.[3]

extended until after the other antibiotic regimens have been stopped.

Avoid probiotics in this group. The use of probiotics, both for prevention and to help restore normal bowel flora in patients with CDI, has been advocated for many years. One RCT showed that a yogurt drink containing *Lactobacillus* and other bacteria reduced the risk of CDI in individuals ≥50 years of age who were taking antibiotics,[17] but the guideline development panel recommended against using probiotics until larger trials have been completed.[2]

Probiotics are not without risk, and several cases of bacteremia have been reported.[18,19] Immunocompromised patients appear to be at comparably higher risk, and probiotics should be avoided in this group. Numerous adjunctive agents, including intraluminal toxin binders, biotherapeutic agents, monoclonal antibodies, and a *C difficile* vaccine, are in various stages of development.[2]

How to handle recurrences

Relapse rates for CDI range from 6% to 25%,[2] and affect patients who receive either vancomycin or metronidazole for the initial treatment. The mechanism relates to either relapse of the original infection or reinfection of susceptible patients with a new strain of *C difficile*.

Risk of relapse. Elderly patients treated with metronidazole seem to be particularly susceptible to CDI relapse.[20] Other risk factors include the administration of non–*C difficile* antibiotics during or after treatment of CDI, a defective immune response against toxin A, glucocorticoid use, prior stroke, and concurrent use of a proton-pump inhibitor.[21-25]

TABLE 2 lists tapering and/or pulsed dosing of oral vancomycin as treatment for patients with a second recurrence. We often prescribe the following 6-week regimen, telling patients to take 125 mg vancomycin:

- 4 times a day for one week,
- then 2 times a day for one week,
- then once a day for one week,
- then every other day for one week, and
- finally, every 72 hours for 2 weeks.

Oral metronidazole should not be used beyond the first recurrence or for long-term therapy because of cumulative neurotoxicity, which can be irreversible.[2]

Management of patients whose CDI recurs after a long course of vancomycin is challenging. Oral rifaximin therapy (400 mg twice a day for 14 days), started immediately at the end of the oral vancomycin course, was shown to cure 7 of 8 patients with multiple relapses.[26] Other potential treatment options are oral nitazoxanide, IV tigecycline, or IV immunoglobulin.

CASE▶ You explain to Mary S that diagnostic tests are needed before you can deter-

Routine lab studies, including a complete blood count and metabolic panel, can detect the presence and degree of leukocytosis, dehydration, and other metabolic abnormalities.

TABLE 2

Treatment recommendations for *C difficile* infection

Clinical description	Clinical evidence	Recommended treatment
Initial episode (mild or moderate)	Leukocytosis with a white cell count <15,000 cells/mcL and creatinine <1.5 times premorbid level	Metronidazole (oral) 500 mg TID for 10-14 d
Initial episode (severe)	Leukocytosis with a white cell count ≥15,000 cells/mcL or creatinine ≥1.5 times premorbid level	Vancomycin (oral) 125 mg QID for 10-14 d
Initial episode (severe, complicated)	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg QID (oral or by NG tube) plus metronidazole 500 mg (IV). If complete ileus, consider adding rectal instillation of vancomycin
First recurrence		Same as initial episode
Second recurrence		Vancomycin in a tapered and/or pulsed regimen

NG, nasogastric.

Adapted from: Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010.[2]

Oral metronidazole should not be used beyond the first occurrence, or for long-term therapy, because of cumulative neurotoxicity.

mine whether she can safely take loperamide. When she comes in later that day, you collect a stool sample for *C difficile* antigen and toxin testing, and order a complete blood count and electrolyte panel.

The patient's *C difficile* tests come back positive, her white blood cell count is <15,000 cells/mcL, and her creatinine level is ≤1.5 times her baseline, so you start her on oral metronidazole 500 mg every 8 hours for 14 days. (If the antigen assay had been positive and the toxin negative, you would have either repeated the test or treated Mary S empirically with metronidazole. If the initial antigen assay had been negative, you would have advised her to take the loperamide.)

You schedule a follow-up visit a day or 2 after starting therapy. If the patient is dehydrated or her symptoms have not improved by then, hospitalization may be required. **JFP**

CORRESPONDENCE
Richard R. Watkins, MD, MS, Division of Infectious Diseases, Akron General Medical Center, 224 West Exchange Street, Suite 290, Akron, OH 44302; rwatkins@agmc.org

References

1. Gerding DN. Global epidemiology of *Clostridium difficile* infection in 2010. *Infect Control Hosp Epidemiol*. 2010;31(suppl 1):S32-S34.
2. Cohen SH, Gerding DH, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31:431-455.
3. Bartlett JG. Detection of *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2010;31(suppl 1):S35-S37.
4. Dial S, Alrasadi K, Manoukian C, et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. *CMAJ*. 2004;171:33-38.
5. Dial S, Delaney JA, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA*. 2005;294:2989-2995.
6. Cunningham R, Dale B, Undy B, et al. Proton pump inhibitors as a risk factor for *Clostridium difficile* diarrhoea. *J Hosp Infect*. 2003;54:243-245.
7. Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med*. 2010;170:784-790.
8. Shah S, Lewis A, Leopold D, et al. Gastric acid suppression does not promote clostridial diarrhoea in the elderly. *QJM*. 2000;93:175-181.
9. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. *Clin Infect Dis*. 2008;46(suppl 1):S12-S18.
10. Henrich TJ, Krakower D, Bitton A, et al. Clinical risk factors for severe *Clostridium difficile*-associated disease. *Emerg Infect Dis*. 2009;15:415-422.
11. Kutty PK, Woods CW, Sena AC, et al. Risk factors for and estimated incidence of community-associated *Clostridium difficile* infection, North Carolina, USA. *Emerg Infect Dis*. 2010;16:197-204.
12. Pituch H. *Clostridium difficile* is no longer just a nosocomial infection or an infection of adults. *Int J Antimicrob Agents*. 2009;33(suppl 1):S42-S45.
13. Mohan SS, McDermott BP, Parchuri S, et al. Lack of value of repeat stool testing for *Clostridium difficile* toxin. *Am J Med*. 2006;119:356.e7-e8.

CONTINUED

Psychiatric disorders: euphoric mood, disorientation, restlessness, agitation, nervousness, thinking abnormal
Renal and urinary disorders: urinary hesitation, pollakiuria
Respiratory, thoracic and mediastinal disorders: oxygen saturation decreased, cough, dyspnea, respiratory depression
Skin and subcutaneous tissue disorders: urticaria
Vascular disorders: blood pressure decreased

In the pooled safety data, the overall incidence of adverse reactions increased with increased dose of NUCYNTA®, as did the percentage of patients with adverse reactions of nausea, dizziness, vomiting, somnolence, and pruritus.

Post-marketing Experience

The following additional adverse reactions have been identified during post-approval use of NUCYNTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably. **Immune system disorders:** angioedema **Nervous system disorders:** headache **Psychiatric disorders:** hallucination

DRUG INTERACTIONS

NUCYNTA® is mainly metabolized by glucuronidation. The following substances have been included in a set of interaction studies without any clinically significant finding: acetaminophen, acetylsalicylic acid, naproxen and probenecid *[see Clinical Pharmacology (12.3) in full PI]*.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively *[see Clinical Pharmacology (12.3) in full PI]*.

Drugs Metabolized by Cytochrome P450 Enzymes

In vitro investigations indicate that NUCYNTA® does not inhibit or induce P450 enzymes. Thus, clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3) in full PI]*.

Drugs That Inhibit or Induce Cytochrome P450 Enzymes

The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. To a lesser extent, tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Since only a minor amount of NUCYNTA® is metabolized via the oxidative pathway clinically relevant interactions mediated by the cytochrome P450 system are unlikely to occur *[see Clinical Pharmacology (12.3) in full PI]*.

Centrally-Acting Drugs and Alcohol

Patients receiving other opioid agonist analgesics, general anesthetics, phenothiazines, antiemetics, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol) concomitantly with NUCYNTA® may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with NUCYNTA®. When such combined therapy is contemplated, a dose reduction of one or both agents should be considered *[see Warnings and Precautions]*.

Monoamine Oxidase Inhibitors

NUCYNTA® is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due to potential additive effects on norepinephrine levels which may result in adverse cardiovascular events *[see Contraindications]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

Tapentadol HCl was evaluated for teratogenic effects in pregnant rats and rabbits following intravenous and subcutaneous exposure during the period of embryofetal organogenesis. When tapentadol was administered twice daily by the subcutaneous route in rats at dose levels of 10, 20, or 40 mg/kg/day [producing up to 1 times the plasma exposure at the maximum recommended human dose (MRHD) of 700 mg/day based on an area under the time-curve (AUC) comparison], no teratogenic effects were observed. Evidence of embryofetal toxicity included transient delays in skeletal maturation (i.e. reduced ossification) at the 40 mg/kg/day dose which was associated with significant maternal toxicity. Administration of tapentadol HCl in rabbits at doses of 4, 10, or 24 mg/kg/day by subcutaneous injection [producing 0.2, 0.6, and 1.85 times the plasma exposure at the MRHD based on an AUC comparison] revealed embryofetal toxicity at doses ≥ 10 mg/kg/day. Findings included reduced fetal viability, skeletal delays and other variations. In addition, there were multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia, and cleft palate at doses ≥ 10 mg/kg/day and above, and ablepharia, encephalopathy, and spina bifida at the high dose of 24 mg/kg/day. Embryofetal toxicity, including malformations, may be secondary to the significant maternal toxicity observed in the study.

In a study of pre- and postnatal development in rats, oral administration of tapentadol at doses of 20, 50, 150, or 300 mg/kg/day to pregnant and lactating rats during the late gestation and early postnatal period [resulting in up to 1.7 times the plasma exposure at the MRHD on an AUC basis] did not influence physical or reflex development, the outcome of neurobehavioral tests or reproductive parameters. Treatment-related developmental delay was observed, including incomplete ossification, and significant reductions in pup body weights and body weight gains at doses associated with maternal toxicity (150 mg/kg/day and above). At maternal tapentadol doses ≥ 150 mg/kg/day, a dose-related increase in pup mortality was observed through postnatal Day 4.

There are no adequate and well controlled studies of NUCYNTA® in pregnant women. NUCYNTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

The effect of tapentadol on labor and delivery in humans is unknown. NUCYNTA® is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of NUCYNTA®, neonates whose mothers have been taking NUCYNTA® should be monitored for respiratory depression. A specific opioid antagonist, such as naloxone, should be available for reversal of opioid induced respiratory depression in the neonate.

Nursing Mothers

There is insufficient/limited information on the excretion of tapentadol in human or animal breast milk. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. NUCYNTA® should not be used during breast-feeding.

Pediatric Use

The safety and effectiveness of NUCYNTA® in pediatric patients less than 18 years of age have not been established. NUCYNTA® is not recommended in this population.

Geriatric Use

Of the total number of patients in Phase 2/3 double-blind, multiple-dose clinical studies of NUCYNTA®, 19% were 65 and over, while 5% were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. The rate of constipation was higher in subjects greater than or equal to 65 years than those less than 65 years (12% vs. 7%).

In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, consideration should be given to starting elderly patients with the lower range of recommended doses *[see Clinical Pharmacology (12.3) in full PI]*.

Renal Impairment

In patients with severe renal impairment, the safety and effectiveness of NUCYNTA® has not been established. NUCYNTA® is not recommended in this population *[see Dosage and Administration (2.1) in full PI]*.

Hepatic Impairment

Administration of NUCYNTA® resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function *[see Clinical Pharmacology (12.3) in full PI]*. NUCYNTA® should be used with caution in patients with moderate hepatic impairment *[see Dosage and Administration (2.2) in full PI]*.

NUCYNTA® has not been studied in patients with severe hepatic impairment, therefore, use of NUCYNTA® is not recommended in this population *[see Warnings and Precautions]*.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

NUCYNTA® contains tapentadol, a mu-opioid agonist and is a Schedule II controlled substance. NUCYNTA® has an abuse potential similar to hydromorphone, can be abused and is subject to criminal diversion.

Abuse

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common.

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

"Drug seeking" behavior is very common in addicts, and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated claims of loss of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of mu-opioid agonists can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Abuse of NUCYNTA® poses a risk of overdose and death. This risk is increased with concurrent abuse of NUCYNTA® with alcohol and other substances. In addition, parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of drugs with mu-opioid agonist properties.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Warnings and Precautions]*. Use of NUCYNTA® in this population has not been characterized. As NUCYNTA® has mu-opioid agonist activity, infants whose mothers have taken NUCYNTA®, should be carefully monitored.

Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, increased blood pressure, respiratory rate, or heart rate.

Generally, tolerance and/or withdrawal are more likely to occur the longer a patient is on continuous opioid therapy. In a safety study where drug was administered up to 90 days, 82.7% of patients taking NUCYNTA® who stopped abruptly without initiating alternative therapy and were assessed 2 to 4 days after discontinuation, did not have objective signs of opioid withdrawal using the Clinical Opiate Withdrawal Scale. Moderate withdrawal symptoms were seen in 0.3% of patients with the rest (17%) experiencing mild symptoms. Withdrawal symptoms may be reduced by tapering NUCYNTA®.

OVERDOSAGE

Human Experience

Experience with NUCYNTA® overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid agonist activity are to be expected upon intoxication with

tapentadol. In principle, these symptoms may particularly appear in the clinical setting: miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of Overdose

Management of overdose should be focused on treating symptoms of mu-opioid agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of NUCYNTA® is suspected. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

Pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage is only recommended within 2 hours after intake. Gastrointestinal decontamination at a later time point may be useful in case of intoxication with exceptionally large quantities. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the following issues with patients for whom they prescribe NUCYNTA®:

Instructions for Use

Patients should be advised NUCYNTA® should be taken only as directed and to report episodes of breakthrough pain and adverse experiences occurring during therapy to their physician. Individualization of dosage is essential to make optimal use of this medication. Patients should be advised not to adjust the dose of NUCYNTA® without consulting their physician *[see Dosage and Administration (2) in full PI]*. Patients should be advised that it may be appropriate to taper dosing when discontinuing treatment with NUCYNTA® as withdrawal symptoms may occur *[see Drug Abuse and Dependence]*. The physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Misuse and Abuse

Patients should be advised that NUCYNTA® is a potential drug of abuse. Patients should protect NUCYNTA® from theft, and NUCYNTA® should never be given to anyone other than the individual for whom NUCYNTA® was prescribed *[see Warnings and Precautions]*.

Interference with Cognitive and Motor Performance

As NUCYNTA® has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles *[see Warnings and Precautions]*.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Nursing

Patients should be advised not to breast-feed an infant during treatment with NUCYNTA® *[see Use in Specific Populations]*.

Monoamine Oxidase Inhibitors

Patients should be informed not to take NUCYNTA® while using any drugs that inhibit monoamine oxidase. Patients should not start any new medications while taking NUCYNTA® until they are assured by their healthcare provider that the new medication is not a monoamine oxidase inhibitor.

Seizures

Patients should be informed that NUCYNTA® could cause seizures if they are at risk for seizures or have epilepsy. Such patients should be advised to use NUCYNTA® with care *[see Warnings and Precautions]*. Patients should be advised to stop taking NUCYNTA® if they have a seizure while taking NUCYNTA® and call their healthcare provider right away.

Serotonin Syndrome

Patients should be informed that NUCYNTA® could cause rare but potentially life-threatening conditions resulting from concomitant administration of serotonergic drugs (including Serotonin Reuptake Inhibitors, Serotonin and Norepinephrine Reuptake Inhibitors and tricyclic antidepressants) *[see Warnings and Precautions]*.

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs as there is a potential for interactions *[see Drug Interactions]*.

Alcohol

Patients should be advised to avoid alcohol while taking NUCYNTA® *[see Drug Interactions]*.

Medication Guide

See Medication Guide (17.10) in full PI. Revised: November 2010

Manufactured by:
Janssen Ortho, LLC, Gurabo, PR 00778

Manufactured for:
PriCara®, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., Raritan, NJ 08869

PriCara
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

 10169803B

CONTINUED FROM PAGE 132

14. Bryant K, McDonald LC. *Clostridium difficile* infections in children. *Pediatr Infect Dis J*. 2009;28:145-146.
15. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45:302-307.
16. Belmares J, Gerding DN, Parada JP, et al. Outcome of metronidazole therapy for *Clostridium difficile* disease and correlation with a scoring system. *J Infect*. 2007;55:495-501.
17. Hickson M, D'Souza AL, Muthu N, et al. Use of probiotic *Lactobacillus* preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial. *BMJ*. 2007;335:80.
18. Ledoux D, Labombardi VJ, Karter D. *Lactobacillus acidophilus* bacteraemia after use of a probiotic in a patient with AIDS and Hodgkin's disease. *Int J STD AIDS*. 2006;17:280-282.
19. Hammerman C, Bin-Nun A, Kaplan M. Safety of probiotics: comparison of two popular strains. *BMJ*. 2006;333:1006-1008.
20. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis*. 2005;40:1586-1590.
21. Nair S, Yadav D, Corpuz M, et al. *Clostridium difficile* colitis: factors influencing treatment failure and relapse—a prospective evaluation. *Am J Gastroenterol*. 1998;93:1873-1876.
22. Garey KW, Sethi S, Yadav Y, et al. Meta-analysis to assess risk factors for recurrent *Clostridium difficile* infection. *J Hosp Infect*. 2008;70:298-304.
23. Das R, Feuerstadt P, Brandt LJ. Glucocorticoids are associated with increased risk of short-term mortality in hospitalized patients with *Clostridium difficile*-associated disease. *Am J Gastroenterol*. 2010;105:2040-2049.
24. Cadena J, Thompson GR 3rd, Patterson JE, et al. Clinical predictors and risk factors for relapsing *Clostridium difficile* infection. *Am J Med Sci*. 2010;339:350-355.
25. Linsky A, Gupta K, Lawler EV, et al. Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection. *Arch Intern Med*. 2010;170:772-778.
26. Johnson S, Schriever C, Galang M, et al. Interruption of recurrent *Clostridium difficile*-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. *Clin Infect Dis*. 2007;44:846-848.